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Economic Evaluation

Value of a QALY for France: A New Approach to Propose Acceptable Reference Values

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ABSTRACT

Objective: France has included health economic assessment (HEA) as an official criterion for innovative drug pricing since 2013. Until now, no cost-effectiveness threshold (CET) has been officially proposed to qualify incremental cost-effectiveness ratios (ICERs). Although the French health authorities have publicly expressed the need for such reference values, previous initiatives to determine these have failed. The study aims to propose a locally adapted method for estimating a preference-based value for a quality-adjusted life-year (QALY) based on a rational approach to public policy choices in France.

Methods: We used the official French value of statistical life (VSL) of €3 million (USD 3.25 million), proposed in 2013 by the French General Commission on Strategy and Prediction. We first estimated the value of life-year (VoLY) by age category according to life expectancy and official discounts recommended for HEA in France. We then estimated a value of statistical QALY (VSQ) by weighting VoLYs with demographic data and French EQ-5D-3L tariffs.

Results: The estimated average VoLYs and VSQs were €120 185 (USD 130 000) and €147 093 (USD 159 022), respectively, assuming a discount rate of 2.5% and €166 205 (USD 179 681) and €201 398 (USD 217 728), respectively, assuming a discount rate of 4.5%.

Conclusion: Assuming that, as in other public domains, equity in access to healthcare across all disease areas and between all users is desirable, we propose an estimate of VSQ that is consistent with this goal. Our estimates of €147 093 (USD 179,681) to €201 398 (USD 217 728) should be perceived as breakeven costs for a QALY rather than a market access threshold. Such VSQs could be used as reference values for ICERs in HEA in France.

Keywords: drug pricing, cost-effectiveness, France, health-economic assessment, incremental cost-effectiveness ratio, preference-based value.

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Introduction

Introducing health-economic assessment (HEA) in national market access processes is becoming more and more frequent. Cost-effectiveness analyses are generally used in HEA in 1 of 3 contexts, namely, (1) to inform price negotiations, as in Japan,[1] Taiwan,[2] and theoretically Germany[3]; (2) to establish the reimbursement rate, as in Sweden[4]; or (3) as a mandatory condition for reimbursement, as in England and Wales.[5]

In France, HEA has been integrated into the regulatory process for market access since October 2013.[6] Drug and medical device manufacturers have been required to submit a health-economic dossier to the French Health Authority (HAS) for every new indication for products that claim moderate (III) to major (I) clinical added value (Amelioration du Service Medical Rendu for drugs and ASA for medical devices) and that are anticipated to have a substantial financial impact on healthcare expenditure (>€20 million).[6] The dossier consists of a cost-effectiveness analysis that aims at estimating efficiency with respect to a defined efficiency frontier, together with estimates of uncertainty. An additional budget impact analysis is mandatory if sales after 2 years are anticipated to exceed €50 million.

The Economic and Public Health Assessment Committee (Commission Evaluation Economique et de Santé Publique; CEESP), an independent commission for the HAS, is in charge of this appraisal, and its reports are made publicly available. However, no threshold value for qualifying cost-effectiveness results officially exists in France. Consequently, the efficiency assessment provided by the CEESP focuses on the reliability of the model and the methodological robustness of the dossier with respect to the HAS guidelines.[7] This qualitative opinion provides the French Pricing Committee (Comité Economique des Produits de Santé;

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CEPS) with arguments for negotiating a price below that applied in neighboring countries for drugs with a European price.

The relevance of a cost-effectiveness threshold has been the subject of a longstanding debate in France. Unlike other countries where a cost-effectiveness threshold exists, such as England and Wales,[5] Ireland,[8] Netherlands,[9] Slovakia,[10] and Slovenia,[11] it was originally decided in France that such a threshold was irrelevant in a market access process where the reimbursement decision is not based on an incremental cost-effectiveness ratio (ICER).[12] In France, access to reimbursement is determined solely by the medical service (Service Médical Rendu), which takes into account the efficacy and safety of the treatment, its expected use relative to existing treatment strategies, the severity of the condition to be treated, the treatment goal (symptomatic, disease-modifying, or prophylactic), and its anticipated public health interest. For this reason, appraisal of efficiency is taken into account only for price setting. One of the main objections to using an ICER threshold was that this would create an "anchoring" effect on price, which could limit the negotiating margin for the CEPS. Consequently, the latter considers HEAs only as ancillary information for use in the negotiation process.

