THE GOAL OF VALUE-BASED MEDICINE ANALYSES: COMPARABILITY. THE CASE FOR NEOVASCULAR MACULAR DEGENERATION

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ABSTRACT

Purpose: To evaluate the comparability of articles in the peer-reviewed literature assessing the (1) patient value and (2) cost-utility (cost-effectiveness) associated with interventions for neovascular age-related macular degeneration (ARMD).

Methods: A search was performed in the National Library of Medicine database of 16 million peer-reviewed articles using the key words *cost-utility*, *cost-effectiveness*, *value*, *verteporfin*, *pegaptanib*, *laser photocoagulation*, *ranibizumab*, and *therapy*. All articles that used an outcome of quality-adjusted life-years (QALYs) were studied in regard to (1) percent improvement in quality of life, (2) utility methodology, (3) utility respondents, (4) types of costs included (eg, direct healthcare, direct nonhealthcare, indirect), (5) cost bases (eg, Medicare, National Health Service in the United Kingdom), and (6) study cost perspective (eg, government, societal, third-party insurer).

To qualify as a value-based medicine analysis, the patient value had to be measured using the outcome of the QALYs conferred by respective interventions. As with value-based medicine analyses, patient-based time tradeoff utility analysis had to be utilized, patient utility respondents were necessary, and direct medical costs were used.

Results: Among 21 cost-utility analyses performed on interventions for neovascular macular degeneration, 15 (71%) met value-based medicine criteria. The 6 others (29%) were not comparable owing to (1) varying utility methodology, (2) varying utility respondents, (3) differing costs utilized, (4) differing cost bases, and (5) varying study perspectives.

Among value-based medicine studies, laser photocoagulation confers a 4.4% value gain (improvement in quality of life) for the treatment of classic subfoveal choroidal neovascularization. Intravitreal pegaptanib confers a 5.9% value gain (improvement in quality of life) for classic, minimally classic, and occult subfoveal choroidal neovascularization, and photodynamic therapy with verteporfin confers a 7.8% to 10.7% value gain for the treatment of classic subfoveal choroidal neovascularization. Intravitreal ranibizumab therapy confers greater than a 15% value gain for the treatment of subfoveal occult and minimally classic subfoveal choroidal neovascularization.

Conclusions: The majority of cost-utility studies performed on interventions for neovascular macular degeneration are value-based medicine studies and thus are comparable. Value-based analyses of neovascular ARMD monotherapies demonstrate the power of value-based medicine to improve quality of care and concurrently maximize the efficacy of healthcare resource use in public policy. The comparability of value-based medicine cost-utility analyses has important implications for overall practice standards and public policy. The adoption of value-based medicine standards can greatly facilitate the goal of higher-quality care and maximize the best use of healthcare funds.

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INTRODUCTION

Recent pharmaceutical advances have increased the modalities available to treat subfoveal choroidal neovascularization. Laser therapy has been the mainstay of treatment for over a decade,[1,2] but photodynamic therapy with verteporfin,[3-5] intravitreal pegaptanib therapy,[6] and intravitreal ranibizumab therapy[7] have been more recently introduced.

Concurrent with the development of new therapeutic modalities for neovascular macular degeneration, value-based medicine has gained increasing popularity.[5,8,9] Value-based medicine is the practice of medicine based on the patient value (improvement in length of life or quality of life or both) conferred by an intervention.[8,9] This patient value gain is then integrated with its associated incremental costs in the form of cost-utility analysis. Value-based medicine analyses are generally comparable, since they use similar input and output variables.[8,9] The concept of value-based medicine has been specifically designed to allow a user-friendly system for physicians, patients, healthcare decision makers, patients, and other healthcare stakeholders.[8,9]

Whereas the difference in patient benefit of many therapies is obvious from evidence-based clinical trial data alone, in select instances it is difficult to ascertain which interventions provide the most beneficial effect. For example, which confers the greatest benefit—the improvement in mean long-term vision from 20/500 to 20/320 with laser photocoagulation,[2] the improvement in mean long-term vision from 20/320+2 to 20/160+2 in eyes treated with photodynamic therapy with verteporfin,[5] or the improvement from 20/200+1 to 20/126-1 in eyes treated with pegaptanib[6]? Furthermore, how do the adverse events, and the incidence of adverse events,

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associated with each of the respective interventions factor into the therapeutic equation?

With increasing numbers of utility and cost-utility analyses present in the peer-reviewed literature,[10-40] it is critically important to ascertain which are comparable. For example, the use of utilities from patients vs those from physicians, vs those from the community, can result in dramatically different outcomes,[11-13] as can the use of different cost perspectives, such as the third-party insurer and societal perspectives.[9] Different cost bases, such as with the use of healthcare system costs from different countries, can also cause large variations in outcomes. For these reasons, we undertook an evaluation of cost-utility analyses in the peer-reviewed literature dealing with interventions for neovascular macular degeneration.

