MILLIMAN REPORT

A new framework for quantifying healthcare value using real-world evidence

August 2024

Bruce Pyenson, FSA, MAAA
Rebecca Smith, MBA
Allison Halpren, MPH
Parsa Entezarian, BA

Commissioned by the Alliance for Aging Research


Milliman

Table of contents

Introduction

Concerns about value in healthcare are widespread, with terms like “value-based care” and phrases such as “value not volume” frequently mentioned. However, the question remains: how should value be measured? High overall healthcare spending and the emergence of high-priced therapies has led to pervasive concern over whether particular therapies are worth their prices. The Inflation Reduction Act’s (IRA) establishment of government price intervention for select pharmaceuticals for Medicare beneficiaries has also raised questions of whether price can and should be tied to some measure of value. The status quo for comparing the value of therapies relies upon the therapies’ potential to increase the patient’s quality-adjusted life years (QALYs),[1] but the use of QALYs and other traditional methods is subject to criticism on policy, ethical, and technical grounds. The growing abundance of health information, in its various forms and sheer volume, increases the range of sources and options for informing value measures.

In recent years, real-world evidence (RWE) and real-world data (RWD) have become increasingly important in healthcare decision making. RWD are routinely collected from sources like electronic health records, medical claims, and digital health technologies.[2] RWE is the clinical evidence derived from analyzing this RWD, offering insights into the practical use, benefits, and potential risks of a medical product.[2] RWE has been used to support coverage decisions, guide clinical practice, spur support of new indications for approved drugs, and more.[3] Technological advancements in data collection have allowed for a massive shift in the availability of RWE and in the methodological approaches to RWD analysis. Governments across the world have allocated significant funding to the development of RWE.

Still, advances in RWD collection and RWE use have not yet fully permeated discussions or estimations of treatment value in the United States. Typically, outcomes derived from randomized controlled trials are used in value assessment calculations, but these trials can be based on narrow or homogenous populations. This is problematic because a key use of value assessments is to inform practical coverage and reimbursement decision making for broad populations.

Recognizing a perceived need for a new transparent and sound methodology for assessing therapeutic value, the Alliance for Aging Research engaged Milliman to evaluate an approach that uses real-world evidence. In this paper, we explore Standard of Living Valuation (SoLV), a novel approach to quantifying value using real-world data that may offer a path to valuing therapies without the use of QALYs.

An individual’s medical care is known to influence their health, but socioeconomic factors—such as a person’s standard of living (SoL)—are much more significant contributors to personal health outcomes.[4] The approach described in this paper connects differences in populations’ health outcomes to the populations’ higher or lower SoL and uses this information to estimate the relationship between financial inputs and the real-world value of those health outcomes. We believe this approach can be used to inform the value of medical interventions, while having the advantage of using RWD about differences in populations’ health and their socioeconomic conditions.

Under the SoLV framework, therapies for conditions with greater discrepancies in health outcomes by socioeconomic factors will generate higher values, all else being equal. This methodology taps the wealth of RWD about income, social determinants of health, and outcomes.

While this approach has similarities to other valuation methods, to our knowledge the SoLV method we evaluate here is original and novel. The SoLV approach offers numerous advantages, including the use of reference values that are not derived from healthcare spending (which avoids assuming the appropriateness of current healthcare prices); integration of RWE from epidemiology, public health, and clinical practice into calculations; and avoidance of certain policy and technical challenges associated with existing methods. In this paper, we introduce SoLV and suggest ways it can be further developed. This paper should be viewed as a pilot and not the final word on SoLV. Some analysts may want to use the SoLV framework to advocate for or against government income support, but our purpose in this paper is independent of such considerations.

This work was commissioned by the Alliance for Aging Research, a nonprofit organization dedicated to changing the narrative to achieve healthy aging and equitable access to care, including assigning appropriate value for therapies.

The need for a new value framework

CURRENT QALY FRAMEWORK FOR VALUE ASSESSMENT

The Quality-Adjusted Life Year (QALY) is currently the dominant method for measuring the effectiveness of health interventions. For over three decades, QALYs have been integral to cost-effectiveness analyses, facilitating comparisons across different health conditions.[5,6] QALYs are used to make benefit coverage decisions or compare the value of different treatments by national health systems, such as The National Institute for Health and Care Excellence (NICE) in the United Kingdom.[7] Much academic research in the field of pharmacoeconomics and outcomes research also uses QALYs, and in the U.S., the Institute for Clinical and Economic Review (ICER), a prominent value assessment organization, uses QALYs extensively.

QALYs combine quality of life and life duration into a single metric.[5,6] QALYs operate on a scale of zero to one, where one represents a year with perfect health and zero represents death. This approach enables the estimation of the incremental cost-effectiveness of one treatment compared to another for a particular condition.[6] For example, if a group of individuals is surveyed and is found to believe that, on average, 10 years in a hospital bed equates to one year in perfect health, the survey would find that the QALY for being bed-bound would be 0.1. This method can then be used to evaluate the cost-effectiveness of treatments by comparing the incremental cost of a treatment or therapy to the incremental QALYs associated with that treatment or therapy.

We provide a simple illustration of how QALYs are used to compare the value of interventions. In this illustration, we assume the status quo treatment for a condition and two alternative treatments each have the same expected survival of four years. The status quo treatment costs $50,000 but results in the patient being wheelchair-bound. Treatment A costs $80,000 and results in the patient using crutches, and Treatment B results in perfect health at a price of $114,000. Of the two alternatives, B would be deemed more cost-effective using a QALY-based approach, as it has a lower incremental cost per incremental QALY (Table 1).

TABLE 1. QALY-BASED VALUE CALCULATION

	STATUS QUO	TREATMENT A	TREATMENT B
Outcome	Wheelchair	Crutches	Perfect Health
Relative QALY For Treatment	0.20	0.45	1
Survival	4 years	4 years	4 years
QALYs Achieved from Treatment	0.8	1.8	4.0
Cost of Intervention	$50,000	$80,000	$114,000
Incremental Cost (ΔCost of Intervention)	n/a	$30,000	$64,000
Incremental Outcome (ΔQALYs)	n/a	1.0	3.2
Cost Effectiveness of Intervention	**n/a**	**$30,000 per additional QALY**	**$20,000 per additional QALY**

In Table 1, Treatment A costs an additional $30,000 per added QALY, while Treatment B costs $20,000 per added QALY, both relative to the status quo treatment. In this simplified example, the cost of the status quo treatment is used as a baseline, and the prices of the two alternatives are specified. In practice, prices may be market-based, observed, or hypothetical. Practitioners may also apply a pre-set “affordability” limit; for example, a program might consider any therapy whose incremental cost is more than $150,000 per added QALY as unaffordable. In this framework, the “value” of a treatment depends on the price assumptions and affordability limits.