Nevertheless, it is regularly argued that there is a need for defined reference values as an indication of value to help qualify ICERs and consequently enlighten decision making and price negotiations.[13,14] In 2018, the end-of-term report of the CEESP stated that it was time for a collective debate to answer the burning question of willingness-to-pay (WTP) for a health gain.[14]

As a contribution to this debate, the HAS published a literature survey in 2014[15] that identified 4 different approaches that had been used in other countries to define an acceptable threshold (Table 1). These approaches are (1) the budget constraint approach, in which the cost-effectiveness threshold is set as the marginal cost of a quality-adjusted life-year (QALY); (2) the WTP approach, in which the value of a QALY is directly estimated from individual preferences; (3) the past decision approach, in which the acceptable value of a QALY is estimated a posteriori based on ICERs determined after attribution of a public price; and (4) the value of statistical life (VSL) approach, in which the value of a QALY is indirectly estimated from a preference-based estimate of the VSL. Table 1 presents these 4 existing alternatives, the underlying methods, and their applicability to the French context.

In the HAS report,[15] the authors concluded that their survey did not allow a "single best method" to be identified and that more research was needed to determine a reference value per QALY based on solid economic theory. Our purpose here is to explore one of these approaches, based on the VSL, that has not yet been evaluated sufficiently, although it presents many attractive advantages.

Official estimates of VSL have been available in France since 1992,[17] and in 2013, a value of €3 million was proposed.[18,19] This VSL was derived directly from a meta-analysis performed by the Organisation for Economic Co-operation and Development (OECD) in 2010[20,21] of preference-based studies aimed at estimating VSL in OECD and non-OECD countries. According to the French General Commission for Strategy and Prediction (FGCSP) report published by Quinet et al in 2013,[18] the VSL should be considered the same for all individuals within a given society and represent "a reference value which reflects the collective willingness to guarantee that, in healthcare, the commitment is the same whatever the healthcare domain and whatever individuals are involved: saving a "statistical life" or lowering a fatality risk should mobilize an identical monetary investment whoever is concerned by the risk."

Given that a robust estimate of VSL is available for France and that such a VSL should ensure equity of access in all healthcare domains and users regardless of the nature of the risk, we have attempted to move the debate forward by proposing acceptable estimates of value of life-year (VoLY) and of value of statistical QALY (VSQ) based on the indirect approach. These estimates could be pertinent for putting ICERs into context and for use in price negotiations between the CEPS and manufacturers.

Methods

Framework

The method was chosen to produce the most appropriate estimate of VSQ for the French healthcare system. The following 2 principles were followed: (1) use of recent French input data wherever possible and (2) use of a single fixed VSL value for all individuals in the system, to comply with the recommendations of the FGCSP report[18] to ensure equity in access to care.

Determination of the VoLY

This determination was directly based on the VoLY equation proposed by Quinet et al[18] in the FGCSP report:

$$VSL = \sum_{i=0}^{T(a)} VoLY(a) \times (1+\delta)^{-i} \quad (1)$$

where $T(a)$ is the life expectancy at a given age a, δ the discount rate, and VoLY(a) is the constant value of a life-year for a given age a, following recommendations by Quinet. This means that for an individual of age a, with a life expectancy $T(a)$, every life-year remaining has the same value VoLY(a). For our study, life expectancy was documented from the French National Statistics Office (Institut National de la Statistique et des Etudes Economiques), which publishes age-specific life expectancy data for the French population annually. We used the most recent data available, which were for 2018.[22]

Considering VSL as a constant, the VoLY can then be estimated:

$$VoLY(a) = \frac{VSL}{\sum_{i=0}^{T(a)} (1+\delta)^{-i}} \quad (2)$$

In equation 2, given that life expectancy decreases with age and that VSL is constant, the value of VoLY(a) increases with age.

Determination of the Value of Statistical QALY

In classical cost-effectiveness analyses, patients progress through different health states until death. Each health state is associated with a utility value between 0 and 1. Over the time horizon of the model, the number of total life-years (LY) lived between model entry and death is estimated. Total QALYs are estimated by weighting average LYs spent in each health state of the model with a specific utility value, according to the following relationship between average LY and average QALY:

$$QALYs = \sum_{k=1}^{n} QALYs(k) = \sum_{k=1}^{n} u(k) \times LYs(k) \quad (3)$$

where k designates a given health state of the model and $u(k)$ the utility associated with health state k, n the number of health states in the model, and QALYs(k) and LYs(k) the total QALYs and LYs associated with health state k, respectively.