METHODS

Value-based medicine is the practice of medicine based on the *value* conferred by healthcare interventions. To appreciate value-based medicine outcomes and the outcomes of other cost-utility analyses in the literature, it is essential to understand how evidence-based data are converted to value-based data. This "Methods" section deals with this conversion and value-based medicine principles in detail. Institutional review board approval was not obtained because this investigation involved no patients directly.

VALUE

The patient *value* gained from an intervention is defined by the improvement it confers in (1) length of life and/or (2) quality of life.[8,9] It is a common misperception that *value* refers to money. This is not the case. Value refers in no way or form to money, but rather to the benefit a patient receives from an intervention.

The improvement in length of life can generally be culled from the evidence-based literature, but the improvement in quality of life is more difficult to ascertain. It can, however, be quantified using utility analysis. Utility analysis allows a measure of the value gain conferred by both length of life and quality of life using the same outcomes.

UTILITY ANALYSIS

Utility analysis allows a measure of the quality of life associated with a health (disease) state.[8-24] By convention, a utility of 1.0 is typically associated with perfect health permanently (or the best possible health), and a utility of 0.0 is associated with death. The closer the utility is to 1.0, the better the quality of life associated with a health state, whereas the closer the utility is to 0.0, the poorer the quality of life associated with a health state. For example, mild angina has been associated with a utility value of 0.90,[9] while a severe stroke has been associated with a utility value of 0.12.[9] Various methodologies have been developed to measure utility values associated with a health state, including the time tradeoff method, the standard gamble method, the willingness-to-pay method, and multi-attribute instruments that assess the pain, anxiety, depression, loss of function, and other parameters associated with a health state.[9]

The form of utility analysis that we prefer is the time tradeoff method, in which a patient is asked how long he or she expects to live. The patient is then offered a theoretical scenario in which time of remaining life can be traded in return for being free of a disease. The corresponding utility value is then calculated by subtracting the proportion of the time traded divided by the anticipated remaining years of life from 1.0. For example, the average patient with diabetes mellitus and a theoretical life expectancy of 25 years was shown to be willing to trade approximately 3 of those 25 remaining years of life to be free from diabetes.[9] Thus, the utility in this instance is 1.0 – (3/25) = 0.88.[15] The reliability (reproducibility) and construct validity (the ability of an instrument to measure what it is designed to measure, in this case quality of life) are excellent.[9] Utility values associated with various systemic health states are shown in Table 1,[8,9,11,12,14,23] and ocular utilities are shown in Table 2.[8,9,13,15,16-22] Utility values are often referred to as patient preferences, since patients can prefer to trade time for better health or prefer not to trade time and continue in the same health state.

DECISION ANALYSIS

Decision analysis can be utilized to ascertain the most probable outcome associated with use of a drug or with the administration of another intervention. When each of the possible adverse events and the respective incidences of the adverse events associated with Drug X are integrated, the most probable utility outcome is 0.88. This is the utility, or quality-of-life level, at which the average person lives if he or she used Drug X. The utility associated with no treatment is 0.80; thus, Drug X confers a (0.88 - 0.80 =) **0.08** improvement in utility for the average person. Of note is the fact that if Drug X has no associated adverse events, the overall utility associated with its use is 1.00.

TOTAL CONFERRED VALUE

With value-based medicine, medical interventions are delivered predicated on the total value conferred by an intervention. A pillar of value-based medicine is the fact that patients should desire, and should receive, the intervention(s) delivering the greatest value. In regard to the selection of therapy with value-based medicine, cost is secondary; it is considered only if the value conferred by two interventions is similar. In this instance, the intervention of the same value which is the least expensive should be considered the preferred treatment. From our experiences, there are innumerable interventions with equal value and differences in cost and therefore countless opportunities to save considerable dollars in the healthcare system.[9]

If a drug provides greater value for less cost than a comparator drug, the drug is *dominant* over the comparator drug. If the drug provides the same value as a comparator drug, but is less expensive, the drug is *preferable* to the comparator drug.[9] If a drug provides greater value than a comparator drug, but for greater cost, then this drug is also *preferable* to the comparator drug.[9]

TABLE 1. TIME TRADEOFF UTILITY VALUES ASSOCIATED WITH SYSTEMIC HEALTH STATES

HEALTH STATE	UTILITY VALUE
Angina, mild	0.90
Agina, moderate	0.70
Angina, severre	0.50
Cancer, breast, early state, lumpectomy or mastectomy	0.94
Cancer, breast, radiotherapy	0.89
Cancer, breast, chemotherapy	0.74
Diabetes mellitus	0.85
Impotence and incontinence after TURP	0.60
Myocardial infarction, mild	0.91
Myocardial infarction, moderate	0.80
Myocardial infarction, severe	0.30
Osteoarthritis, hip, mild	0.69
Osteoarthritis, hip replacement (6 mo)	0.82
Renal disease, end-stage, self-care or home hemodialysis	0.49
Renal disease, transplant (12 mo)	0.74
Stroke, minor residual effects	0.89
Stroke, major	0.30