The QALY approach to value, despite its widespread use, faces challenges on policy and technical grounds.[8] It often undervalues treatments that extend the lives of people with disabilities compared to treatments used for people without disabilities or chronic illnesses.[9,10] This undervaluation may result in restricted access to necessary medications and treatments for these individuals, especially in countries with nationalized healthcare systems, such as the United Kingdom.[10] Moreover, the data that forms the basis of the QALY, as used in standard cost-effectiveness analysis (CEA), does not accurately reflect patients' or societies' experiences with illness and disability.[10] This further contributes to the devaluation of life-extending drugs and treatments.[10] Using QALYs for people with disabilities poses several difficulties.[9] For example, many societies invest resources in supporting severely impaired children, whose quality of life (QoL) estimates may be very low or even zero. Despite these programs not resulting in improved QALYs for the children, they provide government funds for care. Such support socializes the care burden and helps affected families participate in society. A QALY-based valuation approach would assign little or no value to these ubiquitous programs aimed at supporting some affected children, as the societal investment does not result in improved QALYs for the children receiving them.

QALY's transactional methods also lead to challenges. The presumed "fair trade" transaction of offering more time with worse outcomes in exchange for less time with better outcomes focuses on individual patient preferences and overlooks family, caregiver, and cultural considerations.[11,12] Furthermore, from the standpoint of the QALY framework, an individual who is already impaired will be disadvantaged. When someone has multiple impairments, the QALY outcome may be affected by the order of the impairments (e.g., mathematically, non-commutative). For example, a therapy that treats a heart attack will have a lower QALY impact on someone who is already missing the use of one arm. Preventing a condition that would result in a QALY of 0.4 (assuming no survival differences) is more valuable for a patient with a current QALY of 1.0 than for a patient with a current QALY of 0.5. This is because the first patient would experience a decrease from 1.0 to 0.4 (a loss of 0.6 QALY), while the second patient would experience a decrease from 0.5 to 0.4 (a loss of only 0.1 QALY). Therefore, preventing the condition in the first patient yields a larger benefit. Would it be reasonable to deny treatment to the patient who gains fewer QALYs? These challenges make it difficult to characterize or interpret the value of the entire healthcare system as the sum of spending divided by sum of QALY improvements.

The use of QALYs is often coupled with a threshold to evaluate a price. For example, a payer or policymaker may decide that the price for a therapy is reasonable if the price is below a certain threshold, such as $150,000 per QALY gained. Justifying such a threshold is difficult, although current justifications may reference the prices of already approved therapies or the results from "willingness-to-pay" surveys. However, few would find it reasonable to negotiate with a parent on how much the parent would be willing to pay for someone to throw a flotation device to their drowning child. Swimming safety and lifeguard programs represent societal or community investments that meet needs and avoid value amounts based on fictional individual transactions. The use of a hypothetical "fair trade" or "willingness to pay" in QALY calculations oversimplifies decision-making processes. It ignores the findings of behavioral economics, which attempt to explain how people do not act "rationally" as defined by economists.[13] The surveys that produce QALY values present hypothetical alternatives to people who may not be afflicted with relevant conditions, so actual choices and attitudes may differ. Attempts to bridge these gaps with QoL surveys reveal widely differing results depending on the instrument used.[14,15]

In response to these criticisms, several alternatives to the standard QALY-based CEA have been developed. These alternatives aim to address the focus on healthcare delivery, the undervaluation of life extension for people with disabilities, and the lack of consideration for societal and patient perspectives.[10] Advocates of QALYs have defended the approach's use and introduced a complementary metric—the equal value of life years gained (evLYG)—as attempting to offset some of the aforementioned concerns.[16] The evLYG was specifically developed to address concerns that QALYs devalue the lives of those with disabilities by assessing a year of life with a disability as less valuable than a year of life without a disability.[16] Rather than considering how a given treatment may both lengthen and improve the remaining life years of a patient, the evLYG values each additional life year gained from a treatment equally.[10,16] Since 2020, the ICER has used the evLYG as an outcome measure in the assessment of six conditions in addition to the QALY.[16] Generally, the inclusion of the evLYG did not significantly affect the recommendations of any of the six assessments relative to using QALYs alone.[16] Although, in some cases, evLYGs showed additional value compared to QALYs in cases where the treatments resulted in added life years but minimal improvement

toward so-called “perfect” health.[16] Logical inconsistencies from the use of evLYG and a similar metric, health years in total, have been reported.[17] Despite attempts to address concerns through the introduction of additional measures, new legislation has been proposed that aims to prohibit the use of QALYs “and similar measures” in all federal programs.[18]

Concerns about using QALYs in healthcare coverage and reimbursement contexts have led to restrictions on their use by the federal government.[18] For example, the Affordable Care Act (ACA) prohibits the use of QALYs by Medicare,[16] and the more recent IRA reaffirmed this prohibition.[19] The recent implementation of the IRA empowers the federal government, including the Centers for Medicare and Medicaid Services (CMS), to negotiate prices for high-cost drugs. The IRA requires that CMS must not devalue extending the life of elderly, disabled, or terminally ill individuals compared to younger, nondisabled counterparts.[20] The IRA references value assessment, which adds urgency to the need for new healthcare value approaches.

RANDOMIZED CONTROLLED TRIALS

The practicality of any value assessment approach depends on the data available. Currently, value assessments performed to support coverage and reimbursement discussions favor the use of randomized controlled trial (RCT) data, which is often publicly available before a new treatment’s approval or market launch. Indeed, RCTs are designed to demonstrate the efficacy and safety of new therapies to obtain regulatory approvals (e.g., from the Food and Drug Administration). However, RWE generated after treatments have entered the market can provide additional insights beyond initial RCT findings. When the goal of value assessment is to provide guidance on which health policy choices will have better outcomes in the real world, RWE becomes a powerful resource.

RCTs provide a robust framework for evaluating the efficacy of new treatments.[21] The application of RCTs to value assessment often assumes that trial outcomes accurately mirror those that would occur in the real world.[22] The randomized allocation of participants to control and treatment arms in RCTs minimizes selection bias, reducing differences in outcomes within the trial population and the impact of confounding variables and external factors on the RCT’s results.[21,23] Random effects, which refer to variations in study outcomes that come from unintentional differences among individual participants or other unpredictable factors, are also minimized through randomization.[21] Randomization increases the likelihood that observed differences are due to the treatment itself rather than other influences. Additionally, the use of blinding in RCTs further diminishes the risk of bias, as researchers and participants remain unaware of treatment assignments during the trial, thereby preserving study integrity.[21] While RCTs are known for their reliability,[22] they also have limitations.

RCTs are expensive and are usually the last hurdle before new treatments can come to market. Therefore, RCTs tend to have smaller population sizes and shorter durations, potentially missing less common or delayed advantages or side effects and limiting conclusions about long-term efficacy.[21,22,24] Patient profile bias is also a significant concern. RCTs often involve participants who do not represent the diverse patient groups encountered in routine clinical care because of funding limitations, patient availability, or study eligibility requirements. This can lead to skewed patient samples that may reflect non-representative participants, and thus, limit generalizability.[21,22,24–26] Additionally, RCTs may inadequately acknowledge patient heterogeneity, underestimating the diversity of efficacy or side effects across populations or perpetuating health inequalities.[25] For all these reasons, applying values derived from RCTs to real-world situations requires careful consideration of how the underlying assumptions impact interpretations of real-world populations and situations.[25]

CAN REAL-WORLD EVIDENCE BE USEFUL?

