Current implications for the efficacy of noninvasive screening for occult intracranial aneurysms in patients with a family history of aneurysms

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Although the technology exists for accurate noninvasive screening for intracranial aneurysms, the efficacy of screening depends on several key parameters of the natural history of aneurysms. Recent studies suggest that the prevalence of intracranial aneurysms may reach 20% in the subpopulation of patients with a family history of these lesions; other key parameters are less certain. The authors investigated factors that impact the efficacy of screening to establish interim guidelines. Three plausible models for the natural history of aneurysms were constructed. For each model the monetary cost of screening and the average gain in life expectancy were computed for a range of screening ages and prevalence rates. It is shown that the efficacy of screening depends on the pattern of aneurysm rupture. If aneurysms develop and rupture rapidly, then screening has no benefit. On the other hand, if aneurysms remain at risk for some time after formation, then screening may improve average life expectancy depending on when it occurs. The authors recommend that patients with a positive family history of aneurysms who are 30 years of age or younger be screened. This recommendation is based on the belief that the gains attributable to screening, assuming a constant rupture rate, outweigh the losses attributable to screening using a decreasing rupture rate model.

KEY WORDS • intracranial aneurysm • unruptured aneurysm • subarachnoid hemorrhage • noninvasive screening

SUBARACHNOID hemorrhage (SAH) from a ruptured intracranial aneurysm is often a devastating event with mortality and grave morbidity rates exceeding 50%.9 The potential to escape these dire consequences exists, and the risk of a fatal hemorrhage or long-term complication can be minimized if an aneurysm can be identified and treated while the patient is still asymptomatic. Although the technology for an accurate noninvasive screening test is now at hand,17,20,21 the efficacy of the screening process has not been established. Several authors have recommended screening for high-risk populations;3,12,13,21,26 however, key parameters regarding the natural history of aneurysms must be ascertained to establish efficacy. These parameters include the prevalence and incidence of aneurysms in various populations and the behavior of aneurysms over time (that is, the likelihood of bleeding and the significance of size and location relative to the risk of rupture), as well as surgical risk.

Recent studies3,8,18 of the prevalence of aneurysms in patients with asymptomatic polycystic kidney disease and a family history of aneurysms suggest that the prevalence in this subpopulation may reach 20%. Similar findings were obtained in a study of patients without polycystic kidney disease but with a positive family history of aneurysms.15 Unfortunately, other key parameters related to the natural history of aneurysms have been obtained primarily from studies with significant methodological bias.14,24

The decision of whether high-risk patients, such as those with a family history of aneurysms, should be screened is complex. Given the unknowns and variables relative to the natural history of aneurysms, we felt it was reasonable to construct a spectrum of models for the natural history of aneurysms. The costs and benefits of screening under each of these natural history models were evaluated to provide guidance in answering current questions about screening. What follows is a methodological construct intended to address questions about the efficacy of screening high-risk populations for intracranial aneurysms. It is acknowledged at the start that this analysis is an intermediate step that will be modified as validation of key parameters in the natural history of aneurysms is obtained.

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Clinical Material and Methods

Models for the Natural History of Aneurysms

An important parameter of the natural history of aneurysms is prevalence. Four recent studies \(3,8,15,18\) have attempted an unbiased estimation of the prevalence of intracranial aneurysms in asymptomatic subjects, including the subpopulation of patients with a family history of aneurysms. Table 1 summarizes the studies’ findings related to this particular subpopulation. Three of these studies \(3,8,18\) involved patients with polycystic kidney disease; in the fourth study \(15\) patients were volunteers undergoing medical evaluation for possible brain disease although they were not known to have any intracranial disorders. The definition of “positive family history” in the latter subpopulation \(15\) was restricted to parents or siblings with SAH; the other studies applied broader definitions that included aunts, uncles, and grandparents \(8,18\) or all blood relatives \(8\).

The observed prevalence of intracranial aneurysms in these study samples ranged from 7% to 22%. The combined estimate of prevalence is 16% with an associated 95% confidence interval of 0.10 to 0.23. Note that this estimate does not account for the true- and false-positive rates associated with the various diagnostic tests used.

