Volume 13 • Number 6 • 2010
VALUE IN HEALTH

An Ounce of Prevention Is Worth a Pound of Cure: A Cost-Effectiveness Analysis of Incidentally Detected Aneurysms in Functional MRI Research

Mohsen Sadatsafavi, MD, MHSc,[1] Carlo Marra, PharmD, PhD,[1] David Li, MD,[2] Judy Illes, PhD[3]

[1]Collaboration for Outcome Research and Evaluation, Faculty of Pharmaceutical Sciences, The University of British Columbia, Vancouver, BC, Canada; [2]Department of Radiology and Division of Neurology, Department of Medicine, Faculty of Medicine, The University of British Columbia, Vancouver, BC, Canada; [3]Division of Neurology, Department of Medicine, The University of British Columbia, Vancouver, BC, Canada

ABSTRACT

Purpose: Despite ongoing debate about best practices for managing incidentally detected findings in brain research studies using magnetic resonance imaging (MRI), this issue has not been investigated from a health economics viewpoint. We applied a decision-analytic approach to assess the benefit of various strategies for functional MRI (fMRI) studies using intracranial aneurysms (IA) as a model.

Methods: A decision tree and Markov model were created to simulate the impact on the lifetime costs and quality-adjusted life-years (QALY) of four different strategies for review of scans for the presence of IA. To populate the decision model, we used current evidence from the literature and results from a survey of experts.

Results: Review of the anatomical scans by a nonspecialist is not cost-effective in any of the subgroups of participants. Full clinical examination of women with a positive family history before enrollment in a study is cost-effective. Cost-effectiveness of reviewing scans obtained from women without a family history and men with a positive family history of IA depends on the willingness-to-pay (λ) for a QALY: at λ of \$50,000/QALY, review of scans by a specialist is cost-effective, whereas at λ of \$100,000/QALY, a full clinical workup is the best option. Compared with not reviewing any scans, a customized strategy for each subgroup of participants results in an incremental cost-effectiveness ratio of \$12,503 for λ = \$50,000/QALY and \$32,767 for λ = \$100,000/QALY.

Conclusion: Tailored strategies based on the characteristics of research participants and λ for one QALY are needed to address the problem of incidental findings in research fMRI studies.

Keywords: cardiovascular disease, cost-utility analysis, economic evaluation, functional neuroimaging.

Introduction

Incidental findings in healthy subjects or in patients recruited for research are defined as observations of potential clinical significance discovered unexpectedly and unrelated to the purpose of the study [1]. In brain research involving magnetic resonance imaging (MRI) for which the problem of incidental findings has had particular importance, 2% to 8% of anomalies that are detected require clinical follow-up with mostly low, but occasionally a high, degree of urgency [2,3]. The question as to how these findings should be handled in the context of purely experimental imaging research, however, has been a topic of ongoing debate and remains unresolved [1,4]. Strategies vary widely across laboratories and institutions [5,6], with options ranging from inaction (i.e., images are not screened for anomalies) to full clinical-grade imaging of all participants before their enrollment in a study [4].

The value of any strategy for the management of incidental findings hinges upon the trade-off between the benefits that come from the unexpected diagnosis and treatment of potentially health-threatening abnormalities on the one hand, and the extra costs and possible psychological effects caused by false-positive findings and/or overestimation of the significance of findings on the other. Although such trade-offs have been debated extensively in the literature, there has not been any rigorous, quantitative analysis based on decision theory. As a health policy issue, these considerations are pivotal because research and health-care budgets are limited. The decision to spend resources on one particular approach is often at the expense of other alternatives [7].

In the present work, we investigated different strategies to manage incidental findings in brain functional MRI (fMRI) research based on methods of economic evaluation. The literature suggests that vascular anomalies are the most prevalent types of incidental findings [8]. Among the various brain diseases, each with a distinct natural history and diagnostic and therapeutic pathway, intracranial (vascular) aneurysms (IA) are one of the most devastating [9]. If left untreated, IAs may spontaneously rupture and cause subarachnoid hemorrhage (SAH), which can be associated with high mortality and morbidity. There are, however, effective and relatively safe interventions for IAs. This makes IAs a relevant first target to rigorously evaluate the merit of different screening approaches to research fMRI studies. The aim of the present analysis was therefore to use IA as a model, along with current best evidence and expert opinion, to maximize expected benefit in relation to expected costs with respect to incidental findings in the context of research fMRI studies.

Materials and Methods

We investigated four strategies for handling IAs in brain imaging research involving participants 18 years and older who self-report good health: 1) research scans are not routinely reviewed, and no diagnostic or therapeutic workup is performed on any participant; 2) research scans are reviewed by a researcher, often a graduate student or postdoctoral fellow with no formal clinical

Address correspondence to: Carlo Marra, Faculty of Pharmaceutical Sciences, The University of British Columbia, 2146, East Mall, Vancouver, BC, Canada V6T 1Z3. E-mail: carlo.marra@ubc.ca

10.1111/j.1524-4733.2010.00755.x

training in radiology ("nonspecialist"), and are referred to an MR-trained radiologist ("specialist") for evaluation if a brain anomaly is detected; if the finding is confirmed to be suspicious by the specialist, the participant is referred for a full diagnostic workup; 3) research scans are referred directly to an MR radiologist for formal review, and subjects with suspicious findings are sent for full diagnostic workup; and 4) prior to study enrollment, all research participants undergo a full workup including clinical-grade magnetic resonance angiography (MRA).

We simulated the costs and health outcomes of these strategies separately in 12 subgroups of research participants defined by three factors: age group (18–40, 40–60, and >60 years), sex, and family history of IA. Positive family history was defined by at least two first-degree relatives with IA/SAH. These three factors are both easy to elucidate, and predictive of the risk of harboring IAs [9]. The outcomes of the model were the costs (measured in USD for the year 2007) accrued to society and the overall quality of life of research participants. Both costs and health outcomes were estimated through the lifetime of research participants. The perspective of our analysis was societal. Health outcomes were expressed as quality-adjusted life-years (QALYs). We applied a future discount rate of 3% to both cost and effectiveness outcomes.