Considering that quality of life varies with age, each age of life can be associated with a health state having a given utility. By analogy to equation 3, we can propose the following relationship between age and QALY:

Table 1. Available approaches to estimating reference values for a health gain measured with life-years or QALYs.[1]

Approach	Methods	Limits and applicability to the French context
The budget constraint approach Relies on the notion of opportunity cost and that a consideration of efficiency has to reflect the implications of imposing additional costs on the system, which will displace existing services and thus lead to health decrements for patients other than those benefiting from the new technology being appraised.	Two different attempts 1. League tables • Healthcare interventions are ranked according to their ICERs • Healthcare interventions are fully funded, by decreasing rank in the league table until the budget is fully spent • The ICER of the last funded intervention represents the reference value for a QALY 2. Estimating a reference value through the relationship between changes in overall NHS expenditure and changes in mortality • Estimate based on program budgeting (PB) data for the English NHS • £12 936 for a QALY: current NICE thresholds of £20K and £30K represent 89th and 97th percentiles of threshold distribution[16]	Limits: 1. League tables • The value for a QALY is modified when a more cost-effective intervention is proposed or when the budget is modified • Requires a tremendous investment in (1) covering all health interventions and (2) updating data 2. NHS budget approach • Complex method • Hypothesizes the simultaneity of costs and benefits • Finally estimates the marginal cost of a QALY in the whole NHS System • Reflects the budget constraint rather than the willingness to pay from a societal point of view Could be tested in France, but as the annual increase in the national insurance budget is fixed by law, reflecting an implicit opportunity cost, this would lead to estimating an average marginal expenditure for a QALY, rather than a marginal threshold. This would measure the combined effect of the value of new treatments, as measured by an ex ante cost-effectiveness ratio and of the efforts of the French payer to meet budget constraints → Limited applicability for France
The willingness-to-pay approach: Relies on revealed preferences (mainly declared preferences), in which individuals are asked how much they would be willing to pay to compensate for a small reduction in risk.	Two methods: 1. Direct contingent on method • Asks the respondent for their WTP for a public program that would reduce their mortality risk directly as an open-ended maximum WTP question, or as a dichotomous choice approach 2. Indirect approach of choice modeling • Asks respondents to make a series of choices between health risks with different characteristics and costs Main interest: the estimated WTP is acceptable for a broad population and integrates value associated with reductions in both morbidity and mortality.	Limits: • These methods are based on hypothetical scenarios, so that the amounts people say they are willing to pay may differ from what they actually would have been willing to pay, if faced with the given situation.[2] • The sensitivity of the result to the proposed scenario (environmental, health, transportation risk), the level of risk reduction, and the method used to elicit preferences These limits are reflected in the vast range of estimated values (€1800–€25 million), illustrating the difficulty in directly measuring the WTP for a health gain. No preference-based study aiming at estimating the willingness-to-pay for a health gain has ever been conducted in France. No reference value for a QALY exists in France that could easily be used or updated. → Limited applicability for France
The past decision approach Consists of proposing a reference value on the basis of former actual reimbursement or nonreimbursement decisions	Two methods: 1. Deriving a WTP from observed costs of health interventions such as dialysis or factor VIII-replacement for bleeding prevention in hemophilia 2. Consider ICERs of treatments that underwent a health-economic assessment using the public reimbursed price. Such a pragmatic approach allows direct estimation of useful reference values for decision makers, consistent with public budget arbitration and based on real decisions.	Limits • This approach is feasible only when reimbursement decisions follow a clear, consistent, and unique process known to the decision makers → a rarely met condition. • It may not be legitimate to make future decisions based on a historical approach as the medical context evolves over time. • Such a value would reflect past decisions and not what may be desirable to do. On June 1, 2019, among the 97 disclosed efficiency opinions, 59 opinions were free of major methodological limitations and available for estimating a reference value for a QALY. Price regulation of drugs in France is achieved[3] by ensuring a balance between price cutting for drugs that are already reimbursed and reimbursing new drugs at negotiated prices. This is in line with savings objectives fixed annually by law. For this reason, it might be considered that a reference value for a QALY could be derived from reestimates of ICERs using public prices for drugs. The acceptability of such a value should then be considered according to the inherent drawbacks listed above. → High acceptability for France