Based on estimates of the prevalence of intracranial aneurysms, Levey, et al., \(13\) performed a decision analysis to determine the efficacy of screening. They used a very simple model for the natural history of aneurysms. This model depicted aneurysms as fixed quantities over a lifetime, such that 10-year-old patients have as many aneurysms as fixed quantities over a lifetime. The prevalence rate at age \(Z\), assuming that everyone lives to age \(Z\), is then given by: prevalence rate at age \(Z = \text{incidence rate per year} \times Z\).

We considered a range of incidence rates to describe aneurysm formation over time. We studied constant incidence rates, where a fixed number of new aneurysms form each year, and also increasing incidence rates to represent the scenario in which increasing age brings an increasing risk of intracranial aneurysm formation. Specifically, constant incidence rates were chosen such that at age 40 years the prevalence of aneurysms was 5%, 10%, 20%, or 30% (if no SAH occurs before 40 years), whereas at age 10 the prevalence was 1%, 3%, 5%, and 9%, respectively, and at age 70 years the prevalence was 9%, 17%, 33%, and 47%, respectively. A 1% increase in incidence rate per year was also evaluated, with initial incidence rates selected such that at age 40 the prevalence of aneurysms was still 5%, 10%, 20%, or 30%, but at age 10 the prevalence was 1%, 2%, 4%, and 7%, respectively, and at age 70 the prevalence was 10%, 20%, 37%, and 52%, respectively.

We considered two processes for aneurysm rupture. In the first process the rupture rate was constant. This constant rupture rate can be thought of as the average rupture rate of all aneurysms present at any one time (that is, for all sizes of aneurysms) and has been estimated at 2% per year \(7,10,23\); we also considered rupture rates between 0.5% and 5% per year. In the second mechanism for aneurysm rupture, the rupture rate decreased over time, as hypothesized by Wiebers and colleagues \(21\); when the aneurysm is unstable initially but stabilizes with time if it does not initially rupture. We considered an initial rupture rate of 10% that decreases by 50% each subsequent year, that is, 10% risk of rupture during the 1st year after formation, 5% the 2nd year, 2.5% the 3rd year, and so on. A 10% initial risk of rupture was chosen so that the cumulative risk of rupture over the first 10 years is identical to the cumulative risk of rupture if the rate was constant at 2% per year (see Appendix). We also considered a decrease of 10% per year with an initial risk of 3%.

Thus, three models for the natural history of aneurysms were evaluated. Model 1 has a constant incidence rate and constant rupture rate. Model 2 has an increasing incidence rate and constant rupture rate. Model 3 has an increasing incidence rate and decreasing rupture rate. For each model a baseline prevalence rate of 20% at age 40 years was chosen to reflect the subpopulation of patients with a family history of aneurysms. Under Models 1, 2, and 3 the probabilities of detecting an aneurysm in a 40-year-old patient when the “underlying” prevalence is 20% (that is, the prevalence rate if SAH prior to the age of 40 years did not remove patients from the population and if the diagnostic test was 100% accurate) are 0.14, 0.14, and 0.16, respectively, figures which are in agreement with clinical studies (Table 1).

Calculation of Risks

A program written in Fortran was developed to compute the probability of events at various screening ages. For each of the three models the program computes the probability of a true positive result, the probability of a false positive result, and the probability of SAH before screening, between screenings, and after screening.

We considered the noninvasive screening test to have a specificity of 95% and a sensitivity of 85% or 95%. A sensitivity of 85% describes the ability of cranial computerized tomography and magnetic resonance (MR) angiog-
Table 2

Assumptions in estimating life expectancy in patients with a history of aneurysms