A Decision Model for Incidental Finding of IAs

A decision-analytic model was built to simulate the natural history of IA, the performance of diagnostic modalities, and the impact of treatment for a hypothetical cohort of research participants. A simplified illustration of the structure of the decision model is presented in Figure 1. The analytic model consisted of a decision tree representing alternative strategies for initial management and further workup of a finding on an fMRI scan, and a Markov model that simulated the remaining life-years of a hypothetical individual. Each cycle in the Markov model corresponded to 1 year, and the model was run for the lifetime of the simulated subjects. In all strategies, individuals with a confirmed IA were given appropriate therapy, which might be surgical treatment (clipping), nonsurgical endovascular treatment (coiling), or assigned to "watch and wait" period during which the subject does not receive treatment but is followed on a regular basis [10,11]. Treatment has its own risk of immediate mortality or permanent morbidity.

The model further assumed that subjects with an aneurysm that did not undergo a formal review of their scans, or those whose scans were reviewed but incorrectly classified as negative, will live without the knowledge of their condition. They might develop SAH or die from other causes. Those who develop SAH might die immediately or might receive surgical/endovascular treatment, which in turn has its own risk of adverse events resulting in mortality or morbidity. Those who survive SAH and surgical/endovascular intervention might still suffer from permanent disability.

Evidence Synthesis

The point estimates and probability distribution of parameters used in the model are presented in Table 1. We used the published literature to estimate the model parameters. If the literature did not provide evidence on a particular aspect of the model, we sought expert opinion. The latter was the case for estimating the accuracy of detecting IAs on the anatomical scans obtained before the acquisition of functional data by an MR radiologist or a non–clinically trained researcher. We used a survey questionnaire (please see the online Supporting Information at: http://www.ispor.org/Publications/value/ViHsupplementary/ViH13i6_asp) to systematically investigate expert opinion about sensitivity and specificity of detecting an IA as a function of IA size and reviewer expertise. Responders were asked to choose the option that was closest to their opinion on a 10-category scale (with 10% increments). The survey was sent to 33 MR radiologists, neuroradiologists, and neuroimagers with known research and clinical MR expertise in North America and Europe. We received 10 responses (response rate 30%).

Costs were modeled in USD ($) for the year 2007 (Table 1). We assigned zero costs to the initial evaluation by the nonspecialists and considered elicitation of age and sex, and family history of aneurysm from participants as a routine part of the prescan interview, thus accruing no additional costs. We used the medical component of the consumer price index [12] to adjust costs reported in the literature for years other than 2007. Annual direct costs for the first 2 years after SAH were estimated from Taylor et al. [13]. To calculate annual costs for the third and subsequent years, we first ran the model to estimate the remaining life expectancy of individuals after SAH within each age group. The discounted value of lifetime costs (adjusted to year 2007 values) after the second year was considered equivalent to the lump-sum cost of stroke at the start of the third post-SAH year. This value, estimated from Taylor et al. [13], was then amortized into installments of equal size over the estimated remaining years, with a discount rate of 3%. SAHs that resulted in death in the same admission were assumed to incur 65% of the total direct costs of the first year [14]. We assumed that the costs of the complication of treatment for IA equal that of ischemic stroke, and estimated the lifetime costs of IA treatment complication accordingly [13]. We followed the recommendation of the US Panel on Cost-Effectiveness in Health and Medicine [15] and excluded productivity costs from the reference case analysis.

Utilities were estimated from various sources from the literature and are presented in Table 1. We used US norm values of EQ-5D, by age group and sex, as the baseline utility for the normal population [16]. Because the literature is very limited regarding the psychological impact of knowing about the presence of an IA, we used the results of a prospective Danish study on aortic abdominal aneurysm treated conservatively ("watch and wait"), which reported 5% to 7% lower quality of life scores than in the general population (measured by screen QL, a generic quality of life questionnaire) [17]. The quality of life of patients improved after surgical treatment and was comparable to that of the normal population. Based on these results, we assumed a reduction in utility of 0.05 for individuals who are diagnosed with IA but are being followed with a "watch and wait" conservative approach. We assumed that the experience of having a brain aneurysm or SAH in the past does not reduce the quality of life after successful treatment without residual morbidity.

Analysis

We calculated the incremental cost-effectiveness ratio (ICER) between successively more expensive strategies (strategy 2 vs. 1, strategy 3 vs. 2, and strategy 4 vs. 3). However, if a strategy was dominated (higher costs and lower QALYs) by the previous strategy, it was removed from the subsequent ICER calculations.

In determining the cost-effective strategy for each subgroup of individuals, a threshold value for QALY (willingness-to-pay, λ) has to be established [18]. The most common value for λ used in the contemporary literature is $50,000/QALY; however, there has been recent evidence that society is actually paying a much higher value for one QALY or life-years gained [19,20]. Therefore, we conducted the analysis for both willingness-to-pay