continued on next page

Table 1. Continued

Approach	Methods	Limits and applicability to the French context
The VSL "indirect" approach Relies on estimates of VSL. The VSL is defined as the monetary value of a small fixed reduction in mortality risk that would prevent one statistical death. It is generally used to assess public policies and investments that affect mortality risk, for example, in the transportation, environmental, and energy sectors	VSL can be estimated following two methods: 1. Capital approach: for example, based on productivity loss as a consequence of a transportation accident 2. The revealed/stated preference methods in which the WTP to reduce mortality risk is estimated either from individual behavior in markets in which prices reflect differences in mortality risks or from hypothetical scenarios[2,6] The VoLY is then derived directly from the VSL. The VSQ should then be estimated by weighting the VoLY with a quality-of-life related score.	Limits • Same drawbacks as for the WTP approach, although VSL can probably be estimated more robustly than direct VoLY or VSQ. • Although methods have been proposed to determine VSL and then derive VoLY and VSQ, no VoLY or VSQ has yet been estimated using such an approach, to our knowledge. Regarding the last approach, official VSL have been estimated in France since 1992.[7] In 2013,[5] a VSL value for France of €3 million was proposed. EQ-5D-3L data are available for the French population → High acceptability for France

ICER indicates incremental cost-effectiveness ratio; NHS, National Health Service; QALY, quality-adjusted life-years; WTP, willingness to pay; VoLY, value of a life-year; VSL, value of statistical life; VSQ, value of statistical QALY.

$$QALY(a) = u(a) \times LY(a) \quad (4)$$

where a is a given age, $u(a)$ the utility of a population at this given age, and LY(a) corresponds to a year of life at given age a. Consequently, LY(a) = 1, and living a full year at given age a is equal to living $u(a)$ QALY.

Using this relationship and the estimate of a VoLY (equation 2), we can propose an estimate of the VSQ at a given age a, according to life expectancy at this given age:

$$VSQ(a) = \frac{VSL}{\sum_{i=0}^{T(a)} u(a+i) * (1+\delta)^{-i}} \quad (5)$$

As VoLY(a) increases with age, VSQ(a) also increases as a function of age, meaning that the value of a QALY is high when life expectancy is short, even though this may appear counterintuitive.

To remain consistent with the goal of producing reference values that reflect a commitment of equity in access to healthcare,[18] VoLY(a) and VSQ(a) cannot be used directly because this would create a risk of introducing disparity between individuals of different ages. For this reason, it was necessary to estimate a single reference VoLY and VSQ independent of age, which could be considered as universal in France.

To address this goal, we estimated a weighted-average of VoLY and VSQ, according to the demographic structure of the French population aged 0 to 99 years in 2018. We did not consider centenarians, because life expectancies beyond 99 years of age rely on unconsolidated data.

$$VoLY = \sum_{a=0}^{99} VoLY(a) \times \frac{N(a)}{N} \quad (6)$$

and

$$VSQ = \sum_{a=0}^{99} VSQ(a) \times \frac{N(a)}{N} \quad (7)$$

where a is the age, $N(a)/N$ the proportion of the French population aged a, VoLY(a) and VSQ(a) the estimated VoLY, and VSQ at age a, estimated from equations 2 and 5, respectively. For our study, the age distribution of the French population in 2018 was taken from data provided by the National Institute for Demographic Studies (https://www.ined.fr/; Figure 1).

Base-Case Analysis

VSL

We used the €3 million VSL recommended in the FGCSP report.[18]

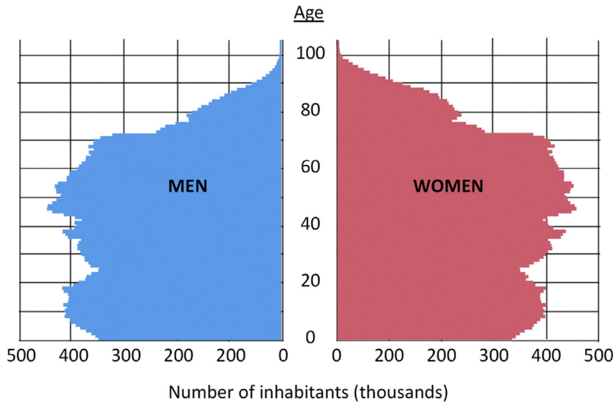
Discount Rate

The FGCSP report[18] recommends 2 different discount rates: a baseline discount rate of 2.5% that can be completed by a 2% additional hazard bonus. It is stated that a 4.5% discount rate should prevail in investment areas where risk aversion is particularly high, such as in public health. This is justified in the healthcare field because investments made for reimbursing a new treatment rely on clinical trials, and there is some uncertainty as to how the observed effectiveness will be transferred to the real-world setting. Nevertheless, both the 2.5% and 4.5% discount rates have been tested.