<table>
<thead>
<tr>
<th>Factor*</th>
<th>Baseline Value</th>
<th>Range of Values Considered</th>
</tr>
</thead>
<tbody>
<tr>
<td>prevalence of intracranial aneurysms at age 40 yrs</td>
<td>20%</td>
<td>5%–30%</td>
</tr>
<tr>
<td>rupture rate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>constant annual rate</td>
<td>2%</td>
<td>0.5%–5%</td>
</tr>
<tr>
<td>annual rate of decrease</td>
<td>50%</td>
<td>10%–50%</td>
</tr>
<tr>
<td>specificity of screening test</td>
<td>95%</td>
<td>85%–95%</td>
</tr>
<tr>
<td>specificity of screening test</td>
<td>95%</td>
<td></td>
</tr>
<tr>
<td>permanent neurological complication</td>
<td>0.1%</td>
<td></td>
</tr>
<tr>
<td>rate after arteriography</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mortality rate after SAH</td>
<td>55%</td>
<td></td>
</tr>
<tr>
<td>morbidity rate after SAH</td>
<td>15%</td>
<td></td>
</tr>
<tr>
<td>mortality rate after surgery</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>morbidity rate after surgery</td>
<td>6%</td>
<td></td>
</tr>
<tr>
<td>disability value</td>
<td>75% of perfect health</td>
<td></td>
</tr>
</tbody>
</table>

*SAH = subarachnoid hemorrhage.

We assumed that the monetary cost of screening to detect aneurysms less than or equal to 6 mm in diameter; a sensitivity of 95% describes the ability of the tests to detect aneurysms 10 mm or larger.17,20,21

We assumed that average life expectancy for patients without intracranial aneurysms is 80 years. Further details on the calculation of risks are provided in the Appendix.

Monetary Cost of Screening

Screening of asymptomatic patients for intracranial aneurysms incurs two types of costs: the cost of the diagnostic test and the cost of treatment. At our institution the direct cost of a noninvasive diagnostic test such as MR angiography is approximately $750. Furthermore, a positive MR angiography study at our institution is usually followed by an angiogram with a cost of $1000.

There are two costs associated with the treatment of intracranial aneurysms detected by screening. First, there is the differential cost of treating a patient with aneurysmal SAH versus treating a patient with a detected, unruptured intracranial aneurysm that would eventually rupture if left untreated. This differential cost involves: 1) the frequency with which patients with aneurysmal SAH reach the hospital for medical care; 2) the cost of treating patients with aneurysmal SAH who receive medical care; and 3) the cost of managing patients with unruptured aneurysms. The cost of hospitalization and surgery for an unruptured intracranial aneurysm has been estimated at $27,800.25 However, not all asymptomatic patients will elect surgery. The cost of hospitalization and surgery for aneurysmal SAH is estimated at $38,000.25 However, not all patients with aneurysmal SAH will receive medical care, and it is estimated that only approximately 25% of those who receive medical care undergo surgery.25

The second cost associated with the treatment of intracranial aneurysms detected by screening is the cost of treating a patient with a detected, unruptured intracranial aneurysm that, if left untreated, would never rupture. In terms of patient management these are really false positive aneurysms. Work up of these patients may involve immediate surgery or periodic follow-up examination to detect growth or other changes and, in some cases, eventual surgery.

We restricted this analysis to the direct costs associated with screening, that is, the cost of the screening test itself, the cost of angiography for positive findings, and the cost of managing patients whose aneurysms would never rupture. The average cost D of diagnostic testing per patient was computed as: $750 + p (positive test) × $1000, where p (positive test) is the probability of a positive screening test result. We computed the work-up cost W of managing patients whose detected aneurysms would never rupture as: W = p (TP but never ruptures) × K, where TP is a true positive result and K is the cost of managing these patients. The value of K ranges from zero (if we were able to distinguish aneurysms that were likely to rupture from aneurysms that were unlikely to rupture) to $27,800 (if all patients underwent immediate surgery). For this comparison we set K equal to $27,800. For each of the three natural history models we computed D and W for several screening strategies: a single screening per patient and multiple screens at various ages.

Benefit of Screening for Average Life Expectancy

Table 2 summarizes the assumptions made in estimating average life expectancy. The mortality rate from aneurysmal SAH includes both death before patients reach the hospital and death from complications in the 3 months following the event; it is estimated at 55%.1,16,23 Morbidity after SAH includes hemiparesis, dysphasia, and mental deterioration and the rate is estimated at 15%.22 The mortality and morbidity rates associated with surgical repair have been estimated for the “average” clinical center at 2% and 6%, respectively.22 We assumed that there is no life-threatening risk associated with performing the noninvasive screening test and that patients with a positive test result will be referred for arteriography. The permanent neurological complication rate associated with arteriography was set at 0.1%.6

We assumed that all detected aneurysms would undergo surgical repair. This approach will provide a conservative estimate of the potential gains attributable to screening. As did Levey, et al.,23 we assumed that once a patient with an aneurysm is identified, the patient will be man-
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aged such that the risk of SAH from other aneurysms is negligible. Details of the computation of average life expectancy are given in the Appendix.