TURP, transurethral resection of the prostate.
Adapted from Brown MM et al.[8]

TABLE 2. TIME TRADEOFF UTILITY VALUES ASSOCIATED WITH VISUAL LOSS

VISUAL ACUITY IN THE BETTER-SEEING EYE	UTILITY VALUE
20/20 bilaterally, permanently	1.00
20/20 (with 20/20 to 20/25 in the other eye)	0.97
20/20 (with ≤20/40 in the other eye)	0.92
20/25	0.87
20/30	0.84
20/40	0.80
20/50	0.77
20/70	0.74
20/100	0.67
20/200	0.66
20/300	0.63
20/400	0.54
Counting fingers	0.52
Hand motions	0.35
Light perception	0.35
No light perception	0.26

Adapted from Brown MM et al.[8]

The total value conferred by an intervention is ascertained by multiplying as follows: (the improvement in utility conferred by the intervention) × (duration of interventional benefit in years). For example, if the benefit from Drug X lasts for 20 years, the total value gain is: (0.08 utility gain) × (20 years) = 1.60 QALYs (quality-adjusted life-years). If Drug X confers an extra 2 years of life as well, the additional QALY gain is calculated by multiplying: (utility associated with the use of Drug X, or 0.88) × (2 years) = 1.76 QALYs. Thus, the total value conferred by Drug X = 1.60 QALYs + 1.76 QALYs = **3.36 QALYs**.

This outcome of QALYs can be compared to the QALYs gained from any other intervention in medicine, whether medical, surgical, or pharmacologic.[9] The QALY is extraordinarily inclusive, incorporating the degree of improvement in quality of life, the duration of the quality-of-life benefit, and the improvement in the length of life, in essence all the possible aspects of value conferred by an intervention. For ophthalmologic interventions, the total value is generally calculated using the improvement in quality of life alone, since there is most often no change in length of life.

The total conferred value can also be expressed in the form of percent improvement in value. For most ophthalmic interventions, this percent improvement in value equates with percent improvement in quality of life.

COSTS

The costs used in value-based medicine cost-utility analyses are direct medical costs[9] (eg, physician fees, hospital charges, pharmaceutical costs, durable goods costs). The direct medical cost perspective is also known as the third-party insurer perspective, since these costs are those a third-party insurer would be expected to cover. Societal costs[9] are all-inclusive and encompass direct medical costs as well as direct nonmedical costs (eg, travel costs to doctors, caregiver costs) and indirect costs (eg, disability payments, loss of contribution to the gross domestic product). Unfortunately, there is a lack of agreement about which societal costs to use as well as their cost basis. Thus, the direct costs used with value-based medicine cost-utility analyses currently allow the best comparability among cost-utility studies.[9] Should common standards for the societal cost perspective be established, we believe this perspective would be the most desirable. Until then, we will continue to use the direct medical cost perspective.

The cost basis utilized in value-based medicine analyses is the average Medicare Fee Schedule across the country. The cost basis differs depending on the country in which the value-based medicine analysis is performed. Nonetheless, value-based medicine analyses can be considered to be such in other countries if time tradeoff utilities are used, patient utility respondents are utilized, and a third-party insurer perspective is undertaken.

A list of the direct medical costs used in value-based medicine cost-utility analyses in the United States is shown in Table 3.

TABLE 3. STANDARDIZED VARIABLES FOR USE IN COST-UTILITY ANALYSIS

VARIABLES	RECOMMENDED PARAMETERS
Utility analysis instrument	Time tradeoff
Utility respondents	Patients with a health state
Methodology	Interview
Perspective	Third party
Discount rate	3% per year
Costs	
Physicians	Average CMS reimbursement
Hospitals	Average CMS reimbursement
Ambulatory surgical centers	Average CMS reimbursement
Pharmaceuticals	AWP*
Durable goods	Average CMS reimbursement

AWP, average wholesale price; CMS, Centers for Medicare and Medicaid Services.
*AWP obtained from *Fleming T, ed. Red Book 2006 Drug Topics. Montvale, NJ: Thomson Medical Economics; 2006.* The AWP will shortly be replaced by the Average Sales Price, the average price that pharmaceutical manufacturers sold their goods for during the preceding year.
Adapted from Brown MM et al.[9]

COST-UTILITY

Cost-utility analysis utilizes an outcome of dollars spent per QALY, or $/QALY. Some have referred to studies with this outcome as cost-effectiveness analyses,[24] but we[9] and others[21] believe that cost-effectiveness analyses should include only measures other than $/QALY, such as cost per life-year and cost per good-vision year.