Utilities

HAS guidelines[7] recommend the use of the EQ-5D questionnaire (https://euroqol.org/) to measure utilities in clinical trials and for documenting utilities in cost-effectiveness models designed to estimate QALYs associated with medical interventions. Chevalier et al[23] have derived the French value set of the EQ-5D-3L. A sample of 452 respondents older than 18 years, representative of the French adult population with regard to age, gender, and socioprofessional group, participated in the study.

Figure 1. Age distribution of the French population in 2019 (Institut Nationale d'Etudes Démographiques).



Utility values were estimated by gender and age from EQ-5D-3L scores collected from the 452 participants using the previously derived French value set (Table 2).

For the weighted average VSQ, our base-case scenario uses the age-specific utilities described in Table 2, making the conservative assumption of a perfect quality of life ($u_{(0\text{-}17y)} = 1$) for people younger than 18 years.

Sensitivity Analysis

A sensitivity analysis was performed using a more recent estimate of $6 975 000 VSL for France based on US estimates and considering a 1.0 income elasticity.[24]

Scenario Analyses

In addition, further scenario analyses were performed using 4 different hypotheses for the utility values (Table 3). The first 3 scenarios (1-3) used the utility values provided by Chevalier et al[23] (Table 2), as in the base-case analysis. In scenario 1, a unique age-independent utility value was applied to all age groups ≥18 years, keeping a utility value of 1 for individuals younger than 18. This value was the weighted average of the utility values in each individual adult age group and corresponded to 0.821 for women and 0.847 for men. Scenario 2 retained the age-specific utility values of the base case for adults and used identical values to the 18- to 24-year age group for the 0- to 18- year age group (0.915 for girls and 0.967 for boys). Scenario 3 applied the age-independent utility value used in scenario 1 to all ages including the 0- to 18-year age group. Finally, scenario 4 used an alternative source of age-specific utilities derived from a previous EuroQoL study that estimated EQ-5D-3L–based utilities for 24 European countries including France (2892 individuals in France participated).[25] In addition, for each of these 4 scenarios, we determined the effect on the weighted average VSQ of varying the utility values by ±10%.

Results

Base-Case Scenario

Using the 2.5% discount rate, the weighted average VoLY was estimated to be €120 185 (Table 4), and the weighted average VSQ was estimated to be €147 093 (Table 5). Using the 4.5% discount rate, the weighted average VoLYs were estimated to be €166 205 (Table 4), and the weighted average VSQs were estimated to be €201 398. Both VoLY and VSQ increase with the discount rate because the denominator in equation 5 decreases with the discount rate.

Table 2. Age-related utility values for France.*

Age, y	Women		Men	
	n	Mean utility ± SD	n	Mean utility ± SD
18-24	30	0.915 ± 0.286	23	0.967 ± 0.079
25-34	41	0.882 ± 0.131	34	0.904 ± 0.163
35-44	49	0.825 ± 0.159	38	0.898 ± 0.122
45-54	39	0.837 ± 0.225	36	0.762 ± 0.291
55-64	32	0.804 ± 0.184	49	0.796 ± 0.219
65-74	34	0.71 ± 0.224	24	0.852 ± 0.201
+75	11	0.665 ± 0.264	11	0.737 ± 0.286
Total	236	0.821 ± 0.217	216	0.847 ± 0.212

*These utility values were kindly provided by Dr Julie Chevalier, ESSEC Business School, Cergy-Pontoise, France.

Sensitivity Analysis

In the scenario using an alternative VSL estimate,[24] the weighted average VoLYs were €248 693 to €343 919, and the weighted average VSQs were €304 374 to €416 743, depending on the discount rate.

Scenario Analysis

When utility values were varied by ±10%, the weighted average VSQs ranged from €127 855 to €164 267 and from €175 848 to €225 191 according to the discount rate (Table 5).

Discussion

There is a growing demand for defining reference values for qualifying cost-effectiveness of new products coming to price negotiation in France. Although the issue was first raised in 2012,[12] no such proposal has yet been made. The HAS has conducted a comprehensive literature review exploring methods to measure WTP for a health gain and studies performed to estimate WTP. However, no valid reference values for France were proposed from this review.