With these limitations of RCTs in mind, RWE derived from real-world patient data or retrospective data from administrative claims databases, health records, and electronic medical records (EMRs)[24] can improve value assessments (Table 3).[24] RWE encompasses information gathered from actual patient experiences outside of the structured environment of controlled trials. This type of evidence can offer numerous advantages in healthcare research, providing a more realistic evidence base by reflecting populations and health service delivery in real-world situations.[27,28] Furthermore, RWE can draw from large heterogeneous patient populations compared to the significantly smaller homogeneous samples that are often necessitated by RCTs. Larger patient populations can enable more robust studies of rare and orphan diseases, and with larger samples, researchers can consider socioeconomic and demographic factors in their analyses.[25,26]

RWE is not bound by the design constraints of RCTs, which often measure a treatment's efficacy in a narrowly defined patient group via a specific delivery pathway. Consequently, conclusions drawn from large RWE studies may be easier to generalize across broad patient populations. RWE can provide information on efficacy within certain environmental or socioeconomic contexts and can inform how the distribution or management of a therapy can affect its value.[22,25–27] For example, a new blood-based cancer screening tool could be found to be less sensitive than existing radiological techniques and therefore less effective during clinical trials. Yet, when adopted in real-world settings, this screening could be significantly more effective in lower-income or rural communities with healthcare resource constraints due to its ease of deployment. Studies leveraging RWD can capture and quantify these benefits, which clinical trials might not.

Similarly, RWE often reflects utilization management practices, which can impact the effectiveness of treatments when deployed in real-world settings. Utilization management strategies, such as prior authorization and step therapy, can influence how and when patients receive treatments, potentially affecting provider and patient behavior. For example, patients' use of and adherence to a drug may be affected by these administrative processes. These effects may not be observable or relevant in a clinical trial setting but could be examined using RWD, which would reveal their implications for the real-world value of that drug.

RCTs tend to have a patient-centric focus—that is, the effect of a treatment or intervention on only the patient is considered. In contrast, RWE can delve into broader effects, focusing not only on a treatment's impact on the affected individuals but also on their families, providers, and communities. Effects of a treatment that might not appear in an RCT, such as the impact of cost on a family, can become critical when assessing its real-world value. These studies may identify communities and contexts where a treatment has greater or lesser value and could therefore be evaluated for services such as case management, patient education, or housing.

TABLE 3. ADVANTAGES AND DISADVANTAGES OF RCTS AND RWE FOR VALUE ASSESSMENT

VARIABLES	RCT	RWE
AVAILABILITY	May be available prior to therapeutic launch or approval (e.g., clinical trial data)	Requires a treatment or intervention to be available in the target population
POPULATIONS STUDIED	Often homogeneous study populations are used to minimize confounding factors and isolate treatment effects	May use homogeneous or heterogenous populations, depending on the study
BIASES	May have biases due to patient inclusion criteria (e.g., disease severity, diagnosis, age, or sex), small study population size, or short study durations	May have biases due to sources of data used in the study (typically insurance or provider-related), inconsistent data reporting, loss of follow-up, and unknown patient characteristics
STUDY FOCUS	Almost always studies effects on patients only	Can be patient-focused or can examine secondary effects of treatment on systems of care, informal caregivers, or society
RANDOM EFFECTS AND UNKNOWN FACTORS	Minimizes random effects and unknown factors through patient randomization into treatment and control arms, which may not accurately reflect real-world patient behavior, treatment availability, or provider practice patterns	Minimizes random effects by including large study populations where possible and examining included populations for differences in characteristics that may affect results; these studies may not always successfully control for confounding variables

Despite its many advantages, RWE can have limitations or characteristics that require careful consideration by researchers using it. Depending on the data sources and application, there may be a lack of regulatory guidance and transparency on study design and data reporting, difficulties in identifying causal effects due to the absence of randomization, or challenges in data collection and management.[22,24,25,27] Like RCTs, RWE can also be subject to bias. For example, while the strength of some types of RWE lies in their ability to assess large and diverse patient samples, this advantage may also be a weakness, as the data scrubbing process may inadvertently exclude a substantial portion of potential research subjects or introduce bias.[22,29] For example, these exclusions may arise when meaningful follow-up data are not observed or patients transfer to another payer or hospital during the course of the study.[22,29] A similar bias can occur if large portions of patient samples in EMR-based clinical research are excluded.

Moreover, reliance on RWE must deal with potential inaccuracies in coding or charting. Although healthcare systems may strive for precise documentation in their patients' records, financial incentives for coding can introduce variation or errors. RWE remains susceptible to some kinds of errors, especially when compared to highly controlled RCTs.[22]

When integrated with RCT data, RWE can serve as a crucial source of information on treatment outcomes.[30] RWE offers valuable insights into healthcare outcomes and treatment effectiveness in real-world settings, complementing findings from controlled trials. Integrating RWE with RCT data can help address limitations of early controlled studies and enhance the reliability and applicability of research findings in healthcare decision making. By providing a broader understanding of how treatments perform across diverse populations and in everyday clinical practice, RWE also helps to bridge the gap between the controlled environment of clinical trials and the complex realities of patient care. Examining RWE of existing treatments or populations even before a therapy is approved can help account for patient heterogeneity and improve RCT design.

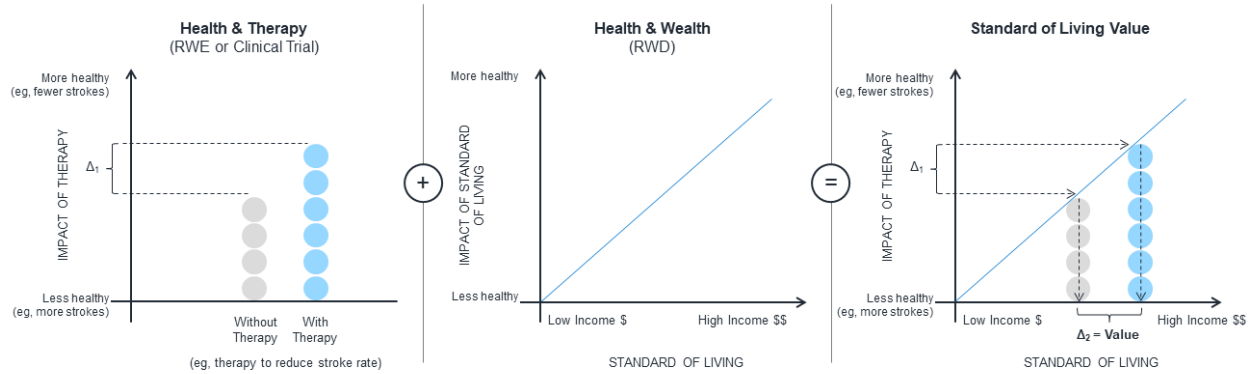
Payers and organizations like ICER may argue that waiting for RWE to assess cost-effectiveness and value is not feasible, as these assessments generally occur before new treatments gain broad access that would generate RWE. This is certainly a limitation for assessments conducted prior to new treatment launches. However, potential solutions include incorporating RWE after sufficient real-world exposure to update the initial valuation of new therapies or assessing ranges of impacts by analyzing RWE analogs in combination with RCT data. These approaches would allow for the advantages of using RWE while providing timely decision-making.