The upper limit for cost-effectiveness generally used in the United States is $100,000/QALY,[25-27] although some have suggested an upper limit of $50,000/QALY.[26,27] The upper limit of cost-effectiveness for the National Institute for Health and Clinical Excellence,[28] the agency in the United Kingdom responsible for assessing which interventions merit insurance coverage, is £20,000 to £30,000/QALY, depending on the intervention. This equates to approximately $40,000 to $60,000/QALY in US dollars.

Despite referring to $/QALY as a "cost-utility" or "cost-utility ratio," an intevention studied with cost-utility analysis is still spoken of as being "cost-effective" or "not cost-effective."

It is generally agreed that outcomes (percent value gain, QALYs, $/QALY) should be discounted to account for the greater worth of money and of good health now than in the future.[9] Both can be used to create additional resources if present now, whereas if accrued in 10 years, they cannot be used to create greater resources over the 10-year period.

RESULTS

Overall, 22 cost-utility analyses dealing with interventions for neovascular macular degeneration were found in the literature search. An analysis was considered to be a value-based analysis if time tradeoff utilities were used, patient utility respondents were queried, and a third-party insurer perspective was utilized.

Analysis of the input and output variables associated with each study revealed that 16 (73%) of the 22 analyses were value-based medicine cost-utility analyses, and 6 (27%) were cost-utility analyses that did not employ value-based medicine principles (Table 4).

TABLE 4. VALUE-BASED MEDICINE AND NON-VALUE-BASED MEDICINE COST-UTILITY ANALYSES OF NEOVASCULAR MACULAR DEGENERATION INTERVENTIONS

INTERVENTION	UTILITY INSTRUMENT	UTILITY RESPONDENTS	COST PERSPECTIVE*	COST BASIS†	CURRENCY	YEAR OF STUDY
I. Value-Based Medicine, Cost-Utility Analyses						
Laser[29] (subfoveal)	TTO	Patients	3rd party	Medicare	US $	2001
Laser[30] (histoplasmosis‡)	TTO	Patients	3rd party	Medicare	US $	2001
PDT (20/40 in better eye)[31]	TTO	Patients	3rd party	Medicare	US $	2001
PDT (20/200 in better eye)[31]	TTO	Patients	3rd party	Medicare	US $	2001
PDT[32]	TTO	Patients	3rd party	Ontario	Canadian $	2001
Laser[33] (extrafoveal§)	TTO	Patients	3rd party	Medicare	US $	2003
PDT[34]	TTO	Patients	3rd party/Societal	NHS	£ Sterling	2003
PDT[35]	TTO	Patients	3rd party	Austral Med	Australian $	2004
AREDS[35] dietary supplements	TTO	Patients	3rd party	Austral Med	Australian $	2004
PDT[36]	TTO	Patients	3rd party	Austral Med	Australian $	2004
PDT[5]	TTO	Patients	3rd party	Medicare	US $	2005
Juxtascleral corticosteroid[37]	TTO	Patients	Societal	Medicare	US $	2005
Laser[38] (subfoveal¶)	TTO	Patients	3rd party	Medicare	US $	2006
PDT[38]	TTO	Patients	3rd party	Medicare	US $	2006
Pegaptanib[38]	TTO	Patients	3rd party	Medicare	US $	2006
Ranibizumab[39]	TTO	Patients	3rd party	Medicare	US $	2006
II. Non-Value-Based Medicine, Cost-Utility Analyses						
PDT[40]	NS	NS	3rd party	Ontario	Canadian $	2004
AREDS[40]	NS	NS	3rd party	Ontario	Canadian $	2004
PDT[41]	TTO	Patients	Governmental	NHS	£ Sterling	2004
PDT[42]	HUI3	Patients	Societal	NHS	£ Sterling	2006
Ranibizumab[43]	NA	NA	Societal	NHS	£ Sterling	2007
Bevacizumab[43]	NA	NA	Societal	NHS	£ Sterling	2007

AREDS, Age-Related Eye Disease Study; HUI3, Health Utilities Index, 3rd edition (a multi-attribute utility instrument that subtracts disutilities, such as those associated with pain, anxiety, loss of function, from 1.0); NA, not yet available due to epublication; NS, not stated; PDT, photodynamic therapy with verteporfin; TTO, time tradeoff utility analysis.
*Third-party insurer is the direct medical cost perspective. Societal encompasses direct medical costs, direct nonmedical costs (eg, caregiver costs), and indirect costs (eg, disability costs). Governmental includes direct medical costs, loss of tax revenue costs, disability costs, loss of contribution to Gross Domestic Product, and so forth.
†Medicare = Medicare Fee Schedule. Ontario = Ontario Health Insurance Plan. NHS = United Kingdom National Health Service; Austral Med = Australian Medicare costs.
‡Choroidal neovascularization secondary to ocular histoplasmosis.
§Laser for extrafoveal choroidal neovascularization secondary to age-related macular degeneration.
¶Laser for subfoveal choroidal neovascularization secondary to age-related macular degeneration.