In this study, we have attempted to provide estimates of VoLY and VSQ that could be used as initial reference values to help qualify ICERs in health technology assessments by the CEESP and in new technology submissions by manufacturers. We have developed a methodology for estimating a VSQ benchmark for cost-effectiveness using only French data (or the specific VSL estimate for France from an international study), which respects the ethical principle of preserving equity of access to healthcare. Using this approach, and applying both the 2.5% and 4.5% discount rates proposed in the Quinet report, the VSQs were estimated to be €147 093 and €201 398, respectively, with the lower discount rate being associated with a lower VSQ. In the sensitivity analysis, this VSQ estimate was sensitive to the value adopted for VSL and ranged from €127 855 to €419 379.

In our methodology, we used a fixed VSL that was independent of age. This is inconsistent with the notion, associated with the work of Adly and Viscusi,[26,27] that VSL is intuitively an age-dependant function. For these workers, VSL can be estimated in 2 different ways: as a function of VoLY considered as a constant or as a function of wages and investments made by individuals to reduce health-related risk. Whichever approach is used, VSL is an age-dependent function. Particularly with the second approach, the relationship of VSL with age follows an inverted-U shape. With respect to the objective of the present study, following this approach presents both practical and theoretical problems. From a practical perspective, it yields estimates of VSL function, leading to negative values at certain ages. A negative VSL would be incompatible with ethical and economic principles. In addition, preferences regarding healthcare investments cannot be fully derived from wages, age, and investments, notably in countries with collective national healthcare systems. From a theoretical perspective, using an age-dependent VSL would breach the ethical concern to provide equity of access to healthcare, where investments should "reflect the collective willingness to guarantee that, in healthcare, the commitment is the same whatever the healthcare domain and whatever individuals are involved."[18]

In France, official estimates of VSL were published 1992.[17] The initial estimate of €550K for a VSL was based on the human capital approach and estimated from productivity loss after a traffic accident.[28] In 2001, the VSL was updated to €650K[29] using

Table 3. Utility scenarios for estimating VSQ.

Age, y	Base case*		Scenario 1*		Scenario 2*		Scenario 3*		Scenario 4†	
Gender	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men
0-17 y	1	1	1	1	0.915	0.967	0.821	0.847	1	1
18-24 y	0.915	0.967	0.821	0.847					0.953	0.944
25-34 y	0.882	0.904			0.882	0.904			0.941	0.952
35-44 y	0.825	0.898			0.825	0.898			0.910	0.917
45-54 y	0.837	0.762			0.837	0.762			0.920	0.925
55-64 y	0.804	0.796			0.804	0.796			0.843	0.862
65-74 y	0.710	0.852			0.710	0.852			0.771	0.868
+75 y	0.665	0.737			0.665	0.737			0.717	0.767

VSQ indicates value of statistical QALY.
*Based on data from Chevalier et al.[1]
†Based on EuroQol study.[2]

the same approach and then upgraded to €1.5 million to be more in line with WTP-based VSL estimates used elsewhere in Europe. Finally, in 2013,[18,19] a VSL estimate for France of €3 million was proposed, which was derived directly from a meta-analysis performed by the OECD in 2010.[20,21] This meta-analysis was based on 423 contingent valuation studies in which people were asked their WTP to reduce their risk of dying prematurely from environment-, transportation-, or health-related causes. It was found that more than 70% of the variation in VSL was explained by measured variables. In particular, it was found that higher income was associated with a higher WTP and thus a higher VSL, with an elasticity of 0.8, such that a 1% increase in mean income leads to a 1.2% increase in VSL. For the French estimate of VSL, Baumstark et al[19] increased the mean OECD VSL to take into account the higher per capita GDP in France compared with the EU-27 average, by applying the 0.8 elasticity value to the average national income. This provided an estimate of VSL of €3.3 million for France, which was rounded down to €3 million as a conservative approach to take into account the uncertainty of the estimate.[19] Consequently, we consider this VSL to be the most reliable available estimate for France, although it is likely to be a conservative one.

QALYs calculated from time trade-off–based preferences implicitly include a time-preference component. Application of a conventional discount rate on these implicitly discounted QALYs introduces some degree of double discounting.[30] Although this issue has been identified and some solutions suggested in the literature,[31,32] these corrections are not currently used in practice.[33] This may introduce some uncertainty in our calculation.

For the VSQ estimate, 2 sources of utility values were available for the adult French population,[23,25] and both yielded consistent results. Both of these sources used the EQ-5D-3L questionnaire, and our approach will benefit in the future from using other utility value sets measured in a larger sample and using the more discriminating EQ-5D-5L.