SoLV framework for value assessment

To address some of the limitations of QALY-based methods of value assessment, we consider a novel framework: Standard of Living Valuation (SoLV). This framework is built on the understanding that, on a population level, standard of living (SoL) factors—such as education, housing, diet, family support, and leisure activities—are more important to health outcomes than healthcare delivery itself. A higher SoL is associated with improved health, lower incidence of adverse events, and longer life expectancy. This relationship is applicable to a vast array of conditions. SoL is associated with health outcomes in ways that are similar to concepts like health-related social needs or social determinants of health.

The SoLV framework links differences in SoL factors, in particular income, to differences in health outcomes. For almost all adverse health outcomes, individuals with lower incomes experience worse results, and these relationships are explained in terms suggesting causality.[31,32] SoLV measures the relationship between income and specific health outcomes, allowing the value of a change in an outcome to be quantified in terms of real-world spending (Figure 1). Once the real-world value for changing an outcome is established, the relative value of a therapeutic intervention can then be calculated based on its efficacy. For simplicity, we use the term "income" to represent standard of living, but other measures, including savings and assets, could be considered.

FIGURE 1. THE SOLV FRAMEWORK



One feature of the SoLV framework is that effective therapies for conditions with larger differences driven by socioeconomics will generate higher values, all else being equal. However, our use of income differences does not imply that therapies should have different values for people with different incomes. Nor should our framework be interpreted as suggesting that providing a given therapy will address income disparities or other socio-economic differences.

The SoLV framework can use a wide range of RWE for value assessment. Data on income differences and health outcome differences are readily available through a variety of RWD including surveys, public health research, and administrative data. In the United States, several large databases and surveys have information about individuals' health and income, including the Medicare Current Beneficiary Survey (MCBS), the Behavioral Risk Factor Surveillance System (BRFSS), the Medical Expenditure Panel Survey (MEPS), the National Health and Nutrition Examination Survey (NHANES), and the Health and Retirement Survey (HRS). Medicare claims databases also identify individuals eligible for Medicare and Medicaid or for Medicare's Part D low-income subsidy, which indicate low income. Census and geographic data are also potential sources.

SoLV provides a metric that connects value to socioeconomic and health disparities studies. This methodology can tap into a wealth of RWD about income, social determinants of health, and outcomes. While economists have developed theories on the relationship between income and demand for healthcare starting in the 1970s,[33] we believe our approach of linking value to the relationship between income and healthcare outcomes is novel. For example, the National Disability Council's "Policy Brief: Alternatives to QALY-Based Cost-Effectiveness Analysis for Determining the Value of Prescription Drugs and Other Health Interventions" does not mention disparities, SoL, or socioeconomics.[8] Other researchers say they consider social determinants of health, but they do not consider the relationship of income to health outcomes as indicators of value.

SIMPLIFIED SoLV FRAMEWORK METHODOLOGY

In this simple version of the SoLV framework, we examine the relationship between peoples' income and the incidence or prevalence of health outcomes. This relationship allows us to quantify an incremental monetary value associated with differences in a health outcome.

For a very simple illustration of the SoLV framework (Table 4), we examine the rates of a single health outcome (e.g., heart attack) between two distinct populations (Lower Income and Higher Income). Inputs include the average annual income for each group, the incidence rate of the selected health outcome for each group, and the reduction in incidence by a hypothetical treatment. By comparing the difference in income alongside the difference in incidence between the two populations, we can construct a relationship between the SoL of the two groups and their different health outcomes—that is, we can see how much additional income is associated with the lower incidence of the adverse health event. This approach essentially measures the trade-off between personal income and a health outcome. We can then use that personal income trade-off to assess the value of a treatment that lowers the incidence of the adverse event.

In Table 4, we assume that a $40,000 difference in income between two groups, Lower Income (LI) and Higher Income (HI), is associated with a 40% difference in incidence of Disease A. If we independently assume that Therapy X reduces Disease A's incidence by 30% (not the full 40% associated with income), we can use the SoL impact to calculate the value of the treatment. Multiplying the income effect ($40,000) by the relative therapy impact $\left(\frac{30\%}{40\%}\right)$ yields a value for the therapy of $30,000 per year.

TABLE 4: SIMPLIFIED STANDARD OF LIVING MODEL

SIMPLIFIED STANDARD OF LIVING MODEL				
		LOWER INCOME (LI)	HIGHER INCOME (HI)	DIFFERENCE (Δ_{HI}-Δ_{LI})
A	**Annual Income**	$20,000	$60,000	$40,000
B	**Rate of Disease Incidence**	0.001	0.0006	-0.0004
C	**Reduction of Disease Incidence Due to Income** *$1-(B_{Higher\ Income}/B_{Lower\ Income}) = C$*			40%
D	**Therapy's Reduction in Disease Incidence Due to Risk Factor**	30%	30%	
E	**VALUE OF THERAPY** ***$\Delta A*(D/C) = E$***			**$30,000**

Table 4 illustrates a highly simplified example of the SoLV methodology. Realistically, attributing a change in one health outcome with the entire difference in annual income between two groups is an over-simplification. Our case study example below offers an approach to allocate a portion of the SoL difference to one specific condition.

SoLV allows insight into the health outcomes in different populations, leveraging RWD rather than theoretical trade-offs to assess value. The framework has the flexibility to apply to a wide range of health issues and socioeconomic determinants and can account for many factors affecting health outcomes. Using SoLV, we can assign values to outcomes such as the number of healthy days lived at home or days without interaction with the healthcare system, so it can be used for interventions aimed at reducing patient interactions with the healthcare system rather than simply reducing the frequency of an acute event. By examining the income differentials associated with more or fewer healthy days, we can assign a value to each healthy day gained.

The SoLV framework could support analysis of side effects, the price-elasticity of treatment effects, and subgroup analyses. A more complex version of the model could, for example, incorporate additional variables such as therapy uptake rates (including compliance) and health plan utilization controls across different populations. This flexibility would facilitate analysis of utilization management practices or access to healthcare services impact on health outcomes. SoLV can provide valuable insights into evaluating the effectiveness of different healthcare systems in promoting health and mitigating disparities.

Illustrative case study: Stroke, atrial fibrillation, and direct oral anticoagulants

To illustrate a more detailed application of the SoLV framework, we examine the impact of direct oral anticoagulants (DOACs) in reducing stroke risk among patients with atrial fibrillation (AF). This case study represents a more complex, yet still simplified, version of the framework and illustrates how additional factors affecting outcomes and treatment can be introduced.

AF is the most common type of treated heart arrhythmia, affecting more than 2 million people in the United States.[34–37] It can severely inhibit the heart's ability to adequately pump blood out of the atria, causing blood to pool in these

chambers and potentially clot.[34,35,38] When these clots leave the heart, they can obstruct blood vessels leading to the brain,[35,38,39] which often results in ischemic strokes.[39–41] The CDC estimates that about one in seven ischemic strokes are due to AF.[42]

Anticoagulants are the leading form of stroke prevention for AF patients.[43–45] Since its introduction in 1960, Warfarin had been the most common treatment for the prevention of arterial and venous thromboembolic events (VTE).[43–47] Following the FDA's approval for the first DOAC for clinical use in 2010, treatment preferences shifted from Warfarin to DOACs.[48]

ASSUMPTION DEVELOPMENT

We utilized MCBS, a longitudinal survey of the Medicare population conducted by the CMS Office of Enterprise Data and Analytics, to explore differences in stroke rate by income. The MCBS provides comprehensive data on Medicare beneficiaries' expenditures, health insurance coverage, and health outcomes.[49] Our choice of MCBS was based on convenience, acknowledging that other sources may have different advantages or disadvantages, which we did not explore.