Results

Pattern of Risks

Figure 1 illustrates the relationship between the probability of SAH before and after screening under Model 2 (increasing incidence rate, constant rupture rate), with sensitivity and specificity of the screening test equal to 95%. When screening is performed early, say at age 20 years, there is little risk of SAH before screening (< 2%), but there remains a significant risk of rupture after screening (14%). When a later screening age is planned, say at age 40 years, the risk of SAH after screening is reduced (7%), but there is an increased risk of SAH before screening (6%). The probability of a true positive result (dotted line in Fig. 1) increases steadily with age, reflecting the increasing prevalence of intracranial aneurysms. This pattern of change in risks with age is similar for each of the three models of natural history.

Monetary Costs of Screening

Figure 2 depicts the differences in the monetary cost of screening under Model 2 (constant rupture rate) versus Model 3 (rupture rate decreasing by 50% per year). The costs under Model 1 (constant incidence and rupture rates) are similar to the costs for Model 2.

The cost D of diagnostic testing per patient (dotted line in Fig. 2) is similar under both models for aneurysm rupture. For a single screen, the cost increases slightly with the screening age, from $857 to $952 per patient. The diagnostic cost exceeds the cost of the screening test itself ($750) because patients with either true-positive or false-positive results undergo angiography.

The cost associated with both diagnostic testing and work up of patients whose detected aneurysm would never rupture, (D + W), is given by the solid lines in Fig. 2. Work up cost increases steadily with age under both rupture models because the prevalence of detected aneurysms that will never rupture increases with age. Work up cost is nearly three times higher under Model 3 compared with Model 2 because the prevalence of detected aneurysms that will never rupture is nearly three times higher under Model 3.

Benefits in Life Expectancy With Screening

Figure 3 depicts average life expectancy for patients who undergo a single screen at ages between 10 and 70 years under Models 2 and 3, for a screening test with sensitivity and specificity of 95%. In Fig. 3 left the plotting symbols describe the prevalence rate of aneurysms at age 40 years; average life expectancy without screening is indicated by the horizontal lines. Average life expectancy with screening varies with the prevalence rate and the age at which screening occurs. For a prevalence rate of 20%, the greatest gain in average life expectancy is achieved by screening between ages 20 and 30 years: 11 months per patient are gained, on average. In comparison, if screening occurs at age 50 years, the average gain in life expectancy per patient is 6 months.

Similar results are obtained under Model 1. The average gain in life expectancy by screening at age 20 years is 12 months per patient and by screening at 50 years, 5 months.

Table 3 summarizes the months gained in average life expectancy by a second screening as a function of the ages at which the two screens occur. Model 2 is considered here but the results are similar for Model 1. A second screening increases the average life expectancy by 1 to 6 months, depending on when screening occurs. The earlier the first screen occurs, the greater the gain achieved by a second screen. The greatest gain in life expectancy is achieved by screening at ages 20 and 40 years: on average, 17 months of life expectancy per patient are gained.

Similarly, three screens per patient further increase the average life expectancy. A gain of 19 months per patient.
can be achieved by screening at ages 20, 30, and 40 or 50 years, or at ages 20, 40, and 50 years.

Figure 3 right describes average life expectancy for Model 3 when the immediate risk of rupture is 10% or 3% and decreases by 50% or 10%, respectively, each year after aneurysm formation. The plotting symbols denote the percent decrease in the rupture rate per year. If the risk of rupture decreases rapidly over time, that is, a 50% decrease per year, then screening detects so few aneurysms at risk of rupture that the risks associated with arteriography and surgery outweigh any benefits of screening (that is, an average loss in life expectancy of 2 or 3 months by screening at age 20 years or age 50 years, respectively).