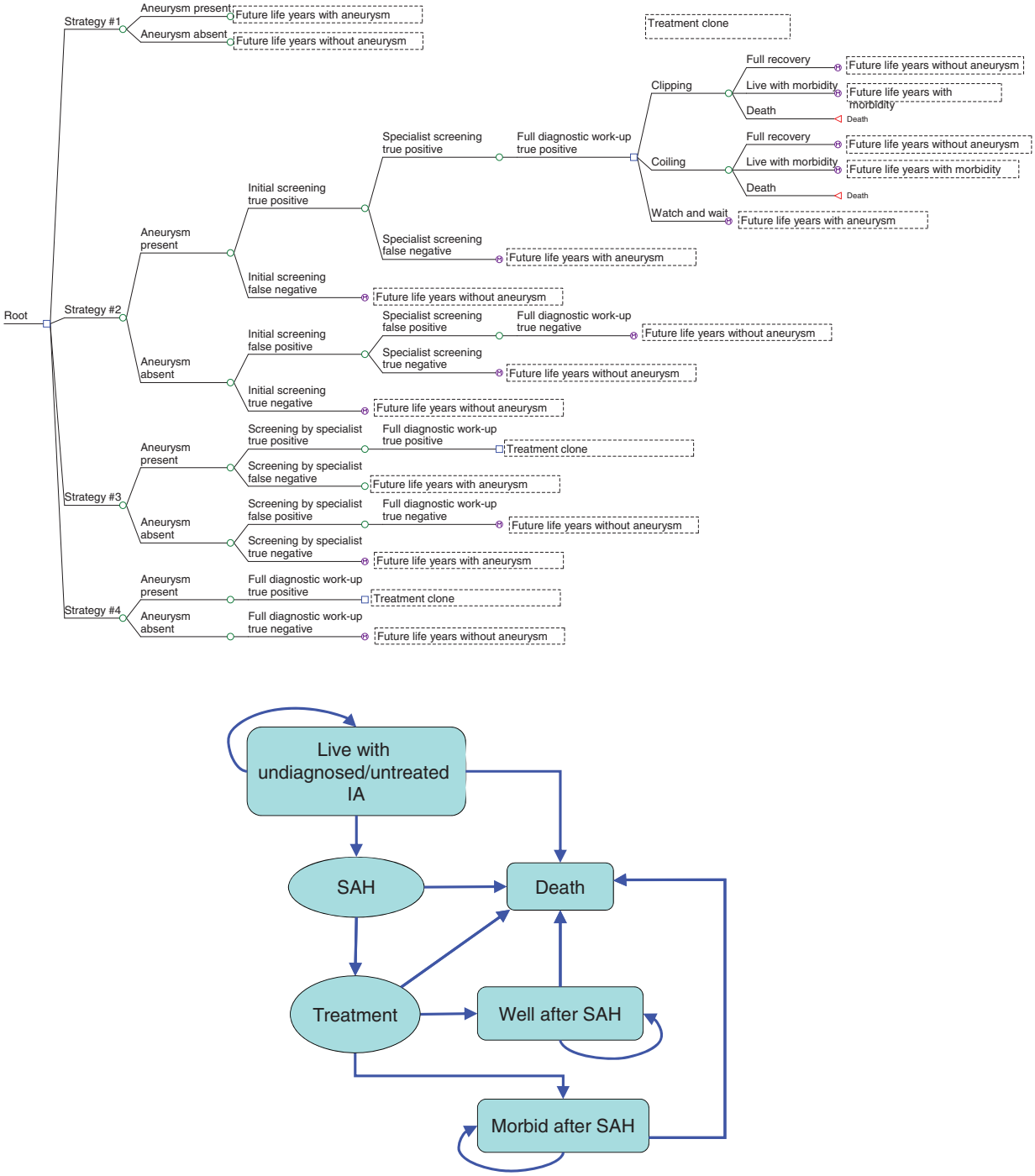

Figure 1 Schematic illustration of the decision tree (top, see text)* and Markov model simulating future life-years of hypothetical individuals with untreated aneurysm in the model (bottom). *For simplicity, stratification on baseline covariates and categorization of aneurysms by size are omitted from the illustration, and the full diagnostic workup is represented as a single step. Rectangles are states at which subjects remain for at least 1 year. Ovals are snapshot events. SAH, subarachnoid hemorrhage.

values of $50,000/QALY and $100,000/QALY. Because the analysis was separately run for each of the 12 subgroups of research participants, we were able to construct a *customized* strategy by picking the optimal strategy within each subgroup. The optimal strategy was determined to be the one with the highest net monetary benefit (NMB) [21]. We then calculated the societal costs and QALYs associated with such customized strategy by weighted-averaging the costs and QALYs of the strategy with the highest NMB within each subgroup, with weights being the relative proportion of each subgroup in the population of typical fMRI research participants. That is, if the proportion of subjects within each of the 12 subgroups is p1, p2, . . . , p12, and

Table 1 Parameters of the model*

Parameter	Mean value (95% CI)	Distribution	Reference
Prevalence of aneurysm			
20–40	0.014 (0.008–0021)	Beta	[34]
40–60	0.018 (0.014–0.021)	Beta	
>60	0.022 (0.018–0.024)	Beta	
RR for aneurysm with a positive family history	4.0 (2.7–6.0)	Log-normal	[34]
RR for aneurysm for female (vs. male)	1.25 (0.9–2.0)	Log-normal	[34]
Proportion of aneurysms by size (mm)			
Small (<6)	0.72	Dirichlet distribution assuming estimates are based on a sample of 100 observations	[34]
Medium (6–10)	0.21		
Large (>10)	0.07		
Sensitivity of the nonspecialist (by aneurysm size, mm)		Multivariate logit-normal distribution	Survey (see text)
Small (<6)	19.2% (6.3–39.6)		
Medium (6–10)	34.1% (17.2–55.1)		
Large (>10)	60.6% (31.9–82.6)		
Specificity of the nontrained researcher	80.8% (93.7–60.4)		
Sensitivity of the specialist (by aneurysm size, mm)			
Small (<6)	33.4% (7.7–74.4)		
Medium (6–10)	49.6% (24.0–80.1)		
Large (>10)	77.5% (54.6–92.8)		
Specificity of the specialist	88.7% (80.2–92.9)		
OR for consistent reading of the same scan by nonspecialist and specialist	2.0 (1.0–3.0)	Uniform	Assumption
Accuracy of clinical-grade imaging			
Sn of CTA (small IA)	0.61 (0.52–0.70)	Beta	[35]
Sn of CTA (medium-sized IA)	0.94 (0.90–0.97)		
Sn of CTA (large IA)	0.99 (0.97–1.0)		
Sp of CTA	0.95 (0.89–0.98)		
Sn of MRA (small IA)	0.47 (0.34–0.61)		
Sn of MRA (medium-sized IA)	0.92 (0.88–0.96)		
Sn of MRA (large IA)	0.99 (0.96–1.0)		
Sp of MRA	0.92 (0.88–0.94)		
Annual incidence of SAH in those with IA			
Based on Wermer et al.			
All aneurysms†	0.00887 (0.0067–0.01)	Log-normal	[29]
RR for medium vs. small	2.3 (1.0–5.2)	Log-normal	[29]
RR for large vs. small	7.5 (3.8–14.2)	Log-normal	[29]
Based on ISUIA (mm)			
Small (<6)	0.00017	Fixed (used only in deterministic sensitivity analysis)	[36]
Medium (6–10)	0.01273		
Large (>10)	0.02672		
RR of SAH for female (vs. male)	1.6 (1.1–2.4)	Log-normal	[29]
Adverse events associated with treatment of aneurysm			
Immediate mortality (clipping)	0.026 (0.02–0.033)	Beta	[37,38]
Immediate mortality (coiling)	0.004 (0–0.012)	Beta	
Long-term morbidity (clipping)	0.058 (0.051–0.065)	Beta	
Long-term morbidity (coiling)	0.028 (0.016–0.047)	Beta	
Adverse events associated with SAH			
Immediate mortality	0.45 (0.32–0.67)	Beta	[39]
Long-term morbidity	0.15 (0.10–0.20)	Beta	[39]
Costs			
CTA	774.3 (467.6–1157.0)	Gamma	[40]
MRA	627.0 (347.1–989.9)	Gamma	[27]
Preoperative angiography	1,569.2 (812.3–2571.2)	Gamma	[27]
Cost of treatment of unruptured aneurysm			
Surgical	32,332 (21,739–44,996)	Gamma	[37]
Nonsurgical	26,560 (15,937–39,853)	Gamma	
Acute cost of SAH			
Annual cost of morbidity due to SAH	Direct costs year 1: 65,887 (40,239–97,731) Direct costs year 2: 8,977 (5,483–13,318) Direct costs other years: 5,588 (3,413–8,290) Annual indirect costs: 22,354 (13,654–33,163)	Gamma	[13]
Annual cost of morbidity due to IA complications	Direct costs year 1: 31,841 (19,449–47,237) Direct costs year 2: 11,021 (6,731–16,350) Direct costs other years: 5,588 (3,413–8,290) Annual indirect costs: 28,850 (17,622–42,801)	Gamma	[13]
Utilities			
Well without aneurysm	Age / Sex / Mean 18–40 / Male / 0.89 Female / 0.89 40–60 / Male / 0.88 Female / 0.87 >60 / Male / 0.86 Female / 0.84	Normal with standard deviation of 0.01	US norm values for EQ-5D [16]
Well with confirmed aneurysm (duration: lifetime)	Utility of "well without aneurysm" minus 0.05 (0.02–0.07)	Beta	[17]
Well after successful treatment of aneurysm/SAH (duration: lifetime)	Same as "well without aneurysm"	Fixed	Assumption
Permanent morbid after treatment of aneurysm (duration: lifetime)	0.7 (0.6–0.8)	Beta	[41]
Permanent morbidity due to SAH (duration: lifetimes)‡	0.26 (0.11–0.39)	Beta	[42,43]
Immediate postsurgery (duration: 1 month)	0.6 (0.5–0.7)	Beta	[41]