We summarized survey responses from 12,783 sampled beneficiaries in the fall 2021 segment of the MCBS Public Use File and derived the prevalence of stroke for men and women ages 65+ across two income categories, Lower Income (LI) and Higher Income (HI), based on household annual income (Table 5). Our LI and HI categories were defined using the MCBS $25,000 income split. However, we calculated the average income within these two categories using 2021 census data. For the HI average, we capped income at $100,000. The weighted average incomes for the LI and HI categories were about $13,000 and $59,000, respectively. The MCBS files include sampling weights to adjust for nonresponses.

TABLE 5. AGE-SEX ADJUSTED OVERALL STROKE PREVALENCE AMONG 65+ MEDICARE BENEFICIARIES BY ANNUAL HOUSEHOLD INCOME

SEX	AGE	TOTAL US POPULATION	PREVALENCE FOR PEOPLE WITH HOUSEHOLD INCOME UNDER $25,000 (LOWER INCOME)	PREVALENCE FOR PEOPLE WITH HOUSEHOLD INCOME OF $25,000 OR MORE (HIGHER INCOME)	RELATIVE RISK
Male	65-74	11,959,369	12.8%	7.0%	
	75+	6,330,190	12.8%	12.3%	
Female	65-74	14,286,079	10.6%	4.3%	
	75+	8,131,529	13.2%	7.6%	
Total		**40,707,167**	**12.1%**	**7.0%**	**1.74***

*12.1/7.0

We calculated stroke rates by multiplying the population of each age, sex, and income stratum by its corresponding weighted stroke rate. The sum of these values was then divided by the total population.

We used the relative risk of stroke by annual income, established from Table 5, to adjust ischemic stroke incidence rates derived from literature (Appendix – Table A1).

APPLICATION OF THE SOLV FRAMEWORK

Using the assumptions described above, we applied the SoLV framework to calculate the differential in annual income associated with the observed difference in AF-related stroke incidence between LI and HI patients (Table 6).

TABLE 6: AF-RELATED STROKE AVOIDANCE VALUE

	AF-RELATED STROKE AVOIDANCE VALUE IN TERMS OF SOL			
		LOWER INCOME (LI)	HIGHER INCOME (HI)	DIFFERENCE (Δ_{HI}-Δ_{LI})
A	Annual income (SoL)	$13,000	$59,000	
B	Population	8,743,000	31,964,000	
C	Portion of SoL related to health outcomes	20%	20%	
D	Annual income connected to health outcomes (A*C)	$2,600	$11,800	$9,200
E	Number of years necessary to live at the higher SoL to see improved health outcomes status (i.e., formative years)	5		
F	Total income required to shift Lower Income group to the Higher Income group's health outcomes status (D_{Δ}*E*B)	$402,178,000,000		
G	Portion of total health outcomes attributable to AF-related strokes	0.89%		
H	Income needed to specifically affect AF-related strokes (F*G)	$3,592,456,000		
I	Share of population with AF	2%		
J	Lower Income population with AF (B*I)	175,000		
K	**ANNUAL INCOME (SOL) ASSOCIATED WITH RWE DIFFERENCE IN AF-RELATED STROKE INCIDENCE (H/J)**	**$20,500**		

We begin by showing each group's average annual income. Literature suggests that on average, healthcare spending typically range from 16% to 34% of household income, varying by annual income level, with middle-income households paying between 19% and 23%.[50] For simplicity, we assume that 20% of SoL relates to healthcare on average. This percentage also approximates healthcare's portion of GDP.[51] By applying this estimate to the average annual incomes of the LI and HI cohorts and calculating the difference between them, we determine a $9,200 differential in annual relevant income between the two groups.

Published studies suggest that living at a higher SoL for multiple years is associated with better health outcomes.[52–58] We assume that members of the LI cohort would need to live at the HI SoL for five years to achieve the health outcomes of the HI group. This equates to $402 billion in additional annual income for the LI group.

Since AF-related stroke is only one of many health outcomes, we must distill this large sum to the portion of health-related SoL relevant to AF-stroke incidence. Using mortality data from CDC Wonder, we estimate that 0.89% of all deaths are driven by AF-related stroke (Appendix – Table A2).[59] We use this figure as a proxy for the portion of total health income needed to reduce the income-related gap in AF-related strokes, estimating that $3.6 billion ($402 billion x 0.89%) in additional annual income for LI people would be needed to reduce AF-related stroke incidence to the level of HI people.

Finally, we distribute the additional income associated with reduced AF-related stroke incidence across the LI patients with AF. According to a 2020 review, the overall prevalence of AF in the United States is 2%.[60] When applied in our model, this results in an estimate of $20,500 annually to equalize AF-related stroke incidence between the LI and HI cohorts.

With this value calculated, we can estimate the real-world value of DOAC treatment in terms of SoL (Table 7) by comparing the assumed DOAC treatment impact to the observed SoL impact.

TABLE 7: VALUE OF DOAC TREATMENT USING SOL

	DOAC TREATMENT VALUE IN TERMS OF SOL			
		LOWER INCOME (LI)	HIGHER INCOME (HI)	DIFFERENCE (Δ_{HI}-Δ_{LI})
L	Annual ischemic stroke rate	0.013	0.008	
M	Share of ischemic strokes attributable to AF	17%	17%	
N	Annual AF-related ischemic stroke rate (L*M)	0.0022	0.0014	-0.0009
O	Assumed improvement in AF-related stroke risk due to DOAC use	-25%		
P	AF-related stroke rate if DOAC were widely used among Lower Income group (N*(1+O))	0.0017		
Q	Reduction in AF-related drug rate due to use of the new drug (P-N)	-0.0006		
K	Increase in income required to move Lower Income AF patients to the Higher Income AF stroke rate (an improvement of -0.0009 (N_Δ))	$20,500		
R	Drug value annually in terms of income (K*(Q/N_Δ))	$13,300		
S	**Monthly value of drug in terms of income (R/12)**	**$1,100**		

Using the MCBS data described above, we derived the annual ischemic stroke rate for LI and HI patients. Given that around 17% of all ischemic strokes are attributable to AF,[61] we estimated the incidence of AF-related ischemic strokes for both groups and calculated the difference in incidence between the two SoL groups (-0.0009 or a 38% decrease). This difference represents the improvement in AF-related stroke incidence we expect to achieve by increasing the income of LI patients with AF by $20,500 annually, as calculated in Table 6 above.

Based on several real-world studies, the use of DOACs improves AF-related ischemic stroke risk by 19% to 39%.[61–63] We use a mid-value and assume that DOACs would reduce the current incidence of AF-related stroke by 25% (or 0.0006). This equates to 65% of the improvement achieved by hypothetically moving all LI patients to a HI SoL. As such, the value of DOAC treatment for these patients is about $13,300 annually (0.65 x $20,500) or $1,100 per month.