Monetary Cost Per Gain in Life Expectancy

Table 4 describes the cost of diagnostic testing and work up per month gained in average life expectancy for Model 2, with sensitivity and specificity of the screening test equal to 95%. For a single screen at age 20 the D + W cost per month gained is $136. The cost increases as the age of screening, whether first or second, increases. By screening at ages 20 and 40 years, the cost per month gained ($199/month) is less than the cost per month gained by a single screen at age 40 years ($279/month).

In comparison, under Model 3 with a decreasing rupture rate of 50%, a single screen at age 20 years costs $2918 per patient and there is a loss of 2 months of life expectancy, on average. If two screenings were to occur at ages 20 and 40 years, the associated monetary cost would be $6065 per patient and the loss in life expectancy 3 months per patient, on average.

Sensitivity Analysis

Prevalence Rate. The gains in average life expectancy attributable to screening under Models 1 and 2 decrease as the prevalence rate decreases; however, a gain in life expectancy is achieved by screening even if the prevalence rate is only 5%. The greatest gain in life expectancy is achieved by screening between ages 20 and 30 years, regardless of the prevalence rate (see Fig. 3 left). The diagnostic testing and work up costs per month of life expectancy gained by screening at age 20 are $373/month and $210/month for prevalence rates of 5% and 10%, respectively.

The loss in average life expectancy attributable to screening under Model 3 decreases as the prevalence rate decreases. However, if the prevalence rate is higher than 20%, say 30%, the loss in average life expectancy increases to 3 months. Likewise, the overall cost decreases if the prevalence rate is lower and increases if the prevalence rate increases.

Accuracy of Screening Test. If the sensitivity of the screening test is 85%, instead of 95%, then the gains and losses attributable to screening and the absolute costs of screening decrease. For example, at a prevalence rate of 20% under Model 2, the gain in life expectancy is 10 months at a cost of $1402 per patient. However, the cost per month gained increases from $136 to $144. Under Model 3, for a single screen at age 20 the loss in life expectancy is reduced by a few days and the cost decreases from $2918 to $2694.

Rupture Rate. If the 10-year cumulative risk of rupture is less than 18%, then the gains in life expectancy attributable to screening under Models 1 and 2 are reduced, and the losses in life expectancy under Model 3 increase. For example, suppose the 10-year cumulative risk of rupture was 5%. Under Model 2, the gain in life expectancy by screening at age 20 years is only 3 months; a second screen at age 40 years adds less than 1 month to the average life expectancy. The cost per month gained by screening at age 20 years is $1038/month and by screening at ages 20 and 40 years is $1694/month. Under Model 3, at a prevalence rate of 20%, the loss in life expectancy increases by about 10 days for a single screen at age 20 years and by 20 days for screening at ages 20 and 40 years; the costs increase by $360 and $772 per patient, respectively.

If the 10-year cumulative risk of rupture is greater than 18%, then the gains in life expectancy attributable to screening under Models 1 and 2 increase, while the costs decrease. Under Model 3 the loss in life expectancy and costs of screening decrease.

Under Model 3, if the rupture rate decreases more slowly, say a 10% decrease annually, then screening at age 20 when the prevalence rate is 20% results in a gain in life expectancy of 1 month per patient, on average (see Fig. 3 right). Two screens at ages 20 and 40 years improve life expectancy by 2 months. However, a single screen at age 50 years results in a loss of 1 month, on average. The cost per month gained by a single screen at age 20 years is $2421/month.

### TABLE 3

*Months gained in average life expectancy by various screening strategies under Model 2*

<table>
<thead>
<tr>
<th>Age (yrs)</th>
<th>Age (yrs) at Second Screen</th>
</tr>
</thead>
<tbody>
<tr>
<td>First Screen</td>
<td>20</td>
</tr>
<tr>
<td>20</td>
<td>10.9 mos</td>
</tr>
<tr>
<td>30</td>
<td>11.0 mos</td>
</tr>
<tr>
<td>40</td>
<td>9.0 mos</td>
</tr>
<tr>
<td>50</td>
<td>5.9 mos</td>
</tr>
<tr>
<td>60</td>
<td>2.7 mos</td>
</tr>
</tbody>
</table>