*The parameters of the distributions were fitted to match the mean and upper bound of the reported CI values.
†Fixed-effect pooling of three categories of follow-up.
‡Based on the moderate/severe disability after stroke.
CI, confidence interval; IA, intracranial aneurysm; OR, odds ratio; RR, relative risk; SAH, subarachnoid hemorrhage; Sn, sensitivity; Sp, specificity.

Table 2 Reference case results

Strategy	Cost (95% CI)	QALY (95% CI)	ICER
1	$225.9 (126.2–373.5)	26.5015 (25.9378–27.0301)	Ref
2	$268.0 (151.3–461.9)	26.4972 (25.9332–27.0401)	Dominated (vs. strategy 1)
3	$404.2 (259.2–608.2)	26.5068 (25.9450–27.0466)	$33,864 (vs. strategy 1)
4	$1,004.0 (699.5–1,335.8)	26.5132 (25.9465–27.0514)	$93,392 (vs. strategy 3)
Customized (λ = $50,000/QALY)	$316.3 (211.9–479.6)	26.5087 (25.9492–27.0421)	$12,503 (vs. strategy 1)
Customized (λ = $100,000/QALY)	$580.6 (422.6–768.1)	26.5123 (25.9468–27.0536)	$32,767 (vs. strategy 1)

Costs and QALYs associated with the four reviewing strategies and two customized strategies.
CI, confidence interval; QALY, quality-adjusted life-years.

the cost is, respectively, c1, . . . , c12, then the cost of the customized strategy is $p1 \times c1 + p2 \times c2 + \ldots + p12 \times c12$. The calculation of the QALY, number of IAs detected, and incidence of SAH are also the same. To determine the weights p1 to p12, we pooled the age and sex distribution from a convenience sample of fMRI studies (studies published in English and indexed in Medline during the last 3 months of 2008). Separate customized strategies were constructed for λ-values of $50,000/QALY and $100,000/QALY. We also calculated the ICER between the two customized strategies compared with the strategy of no screening (strategy 1).

The decision tree and Markov model were created and run using the computer program TreeAge (Pro 2008 suite, TreeAge Software Inc., Williamstown, MA). We used R (version 2.8.1) for joint estimation of the accuracy of nonspecialists and specialists in detecting IA (please see the online Supporting Information at: http://www.ispor.org/Publications/value/ViHsupplementary/ViH13i6_asp for statistical analysis of the survey data).

Deterministic and Probabilistic Sensitivity Analysis

We studied the impact of uncertainty in the underlying evidence on the results by conducting both deterministic and probabilistic sensitivity analyses (PSA). In deterministic sensitivity analysis, the values of parameters were changed one at a time to arbitrarily defined extremes, and calculations were repeated. In the deterministic analysis, we also included alternative assumptions about different discount rates (0% and 5%). There is a lack of consensus in the literature on the inclusion or exclusion of productivity costs in economic evaluations conducted from a societal perspective [22,23]. While in the reference case we followed the recommendations of the US Panel on Cost-effectiveness in Health and Medicine and excluded productivity costs, we repeated all analyses with productivity costs included.

We conducted the PSA by assigning probability distributions to uncertain parameters of the model, randomly drawing from the distributions of all uncertain parameters (second-order simulation), and calculating model outcomes; this cycle was repeated 1000 times. The choice of the probability distribution was based on the scale of the parameter (e.g., beta distribution of probabilities, gamma distribution for costs, log-normal distribution for relative risks). Parameters of the distributions were chosen to match the reported standard error or confidence interval (CI) of the parameter. For sensitivity and specificity of specialists and nonspecialists reading fMRI scans, we picked random samples directly from the posterior distribution of parameters from the statistical analysis. PSA was conducted to calculate 95% CI for outputs of the reference case analysis and to calculate the probability that each of the four individual strategies or the customized strategy would be cost-effective in the overall population depending on society's λ (the cost-effectiveness acceptability curve, or CEAC [24]). In constructing the CEAC, we allowed the composition of the customized strategy to be determined separately at each λ-value.

Results

Table 2 presents the costs, QALYs, and ICERs associated with the four strategies and the two customized strategies for λ-values of $50,000/QALY and $100,000/QALY. Compared with strategy 1, the customized strategy based on λ = $50,000/QALY results in a $90.4 (95% CI 41.4.8–169.2) increase in societal costs during the lifetime of subjects and a gain in QALY of 0.0072 (95% CI 0.0025–0.0165). In other words, by adopting such a customized strategy, society would pay $12,503 for obtaining one additional QALY compared with the strategy of not screening research subjects. Likewise, compared with strategy 1, the customized strategy based on λ = $100,000/QALY results in a $354.7 (95% CI 211.8–520.7) increase in societal costs during the lifetime of subjects and a gain in QALY of 0.0108 (95% CI 0.0078–0.0246). In other words, by adopting such a customized strategy, society pays $32,767 for obtaining one additional QALY compared with the strategy of not screening.