Among the 22 value-based neovascular macular degeneration analyses, the value gain was quantified for 6 interventions, although it could have been readily quantified by authors of the other value-based studies as well. A list of the value gains, which for these ophthalmic interventions are equivalent to quality-of-life gains, is shown in Table 5.

TABLE 5. VALUE GAIN (IMPROVEMENT IN QUALITY OF LIFE) CONFERRED BY INTERVENTIONS FOR NEOVASCULAR MACULAR DEGENERATION

INTERVENTION	TYPE OF NEOVASCULARIZATION*	VALUE GAIN
Laser photocoagulation[38]	Subfoveal classic	4.4%
Pegaptanib, intravitreal[38]	Subfoveal classic	5.9%
	Subfoveal minimally classic	5.9%
	Subfoveal occult	5.9%
PDT (20/200 initial vision)[31]	Subfoveal classic	7.8%
PDT, overall[5]	Subfoveal classic	8.1%
PDT (20/40 initial vision)[31]	Subfoveal classic	10.7%
Ranibizumab, intravitreal[39]	Subfoveal minimally classic	15.8%
	Subfoveal occult	15.8%

PDT, photodynamic therapy with verteporfin.
*Subfoveal classic = 50% or more of the border of the choroidal neovascularization is well defined. Subfoveal minimally classic = less than 50% of the border of the choroidal neovascularization is well defined. Subfoveal occult = borders of the lesion are not well defined.

Laser photocoagulation confers a 4.4% value gain (improvement in quality of life) for the treatment of classic subfoveal choroidal neovascularzation. Intravitreal pegaptanib confers a 5.9% value gain (improvement in quality of life) for classic, minimally classic, and occult subfoveal choroidal neovascularization, and photodynamic therapy with verteporfin confers a 7.8% to 10.7% value gain (improvement in quality of life) for the treatment of classic subfoveal choroidal neovascularization. For 20/40 initial vision in the better-seeing eye, the value gain conferred by PDT is 10.7%, whereas for an initial vision of 20/200, the value gain conferred by PDT is 7.8%. Intravitreal ranibizumab therapy confers greater than a 15% value gain for the treatment of occult and minimally classic subfoveal choroidal neovascularization.

The cost-utilities of interventions for neovascular macular degeneration are shown in Table 6. Cost-utility changes yearly, because medical costs routinely change, whereas the value gain is generally a more stable number unless new data are discovered.

TABLE 6. COST-UTILITY OF INTERVENTIONS FOR NEOVASCULAR MACULAR DEGENERATION

INTERVENTION	TYPE OF NEOVASCULARIZATION*	VALUE GAIN
Laser photocoagulation[38]	Subfoveal classic	$8,179
Pegaptanib, intravitreal[38]	Subfoveal classic	$66,978
	Subfoveal minimally classic	$66,978
	Subfoveal occult	$66,978
PDT[5†]	Subfoveal classic	$31,103
PDT (20/40 initial vision)[31‡]	Subfoveal classic	$86,721
PDT (20/200 initial vision)[31‡]	Subfoveal classic	$173,984
Ranibizumab, intravitreal[39]	Subfoveal minimally classic	$50,691
	Subfoveal occult	$50,691

PDT, photodynamic therapy with verteporfin.

*Subfoveal classic = 50% or more of the border of the choroidal neovascularization is well defined. Subfoveal minimally classic = less than 50% of the border of the choroidal neovascularization is well defined. Subfoveal occult = borders of the lesion are not well defined.

†Data from 5 years (approximation).

‡Data from 2 years.

The Goal of Value-Based Medicine Analyses: Comparability. The Case for Neovascular Macular Degeneration

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DISCUSSION

VALUE-BASED MEDICINE IN OPHTHALMOLOGY

The majority of cost-utility analyses performed on interventions for neovascular macular degeneration are value-based medicine analyses, because they incorporate time tradeoff utilities obtained from patients with macular degeneration and a third-party insurer

cost perspective.[9] This allows the studies to be comparable in regard to value gain in both QALYs and percent value gain (improvement in quality of life). Despite the fact that value gain in percent improvement in value (quality of life) was not published for all of the value-based interventions, it could have been readily calculated and presented by the authors in each study. This percent value gain outcome is one that is readily understood by all stakeholders, a critical factor in regard to the *straightforwardness* necessary for a system of value-based standards to be adopted.