Considering the acceptability of our estimates, a VoLY of €166 205 is much higher than previous estimates for France from the EuroVAQ project,[34] which were between €21 500 and €53 580 for a VoLY. The EuroVAQ estimates are based on approaches proposed by Mason et al[35] to estimate VoLY and VSQ from VSL. The first approach used was to apply a direct ratio of VSL according to age-specific life expectancy and yielded a discounted VoLY of €45 064 for France. This method is very similar to the one that we adopted. The discrepancy between the EuroVOQ estimate and our own can be explained first by the use of an earlier, VSL estimate (€1.5 million),[29] which is 2-fold lower than the more recent estimate of €3 million[18] that we applied and, second, by the difference in discount rate (1% for EuroVAQ vs 4.5% in our study). Applying the inputs of the EuroVOQ estimate in our methodology would yield an estimate of €44 017 for a VoLY. Our methodology and findings are thus consistent with the EuroVOQ findings and emphasize the sensitivity of VSQ to VSL and discount rates that we observed in our scenario analyses. Our estimate is also higher than the threshold of 3 times the national per capita gross domestic product (GDP) proposed by the World Health Organization (WHO), which would correspond to approximately €115K for France. It is noticeable that although the WHO recommendation relies on the fact that estimates of VoLY are generally higher than GDP, the 1 to 3 times GDP threshold has been criticized extensively, particularly for the lack of rationale of the formula[36] and because, for a given country, GDP is neither related to WTP[37] nor affordability.[37,38]

Considering the acceptability of using VSQ as a reference value for a QALY, our estimate could not be compared with former values estimated for France. A €201 398 per QALY threshold appears much higher than those used in other countries such as England and Wales or The Netherlands, where official thresholds are between £20 000 and £30 000 (England and Wales) and €80K in (The Netherlands), and at the top end of the range of "official thresholds" as described for 17 countries by Cameron et al.[39] Nonetheless, because they are based on highly variable principles and methods, these thresholds are difficult to compare between countries. If our methodology is applied to the situation in England and Wales using UK data for demography (https://www.ons.gov.uk/), life expectancy (https://www.ons.gov.uk/), VSL[40] (£3.13 million) and utility data,[41] VSQ is estimated to be £202 913. Such an approach has been used previously for the United Kingdom in

Table 4. VoLY estimates.

VoLY	Discount rates	
	2.5%	4.5%
Base case	€120 185	€166 205
Alternative VSL value*	€248 693	€343 919

VoLY indicates value of life-year; VSL, value of statistical life.
*For France, VSL = $6 975 000 (Viscusi et al, 2017[24]). The authors applied an exchange rate of €0.89 to $1.

Table 5. VSQ estimates according to utility scenarios.

VSQ	Base case	Scenario 1	Scenario 2	Scenario 3	Scenario 4
2.5% discount rate					
Weighted average VSQ	€147 093	€142 218	€147 840	€144 215	€138 214
–10% utilities	€163 437	€158 020	€164 267	€160 239	€153 571
+10% utilities*	€135 093	€130 279	€135 093	€131 104	€127 855
Alternate VSL value†	€304 373	€294 284	€305 918	€298 416	€285 999
4.5% discount rate					
Weighted average VSQ	€201 398	€195 960	€202 672	€199 417	€189 603
–10% utilities	€223 776	€217 703	€225 191	€221 575	€210 670
+10% utilities*	€185 312	€179 856	€185 392	€181 289	€175 848
Alternate VSL value†	€416 743	€405 490	€419 379	€412 645	€392 336

*The maximum utility value was limited to 1.
†For France, VSL = $6 975 000 (Viscusi et al 2017[24]). The authors applied an exchange rate of €0.89 to $1.

the EuroVAQ project, using a previous (lower) estimate for VSL of £1 427 340 VSL and applying a 1.5% discount rate. This generated an estimate of VSQ between £55 708 and £70 765 for the United Kingdom.[34,35] Both these VSL-based estimates are far higher than the threshold used by NICE of £20 000 to £30 000. However, as described by Claxton et al,[16,42] the NICE threshold is based on a ratio between annual budget increases of primary care trusts in the United Kingdom and an estimate of incremental production of QALY. This threshold is actually the marginal cost for a QALY given budget constraints within the NHS rather than a WTP. It reflects affordability rather than desirability, whereas VSL-based methods such as our proposed VSQ yield preference-based estimates, reflecting the desirability of investing in treatments with ICERs lower than the VSQ. Vallejo-Torres et al[43] have observed previously that WTP methods were associated with higher cost-effectiveness thresholds than thresholds resulting from estimating the opportunity costs to the healthcare system.