Depending on different age groups, sex, family history of IA, and decision-maker's λ, different strategies are cost-effective in different subgroups. Findings can be summarized as follows:

- Review of scans for incidental findings by a nonspecialist (strategy 2) is not cost-effective for any of subgroups.
- In men without a family history of IA, no review of scans is cost-effective.
- Clinical-grade MR examinations including MRA (strategy 4) for women with a positive family history before enrollment in a study are cost-effective.
- For women without a family history and men with a positive family history, the cost-effective strategy is different for the two λ-values: for λ = $50,000/QALY, radiologist review of scans (strategy 3) is cost-effective, whereas for λ = $100,000/QALY, a full clinical-level screening (strategy 4) is the cost-effective option.

Figure 2 illustrates the number of aneurysms detected after initial review and the lifetime incidence of SAH per 1000 individuals. As expected, more aggressive review strategies yield higher aneurysms detection rates and lower rate of future SAH events. For both immediate IA detection and SAH incidence, the customized strategy results in more favorable numbers than the strategy of no review and review by nonclinically trained researcher (strategies 1 and 2), but is less favorable than initial review by specialist and a clinical-grade preenrollment MRI (strategies 3 and 4). Compared with strategies 1 and 2, the customized strategy based on λ = $50,000/QALY averts one

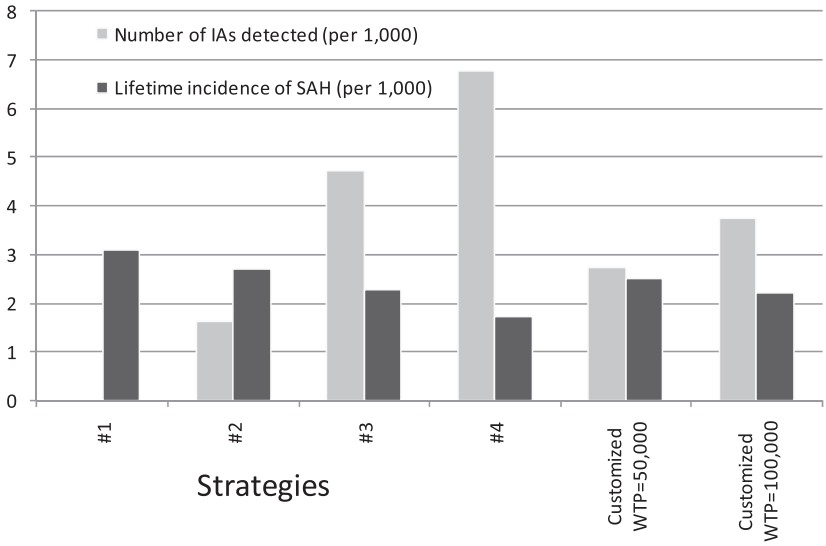

Figure 2 The incidence of true-positive aneurysm detections after initial review and lifetime incidence of SAH corresponding to each strategy. Strategy 1: no review; strategy 2: initial nonspecialist review followed by MR radiologist review; strategy 3: MR radiologist review; strategy 4: clinical-grade MR examination including MRA. IA, intracranial aneurysm; MR, magnetic resonance; MRA, magnetic resonance angiography; SAH, subarachnoid hemorrhage; WTP, willingness-to-pay.

SAH event per 1737 and 5103 participants, respectively, whereas the customized strategy based on λ = \$100,000/QALY averts one SAH per 1150 and 2026 participants.

Deterministic Sensitivity Analysis

When productivity is included in societal costs [13], the lifetime costs of strategies 1 to 4 increases, respectively, to \$408.4, \$434.8, \$552.0, and \$1130.4. The strategies with the highest NMB remain the same, except for the subgroup of male subjects 40 to 60 years old with a positive family history. For this group, strategy 4 is cost-effective at both λ-values. When productivity costs are included, the lifetime cost of the customized strategy is \$477.1 for λ = \$50,000/QALY and \$725.7 for λ = \$100,000/QALY. The corresponding ICERs associated with these two λ-values are \$9429/QALY and \$29,313/QALY, respectively.

We found that the prevalence of IA and the annual rupture rate are the two parameters that have significant impact on the results. At λ = \$50,000/QALY, with either a 20% higher prevalence of IA or 20% higher rupture rate, more aggressive approaches such as full clinical preenrollment screening is cost-effective in female participants, whereas with a 20% lower prevalence or rupture rate, the strategy of not reviewing is cost-effective in male subjects. Results are relatively robust against changes in other model parameters, except when a higher sensitivity (10% higher than the reference case value) is assigned to specialist review, for which strategy 3 becomes cost-effective for male subjects older than 60 years at λ = \$50,000/QALY. More detailed results of one-way sensitivity analysis are presented at http://www.ispor.org/Publications/value/ViHsupplementary/ViH13i6_asp.

Probabilistic Sensitivity Analysis

Results of the PSA are presented in Figures 3 and 4. Figure 3 demonstrates the probability that each of the four strategies has the highest NMB within each subgroup at λ = \$50,000/QALY (a similar graph for λ = \$100,000/QALY is presented in the online Supporting Information at: http://www.ispor.org/Publications/value/ViHsupplementary/ViH13i6_asp). Overall, the uncertainty in the underlying evidence results in considerable doubt in the choice of the cost-effective strategy within each subgroup and hence the composition of the customized strategy. Such uncertainty differentially affects the confidence in the choice of the optimal strategy within each subgroup. For example, there is little doubt that strategy 1 (no review) is the cost-effective option