This use of value-based medicine principles is encouraging. Value-based medicine principles have also been used for ocular interventions other than neovascular macular degeneration, including cataract surgery,[44,45] laser treatment for threshold retinopathy of prematurity,[46] laser treatment for central[47] and branch[48] retinal vein obstructions, laser[49] and surgical[50] treatments for diabetic retinopathy, screening and treatment of amblyopia,[51] surgery for repair of retinal detachment,[52] and repair of senile entropion.[53] The majority of these interventions are very cost-effective by conventional standards.[25-27]

VALUE-BASED MEDICINE AND PUBLIC POLICY

Despite the fact that the QALY was introduced by Klarman and associates[54] in 1968, cost-utility analysis has not yet assumed a major role in healthcare policy in the United States for the creation of medical quality standards. The opposite is the case in countries such as the United Kingdom, where a cost-utility analysis is a prerequisite for generalized use of a new pharmaceutical agent or other intervention.[28] We believe that a major reason cost-utility analysis has not yet assumed a greater role in the US healthcare arena is the lack of standardization of analyses across all specialties.

A *very superficial* analysis of possible utility variants[9] demonstrates that a minimum of 1008 different preference-based, quality-of-life, instrument/respondent alternatives (eg, time tradeoff, standard gamble, willingness to pay, multiattribute, and physician, community, patient respondents) are possible. An equally superficial analysis of costs and cost bases reveals 396 possible variants. Thus, **399,168** (1008 × 396) possible variations are possible for cost-utility analysis just among quality-of-life instruments and costs. Value-based medicine analyses, which utilize time tradeoff utility analysis, direct healthcare costs, and a Medicare cost basis, therefore reduce approximately 400,000 possible cost-utility analysis variants to one.

Value-based medicine principles for the performance of cost-utility analyses provide a sorely needed framework for the standardization of studies. This can facilitate the development of large databases encompassing (1) the *patient value* conferred by interventions and (2) the *cost-utility* associated with interventions. Interventions with superior value can be identified, as can interventions with negligible value or that are actually harmful. In regard to a standardized cost-utility, countries are already using these data for coverage decisions.[34] It is believed there are sufficient resources in the United States, such that if a value-based medicine system is incorporated, all interventions that provide reasonable value can be offered.[9]

Since value-based medicine analyses integrate patient perceptions about quality of life that are often ignored in evidence-based clinical trial outcomes, they allow clinicians to provide interventions that deliver the greatest benefit to patients, thus improving quality of care above what is possible using evidence-based medicine data alone.[9] Nontheless, this should not be construed to mean it is not necessary to use the best evidence-based medicine studies (preferably Level 1 clinical trials and/or meta-analyses[9]) as the foundation for value-based medicine analyses. A value-based medicine analysis can be severely limited in usefulness if the underlying evidence-based medicine data it uses to create value estimates are substandard.

UTILITIES

Standardization of quality-of-life measures is critical to allow comparable value and cost-utility analyses. Just the use of different utility analysis instruments (time tradeoff, standard gamble, willingness-to-pay, and multi-attribute) and varying respondents can result in over 800 different variants of quality-of-life measures, many of which are radically different from others.[11-13,15] For example, ophthalmologists who treat ARMD underestimated the utilities of patients with different levels of ARMD by 96% to 750%![11] When the possible cost perspectives (eg, third-party insurer, governmental, paying patient, societal) are included, the potential cost-utility differences rise into the tens of thousands. Needless to say, this lack of comparability makes the use of cost-utility analysis difficult for public policy decisions. The use of time tradeoff utilities, which are very reproducible,[54,55] and patient respondents in value-based medicine analyses greatly help to improve comparability.

A logical question arises: Are utilities obtained from different groups and different countries comparable? Time tradeoff utilities appear to be innate to human nature.[11-15, 56-62] They have been shown repeatedly to transcend gender, age, level of education, and income levels.[11,56-62] Thus, the average man or woman with an 8th grade or an 18th grade formal education trades the same proportion of time (eg, 12% of their remaining time for improving 20/40 vision in the better eye to 20/20[23]) to be rid of their visual problem. And the average person in their 30s with diabetes mellitus trades the same proportion of time as the average person in their 60s (eg, also 12% of their remaining time, or a utility of 0.88) to be rid of their disease.[60]

Data from the Center for Value-Based Medicine (Center)[64] demonstrate that time tradeoff utilities are similar across state borders. Center utilities have been shown to be similar across national borders as well.[65,66] Although time tradeoff utility analysis is not a perfect quality-of-life instrument, its (1) capability to quantify the qualify of life associated with any health state,[9] (2) good to excellent reproducibility,[9] (3) excellent construct validity,[9] (4) comparability of results with other quality-of-life instruments,[64] and (5) ease of use in economic analyses[9] make it the most reasonable quality-of-life instrument of choice at this time.