Discussion

Although the SoLV framework links differences in SoL with better or worse outcomes, we are not addressing policies for changing personal income. Rather, we explore a method to leverage RWD on health outcomes and SoL to establish the value of treatments. Our approach avoids many of the circularities and limitations of established approaches by not assuming that existing therapies are priced correctly, fairly, or benchmarked against other treatments' costs.

Since this document describes a novel approach, this section primarily addresses identified issues that warrant further exploration to help refine the framework.

SOLV FRAMEWORK LIMITATIONS AND AREAS FOR FUTURE EXPLORATION

The SoLV framework decouples treatment value from existing healthcare costs and examines the value of treatments within the broader context of SoL. While this framework can be constructed using RCT results, making it viable for prelaunch/preapproval discussions, it is also flexible to incorporate and emphasize RWE as it becomes available. Still, we note that many elements of the framework can be refined.

During the development of this new methodology and considering the need to address a broad spectrum of healthcare value issues, we were confronted with a wealth of potential real-world sources. To gain widespread

acceptance, practical guidelines for selecting surveys, studies, and cohorts for SoLV implementation would need to be developed.

Our illustration uses current income of individuals aged 65+ as the SoL metric, but this approach can be refined in several ways. We did not adjust for the impact of aging on income, such as income declines due to deteriorating health. We assumed that income in older populations reflects their income during childhood, which ignores income mobility. These simplifications, and others, can be further refined in various ways while preserving the basic SoLV approach.

LI individuals may tend to avoid the healthcare system. This dynamic may produce counterintuitive real-world results for certain conditions, making lower-income populations appear healthier. While most medical conditions or adverse events are more common among LI people, some conditions do not correlate with income. For such conditions, metrics like contact days, measuring the days of healthcare system interactions, could be applied.[64]

Additionally, the SoLV framework relies on segmentation of populations by income or another SoL-based metric, necessitating the creation of different income groups. Our segmentation into LI and HI groups is as simple as possible. Determining the number of segments and setting appropriate cutoffs will require future refinement.

Of course, SoL is more complex than personal income alone. It could also include additional population inputs such as educational attainment, living arrangement, local socio-economic conditions, or environmental factors, which can be monetized and considered. Other important factors that influence outcomes could include family supports and faith and beliefs, although these may be captured to some extent in an aggregate way in personal income. We believe that the literature on socioeconomic determinants of health could provide valuable insights that will help refine SoLV.

In traditional health value assessments, the time value of money is typically considered, and various financial discounts may be applied. Some assessments also discount the value of a life—e.g., that one year of life next year is worth more than one year of life in five years—although the rationale for discounting future life is unclear to us. Notably, medical cost inflation is less frequently applied in such assessments. In this paper, we have deliberately avoided applying discounts, partly for simplicity and partly because their validity in our context needs separate consideration.

THE TERM “VALUE” IN HEALTHCARE

The word "value” is used in many ways in healthcare, encompassing contexts varying from business profit to patient outcomes. Even within the context of value assessments—the assessment of price versus outcomes—there are different meanings. In this work, we adhere to the following concepts and believe that others in value assessment will find these distinctions useful:

- **What is price?** The total amount paid by an insurance, non-insurance program, or the patient for a therapy.
- **Who pays? Who gets paid?** The price paid may be divided among the insurer, patient, manufacturer, government, or other entities. Similarly, the amount received may be distributed among various entities, potentially including corporations, taxing authorities, foundations, or the public.
- **What is the value?** Value is a financial measurement of a therapy, allowing for consistent and meaningful comparisons and analysis.

We note that in this paper, “value” does not imply “price,” and our analysis does not assume that payers will pay that value to the therapy owner. There are many examples in the U.S. economy where subsidies, taxes, or fees are applied to prices, and funds are allocated to different entities. We do not address these important topics in this paper. Factors such as competition, production costs, patent exclusivity, and non-value social considerations may affect price, but these issues are beyond the scope of this paper.

It might seem odd that these concepts are presented near the end of the report as caveats rather than at the beginning as definitions, but we suspect most readers will appreciate that we did not digress earlier.

A NOTE ON SOCIAL DETERMINANTS OF HEALTH AND SOLV

The approach described in this paper would not be possible without the extensive research performed over years on the social determinants of health. The authors hope that this value approach will contribute to the practical applications of that research, bridging public health, actuarial science, and health economics.

Some patient advocates promote distributive justice, seeking equitable access to reasonable care based on ethical principles of equity and solidarity.[65] Since QALYs cannot achieve distributive justice,[66] our value approach, incorporating RWD, socioeconomic factors, and broader societal issues, may appeal to these advocates. A notable feature of the SoLV framework is that effective therapies for conditions with larger socioeconomic differences will generate higher values. However, our use of income differences does not imply different values for people with different incomes. Furthermore, our framework should not be interpreted as implying that providing a given therapy will address income disparities or many other socioeconomic differences. Instead, we are utilizing the widely observed relationship between income levels and health outcomes to develop a singular value for therapy across an entire population. In medical practice, therapy decisions are typically made in consideration of patient risk factors, and we believe that integrating socioeconomic factors into value assessments enhances this risk-based approach.

References

1. Institute for Clinical and Economic Review. 2020-2023 Value Assessment Framework. 1–76 (2020).
2. U.S. Food and Drug Administration. Real-World Evidence. https://www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence (2023).
3. Joubert, S. Real-World Evidence's Impact on Healthcare: 10 Statistics. https://graduate.northeastern.edu/resources/real-world-evidence-impact-on-healthcare/ (2023).
4. Braveman, P. & Gottlieb, L. The social determinants of health: It's time to consider the causes of the causes. *Public Health Reports,* 129, 19–31 (2014).
5. Institute for Clinical and Economic Review. 2020-2023 Value Assessment Framework. 1–76 (2020).
6. Carlson, J. J., Brouwer, E. D., Kim, E., Wright, P. & McQueen, R. B. Alternative Approaches to Quality-Adjusted Life-Year Estimation Within Standard Cost-Effectiveness Models: Literature Review, Feasibility Assessment, and Impact Evaluation. *Value in Health,* 23, 1523–1533 (2020).
7. National Institute for Health and Care Excellence. Developing NICE guidelines: the manual. *Process and Methods Guides,* 245 (2014).
8. Sullivan, S. D. et al. Alternatives to the QALY for Comparative Effectiveness Research. *Health Affairs Forefront* (2023).
9. Pettitt, D. A. et al. The Limitations of QALY: A Literature Review. *Journal of Stem Cell Research and Therapy,* 6, (2016).
10. National Council on Disability. Alternatives to QALY-Based Cost-Effectiveness Analysis for Determining the Value of Prescription Drugs and Other Health Interventions. https://www.ncd.gov/report/alternatives-to-qaly-based-cost-effectiveness-analysis-for-determining-the-value-of-prescription-drugs-and-other-health-interventions/ (2022).
11. Van Der Pol, M. & Roux, L. Time preference bias in time trade-off. *European Journal of Health Economics,* 6, 107–111 (2005).
12. Guo, J., Konetzka, R. T. & Dale, W. Using time trade-off methods to assess preferences over health care delivery options: A feasibility study. *Value in Health,* 17, 302–305 (2014).
13. Martín-Fernández, J. et al. Willingness to pay for a quality-adjusted life year: An evaluation of attitudes towards risk and preferences. *BMC Health Services Research,* 14, 1–10 (2014).
14. Sawhney, T. & Thakur, N. Drug Cost-Effectiveness Assessments Require Standards for Rigor and Inclusion. *Journal of Health Economics and Outcomes Research,* 10, 28–30 (2023).
15. Sawhney, T. G., Dobes, A. & O'Charoen, S. QALYs: The Math Doesn't Work. *Journal of Health Economics and Outcomes Research,* 10, 10–13 (2023).
16. O'Day, K. P. M. & Dylan J. Mezzio, P. M. Demystifying ICER's Equal Value of Life Years Gained Metric. *Value & Outcomes Spotlight,* 7, (2021).
17. Paulden, M. et al. Logical Inconsistencies in the Health Years in Total and Equal Value of Life-Years Gained. *Value in Health,* 27, 356–366 (2024).
18. Congressional Budget Office. Congressional Budget Office: S.785 Cost Estimate At a Glance. 1–6 (2020).
19. Nichols, L. M. Threats to Medicare's new drug negotiation power. *Brookings* (2023).
20. Seshamani, M. Medicare Drug Price Negotiation Program: Revised Guidance, Implementation of Sections 1191 – 1198 of the Social Security Act for Initial Price Applicability Year 2026. *CMS* 1–198 (2023).