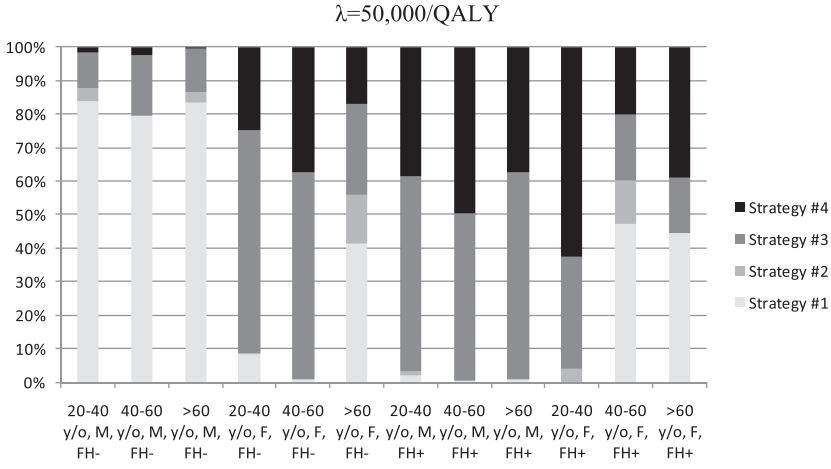

Figure 3 Proportion of times each of the four review strategies was found to be the best option in the stochastic sensitivity analysis. Strategy 1: no review; strategy 2: initial nonspecialist review followed by MR radiologist review; strategy 3: MR radiologist review; strategy 4: clinical-grade MR examination including MRA. MR, magnetic resonance; MRA, magnetic resonance angiography.

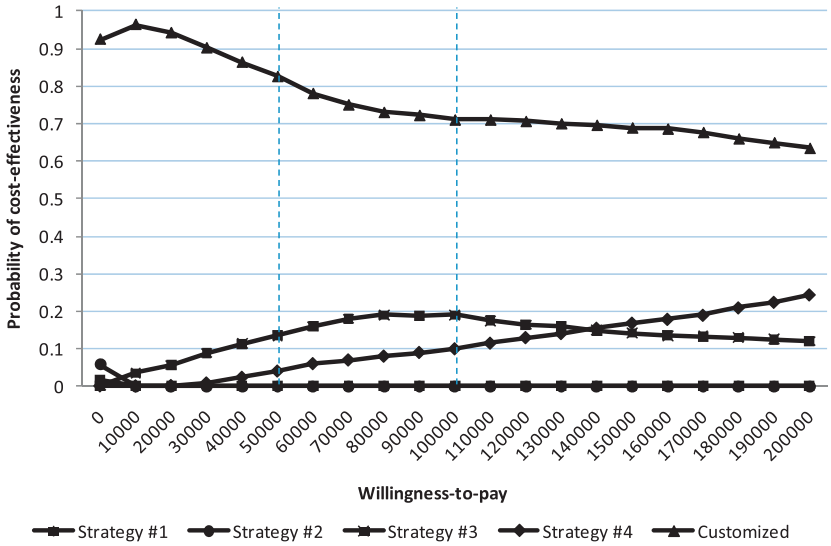

Figure 4 Probability of the cost-effectiveness of different strategies based society's willingness-to-pay for one QALY. Willingness-to-pay: society's willingness to pay to gain one quality-adjusted life-year in an individual. The dashed lines correspond to the willingness-to-pay value of $50,000/QALY and $100,000/QALY. Strategy 1: no review; strategy 2: initial nonspecialist review followed by MR radiologist review; strategy 3: MR radiologist review; strategy 4: clinical-grade MR examination including MRA. MR, magnetic resonance; MRA, magnetic resonance angiography; QALY, quality-adjusted life-years.

for men older than >60 years with a negative family history, whereas strategies 3 and 4 have almost equal chances of being cost-effective for men 40 to 60 years old with a positive family history. However, even with this degree of uncertainty, the strategy of initial review by a nontrained researcher is very unlikely to be a good choice (less than 5% chance in any subgroup).

Figure 4 shows the CEAC for each of the four original strategies and the customized strategy across a wide range of society's λ for one QALY. For the entire range of λ in this figure ($0–200,000/QALY), the probability that the customized strategy is cost-effective is greater than 60%. At the reference values of $50,000/QALY and $100,000/QALY, the customized strategy has 81% and 70% chance of being cost-effective, respectively.

Discussion

The appropriate and efficient use of resources in research, as in health care, is an ethical obligation [7]. Therefore, decisions about how to manage findings detected incidentally in brain imaging studies should be informed by costs that affect both research and health-care budgets [5]. Our results indicate that where the detection of IA in fMRI studies is concerned, there is no single optimal strategy. Rather, from a health economics point of view, an approach that is customized to subjects' sex, age, and family history is needed. We found that review of scans by a researcher not formally trained in radiological interpretation is not appropriate for any of the subgroups. This is mainly due to the fact that the sequential review of scans by the researcher and clinician in this strategy reduces the overall sensitivity (as both should label the scan as positive). Although there is considerable uncertainty as to which option is cost-effective for any particular subgroup, there is little uncertainty that a customized strategy based on the demographic variables of research participants is cost-effective (as demonstrated by the high probability of cost-effectiveness in Fig. 4), and that the strategy of initial review by a nontrained researcher is not a good value for money.

We believe that our results have important public health implications. Our recent review of the literature [25] revealed that from 2002 to 2008, there were 1852 fMRI studies per year involving human subjects on average, with an annual growth rate of 5.8%. Assuming that an fMRI study involves a minimum of 10 subjects, and that results of our analysis will remain valid for the next 10 years [26], implementation of the customized strategy compared with the strategy of initial review by non–clinically trained researcher—a strategy commonly used by research laboratories [6]—will save 1889 QALYs in the next 10 years at the value of $12,503 per QALY. This figure is considered cost-effective based on the interventions in health care that are typically funded [19].

We decided to use two willingness-to-pay thresholds for QALY to compare our results with similar economic evaluations and with the implicit monetary value of a healthy life-year in Western countries. For λ-value of $50,000/QALY, a full clinical workup, including a MRA, is cost-effective for prospective female subjects of all age groups who have a positive family history. Such a strategy also becomes cost-effective for men with a positive family history and all women at λ = $100,000/QALY. Making final decisions on the appropriate screening is the responsibility of investigators, and given the prohibitive costs of clinical examinations for research, an ethically acceptable alternative might be to exclude participants a priori for whom a clinical-level screening is the optimal choice.