COSTS

It is understandable that dissimilar cost bases are used in different countries due to different currencies and diverse reimbursement schedules for medical goods and services. These differences make comparisons of studies across countries difficult, even if performed in a value-based medicine format. Different years of analyses also make comparions of cost-utilities more difficult. Currency conversions, discounting for healthcare inflation, and adjustments for the costs of medical goods and services, however, can overcome these differences.[9]

The use of Medicare average reimbursements as the basis for direct medical costs in the United States facilitates comparability of cost-utility analyses. Although a societal perspective (including direct medical costs, direct nonmedical costs such as caregiver costs, and indirect costs such as disability costs) is probably the most desirable cost perspective, there is no agreement on which costs, much less the cost basis, to include with the societal perspective.[9] Thus, direct medical costs appear to be the most reproducible and comparable at this time.[9]

COST-UTILITY

The upper limits for cost-effectiveness of $100,000/QALY in the United States is soft, meaning that the basis for this number is questionable, having been derived in Canadian dollars from a publication in the *Canadian Medical Association Journal* in 1992.[25] As the cost-utilities of more interventions are studied with value-based medicine principles, these resultant comparable cost-utilities will likely be characterized in terms of deviations from the mean and/or median. The definition of what is "cost-effective" will vary from country to country, depending on how many resources each country has to devote to healthcare.

In summary, value-based medicine cost-utility analyses for neovascular macular degeneration demonstrate the potential of the tool. Needless to say, the goals of higher-quality care and maximization of the efficacious use of healthcare dollars are those everyone would agree on. Value-based medicine is a vehicle to bring these goals to fruition.

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PEER DISCUSSION

DR JOHN D. BULLOCK: I appreciate the opportunity of discussing this most important and interesting paper concerning the intersection of cutting-edge treatments for the leading cause of First World blindness and the perceived American healthcare economic crisis. The good news is that the authors reported a >15% improvement in quality of life with intravitreal Lucentis, but the bad news is that this drug is extremely expensive, costing about $2000/injection. Is it really worth it?

The origin of value-based medicine can be traced to the Hungarian-born polymath, John von Neumann, coinventor of game theory, who later became the inspiration for Stanley Kubrick's *Dr Strangelove.* Von Neumann believed that economics would, like physics, develop into a rigorous mathematical science, a high standard requiring consistency and validity. The Holy Grail for health care payers is the ability to determine, for every medical intervention, the net increase of health care costs to its net utility (dC/dU), expressed in terms of dollars per quality-adjusted life-years.

Unfortunately, as noted by the authors, medical costs are somewhat inconsistent. Utility values are based upon subjective patient perceptions, and even those reported by the present authors are not always consistent from one of their publications to another (Table 1).

Thus, the cost-utility quotient has an uncertain numerator, cost, and an uncertain denominator, utility.

I would appreciate the authors' comments on the following 2 questions:

1. Why did they report "value gain" and not $/QALY for each of the 4 macular interventions, since they had already done so in a prior study, for all except Lucentis (Table 2)? Isn't the cost-utility of Lucentis what we all really want to know, especially

since the authors have stated that the upper limit for cost-effectiveness in the United States is between $50,000 and $100,000/QALY?

2. Data from this and other studies by the authors have shown that early AIDS and early breast cancer actually have higher utility values than having 20/20 vision in one eye and 20/40 in the other (Table 3). Is this really valid, since in another of their studies,[4] the authors emphasized that utility values most closely correlate with the visual acuity in the better-seeing eye?

The authors are to be congratulated for their pioneering work in this very difficult endeavor. Thank you.

TABLE 1. COMPARISON OF UTILITY VALUES

HEALTH STATE	UTILITY VALUE (PRESENT STUDY)	UTILITY VALUE (PRIOR STUDY)
Major/severe stroke	0.30	0.12[1]
Renal transplant	0.74	0.84[1]
Mild angina	0.90	0.88[2]
Home dialysis	0.49	0.64[1]
Diabetes mellitus	0.85	0.88[2]

TABLE 2. VALUE GAIN AND $/QALY FOR MACULAR INTERVENTIONS

INTERVENTION	VALUE GAIN (PRESENT STUDY)	$/QALY (PRESENT STUDY)	$/QALY (PRIOR STUDY[3])
Laser photocoagulation	4.4%	Not reported	6,684
Intravitreal Macugen	5.9%	Not reported	59,787
PDT with verteporfin	7.8%-10.7%	Not reported	27,945
Intravitreal Lucentis	>15%	Not reported	Not reported