A comparison can also be made with WTP for reimbursement of dialysis in France. Dialysis prevents inevitable short-term death, is fully reimbursed, and is unquestioned as a treatment option. Its cost in France was estimated to be between €64 450 and €88 608 per year in 2010[44,45] and €65 091 per year in 2013.[46] Being on dialysis is associated with a poor quality of life, and utilities valued through EQ-5D questionnaires are between 0.58 and 0.61.[45,47] This means that French society considers it acceptable to spend between €105 656 per QALY and €152 772 per QALY to prevent death from renal failure. The upper estimate is consistent with our lowest VSQ estimates and implies that our VSQ does reflect WTP values that are already accepted to prevent short-term death in France.

Preference-based studies, aiming at directly estimating the value of a QALY, face issues related to the fact that they rely on fictional risk assessment scenarios, and their internal validity has been called into question.[15] Moreover, in the few studies that have estimated WTP for a health intervention conducted in OECD countries, it has been observed[19,20,48,49] that people living in developed countries and benefiting from a comprehensive national health insurance are unlikely to be aware of the real cost of healthcare. For these reasons, WTP for a health gain probably cannot be measured realistically in direct and dedicated preference-based studies. To avoid such limitations, we favored an indirect calculation based on the VSL, because it can be assumed that estimates of VSL are less heterogeneous and more robust than estimates of WTP.

Finally, it could be argued that anchoring ICER qualification on a single reference value does not address the important question of affordability and resource allocation.[37,38] The criticism has been raised since the early roundtable discussions[12] on future HEA in France, at which the use of a unique threshold was rejected. At that time, it was considered more convenient to propose several reference values according to criteria that would reflect citizens' preferences for investing in particular products or therapeutic areas. In particular, it was proposed that using a threshold for anchoring reimbursement decision would allow affordability to be integrated into the decision process.[37,38] Such a position would be consistent with the philosophy followed by NICE. In opposition to this position, we would argue that there is a necessary ethical assumption that equity in access to healthcare should be guaranteed for all individuals regardless of the healthcare domain and that the reference values should reflect collective willingness to guarantee this and thus that a single unique VSQ should be considered for all health interventions. In addition, HEA of new technologies in France is now usually complemented by a budget impact analysis, which takes into account the sustainability of the healthcare budget. This means that the preferences of the French population regarding healthcare priorities can be fully addressed, and the VSQ approach provides a standardized approach to do this.

Our proposed VSQs are preference-based estimates, reflecting the desirability of investing in treatments with ICERs lower than €147 093 to €201 398 per QALY. Cost-effectiveness studies are generally hard to conduct and contain many uncertainties. Consequently, it is usually considered that reimbursement decisions should not be based on a single cost-effectiveness threshold but on a country-specific process including clinical assessment, cost-effectiveness, and affordability.[36–39,43] The reimbursement process in France is fully in line with such considerations because the reimbursement decision per se relies solely on a clinical assessment of a new treatment while economic considerations involving cost-effectiveness studies to assess desirability and budget impact studies to assess affordability are taken into account order to enlighten price negotiations. Under these circumstances, price negotiations (European price corridor, rebates) could be then conducted through a trade-off between price cuts and payment for innovation.

Our estimates of VoLY and VSQ are likely to be conservative ones, first because of the choice of VSL for the reference scenario as discussed above and second because it is based on life expectancy. Life expectancy is a theoretical value based on observed mortality at each age. In our estimate, we have assumed that everyone at each given age will live the full life expectancy on average. This could lead to an overestimation of the denominator in VoLY and VSQ estimates and consequently an underestimation of VoLY and VSQ. In future estimates, updating utility values (using EQ-5D-5L data) and discount rates could lead to lower VoLY and VSQ, whereas updating VSL will increase VoLY and VSQ more significantly.

In conclusion, we have attempted to estimate acceptable VSQs that could be used as reference values for QALYs in France. Such VSQs could be considered breakeven values for a QALY in France and be used to address whether a medical intervention at a requested price may or may not be efficient. To this end, the estimated reference values of €147 093 to €201 398 for a QALY may provide appropriate thresholds.

Dedication

In memoriam of Claude Le Pen.

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