In modeling the strategy of review with a clinical-grade MRA, we assumed the information in the fMRI anatomical scan is negligible compared with that of MRA. Thus, the recommendation for an MRA scan for some subgroups implies that mass screening for IAs using MRA would be cost-effective in these subgroups at the population level. This view has been supported recently by a cost-effectiveness analysis by Takao et al. [27]. They found that in family members with two or more affected first-degree relatives, screening compared with no screening had an ICER of $37,400/QALY (year 2003 USD, societal perspective). They did not stratify their analysis on sex. However, by merging the results for men and women, the corresponding ICER for our analysis is $24,630/QALY. Given the complexity of modeling and evidence synthesis, a number of factors might account for this difference. A primary source of difference may be estimates of rupture rates from the International Study of Unruptured Intracranial Aneurysms study by Takao et al. [28] compared with a meta-analysis in our study [29] that included ISUIA in addition to other reports.

Our study has several limitations. Foremost is that the analysis is restricted only to the review of scans for IA, which, although in the category of vascular anomalies seen most fre-

quently [8], is one of many incidentally found brain lesions. According to Vernooij et al. [8], if 1000 healthy volunteers were reviewed with brain MRI, 18 would have aneurysms, 72 would have infarcts, 16 would have benign tumors, 9 would have meningiomas, and many others would have less frequent anomalies. In this context, it is therefore reasonable to expect that the person who reviews the anatomical scans for suspicious findings will look for any abnormality and not just an aneurysm. As such, a finding that may be a false positive with regard to an aneurysm might in fact, with subsequent review by an MR radiologist or with additional clinical imaging, lead to the diagnosis of another condition that could also benefit the research participant. This will definitely alter the numerical values of ICERs reported here and might cause other review strategies to emerge as the best choice. Nevertheless, we believe our results are still valuable. For example, the finding that the strategy of initial review of the scans by non–clinically trained researcher is not an optimal choice because of its low sensitivity is likely to remain valid when other abnormalities are modeled. All in all, given the complexity of incidental findings, a stepwise approach based one lesion type at a time is most practical. Combinations of specific models could be tested in the future to determine the economic value of a general screening strategy for any type of incidental findings.

Although there have been newer studies on the cost of SAH and stroke [30–32] than the one we used as reference for our modeling, none provide lifetime direct and indirect costs of SAH and stroke at the population level. A recent review of cost-of-stroke studies reveals up to 20-fold variation in the estimated costs of strokes even within the same country [14]. The authors of this study reported a pooled value of $28,525 (year 2006 USD) for costs of stroke during the first year, which is very close to the value of $31, 841 (year 2007 USD) reported by Taylor et al. [13] and used in our analysis.

We estimated demographic information and assigned weights to each subgroup to calculate the outcomes of the customized strategy from a convenience sample of fMRI studies. Distribution of age, sex, and family history of IA might be variable across different settings. Although the resulting difference in weights will result in different ICER values for the customized strategy, the composition of the customized strategy will not change by using different weights, and ICER can always be recalculated form the data provided in Table S1 in the online Supporting Information (available at: http://www.ispor.org/Publications/value/ViHsupplementary/ViH13i6_asp).

Because of the lack of information on the diagnostic performance of non–clinically trained researchers and the diagnostic information present in the anatomical but nonangiographic MRI, we had to rely on expert opinion to estimate the relevant components of the model. This method of evidence synthesis is in line with the principle of the hierarchy of evidence [33] and provides, within the limitation of our survey, the best available evidence for our analysis. The performance characteristics of specialists and non–clinically trained researchers might be a critical determinant of the benefit of review, and more systematic approaches to estimate these parameters could be a focus of further research. Nevertheless, in our sensitivity analysis, increasing or decreasing any single index of accuracy (by 10%) had minimal effects on the final results. We also acknowledge that the expertise of the nontrained researcher will vary widely depending on the researcher's experience. The MR experts surveyed gave substantially and consistently lower accuracy ratings to nontrained researchers than to members of the professional groups they represent. Although the statistical model used to pool the results of the survey did allow for the non–clinically trained researcher to have higher accuracy than the specialist, this was the case in only 2% of the PSA samples, consistent with the opinions of the respondents.

As our results show, individual characteristics of research participants have an important bearing on the approach to incidental findings. However, health economics arguments are not the only ones that policymakers and principal investigators might consider in the real world. A customized strategy is naturally more difficult to implement than a universally standardized one, and imperfect adherence will result in reduced cost-effectiveness. If investigators of fMRI studies decide to adopt a universal strategy for research participants, then sending all scans for specialist review (strategy 3) is the best option (see Table 2).

In conclusion, the results of the present decision analysis provide a new source of information toward informed consensus and best practices in the management of incidental findings in fMRI research. We emphasize that many factors play important roles in this interdisciplinary debate that are outside of the realm of a purely decision-theoretic approach. Evidence-based policies forthcoming from all domains—theoretical and empirical—must be kept up to date with the continuously growing body of knowledge about incidental findings.

Acknowledgments

This work is supported by NIH/NIMH #9R01MH84282-04A1 (JI), CIHR/INMHA CNE #85117 (JI), the Canada Research Chairs Program, and the Vancouver Coastal Health Research Institute. Parts of this work were presented at the Canadian Association for Neuroscience Meeting in Vancouver, British Columbia in May 2009. We are grateful of Dr. Stirling Brian, University of British Columbia, for his advice throughout this study, and the two anonymous reviewers for their constructive comments.

References

1 Illes J, Kirschen MP, Edwards E, et al. Ethics. Incidental findings in brain imaging research. Science 2006;311:783–4.
2 Mazziotta JC, Woods R, Iacoboni M, et al. The myth of the normal, average human brain—the ICBM experience: (1) subject screening and eligibility. Neuroimage 2009;44:914–22.
3 Katzman GL, Dagher AP, Patronas NJ. Incidental findings on brain magnetic resonance imaging from 1000 asymptomatic volunteers. JAMA 1999;282:36–9.
4 Illes J, Kirschen MP, Edwards E, et al. Practical approaches to incidental findings in brain imaging research. Neurology 2008;70:384–90.
5 Illes J, Desmond JE, Huang LF, et al. Ethical and practical considerations in managing incidental findings in functional magnetic resonance imaging. Brain Cogn 2002;50:358–65.
6 Illes J, Kirschen MP, Karetsky K, et al. Discovery and disclosure of incidental findings in neuroimaging research. J Magn Reson Imaging 2004;20:743–7.
7 Williams A. Cost-effectiveness analysis: is it ethical? J Med Ethics 1992;18:7–11.
8 Vernooij MW, Ikram MA, Tanghe HL, et al. Incidental findings on brain MRI in the general population. N Engl J Med 2007;357:1821–8.
9 Wardlaw JM, White PM. The detection and management of unruptured intracranial aneurysms. Brain 2000;123:205–21.
10 Takao H, Nojo T. Treatment of unruptured intracranial aneurysms: decision and cost-effectiveness analysis. Radiology 2007;244:755–66.
11 Higashida RT, Lahue BJ, Torbey MT, et al. Treatment of unruptured intracranial aneurysms: a nationwide assessment of effectiveness. AJNR Am J Neuroradiol 2007;28:146–51.
12 U.S. Department of Labor & Bureau of Labor Statistics. Consumer Price Index. Available from: http://www.bls.gov/cpi [Accessed January 1, 2010].