TABLE 3. COMPARISON OF HEALTH STATE AND UTILITY VALUE

REFERENCE	YEAR	HEALTH STATE	UTILITY VALUE
Survey of Ophthalmology[2]	2003	AIDS, CD4 count range 201-300 (normal range, 500-1500)	0.94
Present study	2007	Cancer, breast, early stage, lumpectomy or mastectomy	0.94
Survey of Ophthalmology[2]	2003		
Present study	2007	20/20 (with ≤20/40 in the other eye)	0.92
Transactions of the AOS[1]	1999		

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DR. DAVID K. COATS: I have no conflicts. I just have one question about the methodology you described. For example, you mentioned the time tradeoff example in which a utility of one was 20/20 vision restored permanently. You contrasted that situation with other health states where perfect health was restored, but you did not use the term, "permanently". Do you believe that the use of the term "permanently" in this context may cause patients to overvalue vision acuity?

DR. TIM STOUT: No conflict. If you assume that the average macular degeneration patient will receive intravitreal injections three times every year for five years, and if you also assume equal efficacy for ranibizumab (Lucentis, Genentech, Inc., South San Francisco, CA)) and bevacizumab (Avastin, Genentech, Inc., South San Francisco, CA) could you calculate the benefit for Avastin relative to Lucentis?

DR. MICHAEL H. GOLDBAUM: No conflict. In the beginning of your talk you had to qualify that meaning of “value” because “value” to people in the field means something different than “value” to a knowledgeable lay person. I wonder if the experts in the field could consider a changing the name to something like “utility based medicine” or “utility cost based medicine” and thereby relieve some of the confusion. How would you determine if there is a significant difference in “utility cost” or “utility”?

DR. ALAN L. ROBIN: I would like to make a personal comment about my mother who recently participated in the PRONTO study conducted by Phil Rosenfeld. If you consider the utility value of improving visual acuity in the only eye of a patient from 20/200 to 20/50 with three injections that resulted in avoiding nursing home placement and the need for private care for three years at a cost of $4,000 per month, preventing a fall, and increasing life expectancy, then there is great value. I recommend that the author read Bill Smiddy’s on-line presentation in Ophthalmology on the cost of improving vision with Lucentis treatment, approximately $2,000+ per line of central visual acuity. I also invite him to join me, Kevin Fritz, Steve Kymes, Phil Rosenfeld, and Bill Smiddy in a developing a better evaluation for the cost of these newer expensive therapies.

DR. IRENE H. LUDWIG: No conflicts. I would like to question the broadly held assumption that switching to a generic drug will automatically save many billions of dollars. Because drug companies operate with profit margins of about 5%, switching a profit center from one drug will require increasing the cost of other drugs exponentially. I wonder if you have examined this potential explanation for the extremely high cost of the newer drugs.

DR. GEORGE O. WARING, III: I am a consultant for a refractive surgery company and that is the basis for my question. Gary, do you have a different paradigm for determining the utility of refractive surgery? With this elective intervention we do not prevent blindness, but produce a major impact on the quality of life. Can you comment on how to assess the utility of this somewhat softer kind of value based medicine that does not have the prolongation of life or death as an end result?

DR. JERRY SEBAG: No conflicts of interest. I have a question relating to the calculation of cost. Insofar as patient and office staff involvement in the administration of photodynamic therapy (PDT) is concerned, it is far more laborious, involves more people, takes more time, and impacts more greatly the immediate postoperative lifestyle than does an intraocular injection. I wonder how this is calculated into the outcome.

DR. GARY C. BROWN: I will try to answer as many of the questions as I can. Utilities can vary greatly with different conditions. For example, the outcome of a stroke can vary from 0.99 indicating no effect of the condition, to 0.20 associated with the inability to speak, to 0.40, where if you can move your arms normally. You must define the specific health state and the precise question you wish to assess with the intervention. Someone asked if “perfect health” is the same as “perfect health permanently”. The answer is “no”. You must define the questions and the health status completely. Regarding the utility of Avastin versus Lucentis, we have not yet determined these values. Obviously, if both drugs have the same utility value, then the importance of the difference in cost will be considerable. Mike Goldbaum asks if the term “utility based medicine” may be more acceptable. We believe that “value based medicine” is appropriate. I believe that we co-introduced term to Mark McClellan. Six months after we met him, he described his concept of value based purchasing. Someone asked how to differentiate utilities. You can do this quite well with the use of confidence intervals. A comment was made regarding an excellent paper by Bill Smiddy that considered cost alone. There are many different concepts, such as cost minimization analysis, cost benefit, cost effectiveness, cost utility, and simply cost analysis. When we discuss cost utility, we consider all costs and benefits of the intervention. I believe that drug companies deserve whatever rewards they receive as a result of their hard work, on the other hand, they have had the highest return on equity of any industry over the last three decades, so they are not exactly starving at this point. Remember that they make 60% of their profit in the United States.