21. Monti, S., Grosso, V., Todoerti, M. & Caporali, R. Randomized controlled trials and real-world data: Differences and similarities to untangle literature data. *Rheumatology (Oxford),* 57, vii54–vii58 (2018).

22. Kim, H. S., Lee, S. & Kim, J. H. Real-world evidence versus randomized controlled trial: Clinical research based on electronic medical records. *Journal of Korean Medical Science,* 33, (2018).

23. Eichler, H. G. et al. Randomized Controlled Trials Versus Real World Evidence: Neither Magic Nor Myth. *Clinical Pharmacology and Therapeutics,* vol. 109 1212–1218 Preprint at https://doi.org/10.1002/cpt.2083 (2021).

24. Van Den Broek, R. W. M., Matheis, R. J., Bright, J. L., Hartog, T. E. & Perfetto, E. M. Value-based evidence across health care sectors: A push for transparent real-world studies, data, and evidence dissemination. *Health Economics, Policy, and Law,* 17, 416–427 (2022).

25. Sarri, G. Can Real-World Evidence Help Restore Decades of Health Inequalities by Informing Health Care Decision-Making? Certainly, and Here is How. *Frontiers in Pharmacology,* 13, 1–5 (2022).

26. Dreyer, N. A. Strengthening evidence-based medicine with real-world evidence. *Lancet Healthy Longevity,* 3, e641–e642 (2022).

27. ISPOR. Good Practices for Real-World Data Studies of Treatment and/or Comparative Effectiveness. doi:10.1002/pds.4297.

28. van Harten, W. & IJzerman, M. J. Responsible pricing in value-based assessment of cancer drugs: Real-world data are an inevitable addition to select meaningful new cancer treatments. *Ecancermedicalscience* **11**, 1–4 (2017).

29. Kim, H.-S. & Kim, J. H. Proceed with Caution When Using Real World Data and Real World Evidence. *Journal of Korean Medical Science,* 34, (2019).

30. Villines, T. C., Cziraky, M. J. & Amin, A. N. Awareness, Knowledge, and Utility of RCT Data vs RWE: Results From a Survey of US Cardiologists: Real-world Evidence in Clinical Decision Making. *Clinical Medicine Insights: Cardiology,* 14, (2020).

31. Braveman, P. & Gottlieb, L. The Social Determinants of Health: It's Time to Consider the Causes of the Causes. *Public Health Reports,* 129, 19–31 (2014).

32. The Health Foundation. Relationship between living standards and health. https://www.health.org.uk/evidence-hub/money-and-resources/persistent-poverty/relationship-between-living-standards-and-health (2022).

33. Grossman, M. The Human Capital Model. *Handbook of Health Economics* (eds. Culyer, A. J. & Newhouse, J. P.), vol. 1, 347–408 (Elsevier, 2000).

34. Colilla, S. et al*.* Estimates of current and future incidence and prevalence of atrial fibrillation in the U.S. adult population. *American Journal of Cardiology,* 112, 1142–1147 (2013).

35. American Heart Association. Atrial Fibrillation. https://www.heart.org/en/health-topics/atrial-fibrillation

36. National Hearth, Lung, and Blood Institute. What Is Atrial Fibrillation? https://www.nhlbi.nih.gov/health/atrial-fibrillation#:~:text=Atrial.

37. Wang, G., Joo, H., Tong, X. & George, M. G. Hospital Costs Associated with Atrial Fibrillation for Patients with Ischemic Stroke Aged 18-64 Years in the United States. *Stroke,* 46, 1314–1320 (2015).

38. Johns Hopkins Medicine. What Is Afib? https://www.hopkinsmedicine.org/health/conditions-and-diseases/atrial-fibrillation. .

39. American Stroke Association. Ischemic Stroke (Clots). https://www.stroke.org/en/about-stroke/types-of-stroke/ischemic-stroke-clots.

40. Tsao, C. W. et al. Heart Disease and Stroke Statistics-2022 Update: A Report from the American Heart Association. *Circulation,* vol. 145 E153–E639. Preprint at https://doi.org/10.1161/CIR.0000000000001052 (2022).

41. Centers for Disease Control and Prevention. *Americans at Risk for Stroke*. https://www.cdc.gov/stroke/facts.htm.

42. Centers for Disease Control and Prevention. Atrial Fibrillation. https://www.cdc.gov/heartdisease/atrial_fibrillation.htm (2022).

43. Sikorska, J. & Uprichard, J. Direct oral anticoagulants: A quick guide. *European Cardiology Review,* 12, 40–45 (2017).

44. Heestermans, M., Poenou, G., Hamzeh-Cognasse, H., Cognasse, F. & Bertoletti, L. Anticoagulants: A Short History, Their Mechanism of Action, Pharmacology, and Indications. *Cells,* vol. 11. Preprint at https://doi.org/10.3390/cells11203214 (2022).

45. American Society of Hematology. Antithrombotic Therapy. https://www.hematology.org/about/history/50-years/antithrombotic-therapy#:~:text=Anticoagulant (2008).

46. American Society of Hematology. Milestones in Anticoagulant Drugs. https://www.hematology.org/about/history/50-years/milestones-anticoagulant-drugs (2008).

47. Link, K. P. The Discovery of Dicumarol and Its Sequels. ASA/AHA Journals. http://ahajournals.org.

48. Chen, A., Stecker, E. & A. Warden, B. Direct Oral Anticoagulant Use: A Practical Guide to Common Clinical Challenges. *Journal of the American Heart Association,* 9, (2020).

49. Centers for Medicare and Medicaid Services. Medicare Current Beneficiary Survey. https://www.cms.gov/data-research/research/medicare-current-beneficiary-survey (2024).

50. RAND. Burden of Health Care Payments Is Greatest Among Americans with the Lowest Incomes. (2020).

51. Centers for Medicare and Medicaid Services. NHE Fact Sheet. https://www.cms.gov/data-research/statistics-trends-and-reports/national-health-expenditure-data/nhe-fact-sheet (2022).