13 Taylor TN, Davis PH, Torner JC, et al. Lifetime cost of stroke in the United States. Stroke 1996;27:1459–66.
14 Luengo-Fernandez R, Gray AM, Rothwell PM. Costs of stroke using patient-level data: a critical review of the literature. Stroke 2009;40:e18–23.
15 Weinstein MC, Siegel JE, Gold MR, et al. Recommendations of the Panel on Cost-effectiveness in Health and Medicine. JAMA 1996;276:1253–8.
16 Fryback DG, Dunham NC, Palta M, et al. US norms for six generic health-related quality-of-life indexes from the national health measurement study. Med Care 2007;45:1162–70.
17 Lindholt JS, Vammen S, Fasting H, Henneberg EW. Psychological consequences of screening for abdominal aortic aneurysm and conservative treatment of small abdominal aortic aneurysms. Eur J Vasc Endovasc Surg 2000;20:79–83.
18 Drummond M. Methods for the Economic Evaluation of Health Care Programmes (3rd ed.). Oxford: Oxford University Press, 2005.
19 Hirth RA, Chernew ME, Miller E, et al. Willingness to pay for a quality-adjusted life year: in search of a standard. Med Decis Making 2000;20:332–42.
20 Cutler DM, Rosen AB, Vijan S. The value of medical spending in the United States, 1960–2000. N Engl J Med 2006;355:920–7.
21 Hoch JS, Briggs AH, Willan AR. Something old, something new, something borrowed, something blue: a framework for the marriage of health econometrics and cost-effectiveness analysis. Health Econ 2002;11:415–30.
22 Brouwer WB, Koopmanschap MA, Rutten FF. Productivity costs measurement through quality of life? A response to the recommendation of the Washington Panel. Health Econ 1997;6:253–9.
23 Olsen JA, Richardson J. Production gains from health care: what should be included in cost-effectiveness analyses? Soc Sci Med 1999;49:17–26.
24 Elisabeth Fenwick KCMS. Representing uncertainty: the role of cost-effectiveness acceptability curves. Health Econ 2001;10:779–87.
25 Federico C, Illes J, Lambra S. Intersecting complexities in neuroimaging and neuroethics. In: Illes J, Sahakian BJ, eds. Handbook of Neuroethics. Oxford: Oxford University Press, 2011.
26 Philips Z, Claxton K, Palmer S. The half-life of truth: what are appropriate time horizons for research decisions? Med Decis Making 2008;28:287–99.
27 Takao H, Nojo T, Ohtomo K. Screening for familial intracranial aneurysms: decision and cost-effectiveness analysis. Acad Radiol 2008;15:462–71.
28 The International Study of Unruptured Intracranial Aneurysms Investigators. Unruptured intracranial aneurysms—risk of rupture and risks of surgical intervention. International Study of Unruptured Intracranial Aneurysms Investigators. N Engl J Med 1998;339:1725–33.
29 Wermer MJ, van der Schaaf IC, Algra A, Rinkel GJ. Risk of rupture of unruptured intracranial aneurysms in relation to patient and aneurysm characteristics: an updated meta-analysis. Stroke 2007;38:1404–10.
30 Roos YBWEM, Dijkgraaf MGW, Albrecht KW, et al. Direct costs of modern treatment of aneurysmal subarachnoid hemorrhage in the first year after diagnosis. Stroke 2002;33:1595–9.
31 Lee WC, Christensen MC, Joshi AV, Pashos CL. Long-term cost of stroke subtypes among Medicare beneficiaries. Cerebrovasc Dis 2007;23:57–65.
32 Reed SD, Blough DK, Meyer K, Jarvik JG. Inpatient costs, length of stay, and mortality for cerebrovascular events in community hospitals. Neurology 2001;57:305–14.
33 Barton S. Which clinical studies provide the best evidence? The best RCT still trumps the best observational study. BMJ 2000;321:255–6.
34 Rinkel GJ, Djibuti M, Algra A, van Gijn J. Prevalence and risk of rupture of intracranial aneurysms: a systematic review. Stroke 1998;29:251–6.
35 White PM, Wardlaw JM, Easton V. Can noninvasive imaging accurately depict intracranial aneurysms? A systematic review. Radiology 2000;217:361–70.
36 Wiebers DO, Whisnant JP, Huston J, et al. Unruptured intracranial aneurysms: natural history, clinical outcome, and risks of surgical and endovascular treatment. Lancet 2003;362:103–10.
37 Johnston SC, Gress DR, Kahn JG. Which unruptured cerebral aneurysms should be treated? A cost-utility analysis. Neurology 1999;52:1806–15.
38 Johnston SC, Dudley RA, Gress DR, Ono L. Surgical and endovascular treatment of unruptured cerebral aneurysms at university hospitals. Neurology 1999;52:1799–805.
39 Hop JW, Rinkel GJ, Algra A, van Gijn J. Case-fatality rates and functional outcome after subarachnoid hemorrhage: a systematic review. Stroke 1997;28:660–4.
40 Dehdashti AR, Binaghi S, Uske A, Regli L. Comparison of multislice computerized tomography angiography and digital subtraction angiography in the postoperative evaluation of patients with clipped aneurysms. J Neurosurg 2006;104:395–403.
41 Yoshimoto Y, Wakai S. Cost-effectiveness analysis of screening for asymptomatic, unruptured intracranial aneurysms. A mathematical model. Stroke 1999;30:1621–7.
42 Post PN, Stiggelbout AM, Wakker PP. The utility of health states after stroke: a systematic review of the literature. Stroke 2001;32:1425–9.
43 Gage BF, Cardinalli AB, Albers GW, Owens DK. Cost-effectiveness of warfarin and aspirin for prophylaxis of stroke in patients with nonvalvular atrial fibrillation. JAMA 1995;274:1839–45.