52. Kawachi, I. & Kennedy, B. P. Income inequality and health: pathways and mechanisms. *Health Services Research,* 34, 215–27 (1999).

53. Wang, J. & Geng, L. Effects of socioeconomic status on physical and psychological health: Lifestyle as a mediator. *International Journal of Environmental Research and Public Health,* 16, (2019).

54. McMaughan, D. J., Oloruntoba, O. & Smith, M. L. Socioeconomic Status and Access to Healthcare: Interrelated Drivers for Healthy Aging. *Frontiers in Public Health,* 8, 1–9 (2020).

55. Kivimäki, M. et al. Association between socioeconomic status and the development of mental and physical health conditions in adulthood: A multi-cohort study. *Lancet Public Health,* 5, e140–e149 (2020).

56. Mackenbach, J. P. et al. Socioeconomic Inequalities in Health in 22 European Countries. *New England Journal of Medicine,* 358, 2468–2481 (2008).

57. Barakat, C. & Konstantinidis, T. A Review of the Relationship between Socioeconomic Status Change and Health. *International Journal of Environmental Research and Public Health,* 20, (2023).

58. Nutakor, J. A., Zhou, L., Larnyo, E., Addai-Danso, S. & Tripura, D. Socioeconomic Status and Quality of Life: An Assessment of the Mediating Effect of Social Capital. *Healthcare (Switzerland),* 11, (2023).

59. Centers for Disease Control and Prevention, National Center for Health Statistics. National Vital Statistics System, Mortality 2018-2022 on CDC WONDER Online Database, released in 2024. Data are from the Multiple Cause of Death Files, 2018-2022, as compiled from data provided by the 57 vital

statistics jurisdictions through the Vital Statistics Cooperative Program. http://wonder.cdc.gov/ucd-icd10-expanded.html.

60. Kornej, J., Börschel, C. S., Benjamin, E. J. & Schnabel, R. B. Epidemiology of Atrial Fibrillation in the 21st Century. *Circulation Research,* 127, 4–20 (2020).

61. Hart, R. G., Palacio, S. & Pearce, L. A. Atrial Fibrillation, Stroke, and Acute Antithrombotic Therapy. *Stroke,* 33, 2722–2727 (2002).

62. Lee, S.-R. et al. Effectiveness and Safety of Contemporary Oral Anticoagulants Among Asians With Nonvalvular Atrial Fibrillation. *Stroke,* 50, 2245–2249 (2019).

63. McIntyre, W. F. et al. Direct Oral Anticoagulants for Stroke Prevention in Patients With Device-Detected Atrial Fibrillation: A Study-Level Meta-Analysis of the NOAH-AFNET 6 and ARTESiA Trials. *Circulation,* 149, 981–988 (2024).

64. Ganguli, I. et al. Health Care Contact Days Among Older Adults in Traditional Medicare: A Cross-Sectional Study. *Annals of Internal Medicine,* 177, 125–133 (2024).

65. Rego, G., Brandão, C., Melo, H. & Nunes, R. Distributive justice and the introduction of generic medicines. *Health Care Analysis,* 10, 221–229 (2002).

66. Basu, A., Lynn, N., Peschin, S. & Resendez, J. Value Assessment in Alzheimer's Disease: A Focus on Equity. *Value & Outcomes Spotlight,* 7, S12–S17 (2021).

67. Benjamin, E. J. et al. Heart disease and stroke statistics - 2018 update: A report from the American Heart Association. *Circulation,* 137, E67–E492 (2018).

68. Chen, R.-L., Balami, J. S., Esiri, M. M., Chen, L.-K. & Buchan, A. M. Ischemic stroke in the elderly: An overview of evidence. *Nature Reviews Neurology,* 6, 256–265 (2010).

69. Wilder, K. & Mackun, P. While Number of People Age 65 and Older Increased in Almost All Metro Areas, Young Population Declined in Many Metro Areas From 2020 to 2023. *Census.gov - America Counts: Stories.* https://www.census.gov/library/stories/2024/06/metro-areas-population-age.html (2024).

Appendix

TABLE A1 – CALCULATION OF STROKE INCIDENCE

	DEATHS
Total strokes in U.S., annually* [67]	795,000
Portion of strokes that are ischemic*	87%
Portion of strokes attributable to people >65 years old** [68]	75%
Number of ischemic strokes among people >65 years old	518,738
Estimated U.S. population >65 years old▪ [69]	60,000,000
Annual incidence of ischemic strokes among those >65 years old	**0.0086**

* Source: Benjamin, E. J. et al. Heart disease and stroke statistics - 2018 update: A report from the American Heart Association. Circulation 137, E67–E492 (2018).

** Source: Chen, R.L., Balami, J., Esiri, M. et al. Ischemic stroke in the elderly: An overview of evidence. *Nature Reviews Neurology,* 6, 256–265 (2010).

† Source: U.S. Census Bureau (2024). While Number of People Age 65 and Older Increased in Almost All Metro Areas, Young Population Declined in Many Metro Areas From 2020 to 2023. Accessed July 2, 2024: https://www.census.gov/library/stories/2024/06/metro-areas-population-age.html

	LOWER INCOME	HIGHER INCOME	TOTAL
Population	8,743,000	31,964,000	40,707,000
Hazard ratio	1.74	1.00	1.16
Relative risk	1.50	0.86	1
Annual stroke risk	**0.013**	**0.007**	**0.0086**

TABLE A2 – CALCULATION OF AF-RELATED STROKE MORTALITY BURDEN

	DEATHS
Total U.S. deaths, 2019*	2,854,838
Total cerebrovascular-related deaths, 2019*	150,005
Portion of strokes related to AF†	17%
Estimated deaths related to AF strokes, annually	25,501
AF's portion of total U.S. deaths, annually	**0.89%**

* Source: Centers for Disease Control and Prevention, National Center for Health Statistics. National Vital Statistics System, Mortality 2018-2022 on CDC WONDER Online Database, released in 2024. Data are from the Multiple Cause of Death Files, 2018-2022, as compiled from data provided by the 57 vital statistics jurisdictions through the Vital Statistics Cooperative Program. Accessed at http://wonder.cdc.gov/ucd-icd10-expanded.html on May 1, 2024.

† Source: Hart, R. G., Palacio, S. & Pearce, L. A. Atrial Fibrillation, Stroke, and Acute Antithrombotic Therapy. *Stroke,* 33, 2722–2727 (2002).

Caveats

Bruce Pyenson, Rebecca Smith, Allison Halpren, and Parsa Entezarian are employees of Milliman, Inc. This report is the work of the authors, who do not endorse any legislation or product. It does not represent the opinions of Milliman.

Guidelines issued by the American Academy of Actuaries require members to identify their qualifications for professional work. Bruce Pyenson is a member of the American Academy of Actuaries and meets relevant qualification standards.

Milliman

Milliman is among the world's largest providers of actuarial and related products and services. The firm has consulting practices in life insurance and financial services, property & casualty insurance, healthcare, and employee benefits. Founded in 1947, Milliman is an independent firm with offices in major cities around the globe.

milliman.com

CONTACT

Bruce Pyenson
bruce.pyenson@milliman.com

Rebecca Smith
rebecca.smith@milliman.com

Allison Halpren
allison.halpren@milliman.com

Parsa Entezarian
parsa.entezarian@milliman.com