### TABLE 4

*D + W costs per month gained in average life expectancy by various screening strategies under Model 2*

<table>
<thead>
<tr>
<th>Age (yrs) at First Screen</th>
<th>Age (yrs) at Second Screen</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>$136/mo</td>
</tr>
<tr>
<td>30</td>
<td>$177/mo</td>
</tr>
<tr>
<td>40</td>
<td>$279/mo</td>
</tr>
<tr>
<td>50</td>
<td>$546/mo</td>
</tr>
<tr>
<td>60</td>
<td>$1515/mo</td>
</tr>
</tbody>
</table>

* D = average cost of diagnostic testing per patient; W = average work cost per patient of managing detected aneurysms that would never rupture.
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**Discussion**

The efficacy of screening the subpopulation of patients with a family history of aneurysms will be determined by the pattern of aneurysm rupture. Schievink, et al.,19 and Black2 have noted, as has been demonstrated here by our Model 3, that if aneurysms develop and either rupture rapidly or stabilize over a short period of time, then screening will not benefit those at risk of SAH. Rather, screening will identify those patients with low-risk, stable aneurysms. Without the ability to predict which aneurysms will rupture, these patients are likely to undergo unnecessary surgery. If all patients with unruptured aneurysms were to undergo surgery, a strategy recommended by some11 based on costs and the anxiety of living with an unruptured aneurysm, then a reduction in life expectancy will ensue; we estimate this loss at 2 months, on average, per patient screened at age 20 years. The associated cost of diagnostic testing and work up of false-positive results is $2918 per patient.

If, on the other hand, aneurysms remain at risk of bleeding through a process of constant risk after formation, then screening high-risk, asymptomatic subjects can improve average life expectancy, depending on when screening occurs. We estimate the average gain by screening once at age 20 years to be 11 months, with an associated cost of $1475 per patient or $134 per month gained. As Black2 points out in comparison, mammographic screening for women aged 50 to 70 years is universally recommended and only increases life expectancy by an average of 1 to 2 months per patient screened. The cost of diagnostic testing and work up for false-positive results for women screened annually over a 10-year period is approximately $2500, or $125 per month gained.4

Today’s decision on whether to begin screening patients with a family history of aneurysms is complex because the pattern of aneurysm rupture is still unknown. In addition, some of the assumptions that were made in this analysis greatly impact the results and thus must be considered carefully. First, we have not “discounted” for future effects (that is, adjusted future gains in life expectancy to present-day values). However, “discounting” is commonly used in such analyses to account for most people’s preference for an earlier rather than an extended gain.5 If we apply a 5% discount rate, then the estimated gain under a constant risk model is reduced from 11 months to 5 months. Second, we have assumed a 10-year cumulative risk of rupture of 18% (that is, an annual risk of 2%). Although the risk of rupture for this subpopulation is unknown, the fact that patients are asymptomatic and may tend to have small aneurysms (in recent studies3,8,15,18 only one aneurysm in 20 patients exceeded 10 mm) favors a reduced risk of rupture.22 If, in fact, the risk of rupture is less than the 10-year cumulative risk used here, then the gains achieved by screening under the constant risk model decrease, whereas the losses under the decreasing rupture rate model increase and the costs associated with screening under both scenarios increase. Third, we have assumed for the decreasing rupture rate model that the risk of rupture decreases rapidly (50% decrease in risk per year). However, we have no data on what this rate might be, if indeed aneurysms do stabilize over time. If we assume a slower process toward stabilization, say a 10% decrease in the risk of rupture per year after formation, then screening at age 20 actually increases life expectancy by approximately 1 month per patient, on average. Fourth, we have assumed that all patients with a detected unruptured aneurysm would undergo surgery. This assumption impacts both the estimates of the gain (or loss) in life expectancy and the costs of screening. If we were able to reduce the number of unnecessary surgeries by even 25%, then the gain in life expectancy achievable under the constant risk model would increase by approximately 2 weeks, the loss in life expectancy under the decreased rupture rate model would decrease by 2 weeks, and the costs would decrease by 10% to 15%. Lastly, our models do not consider the possibility of multiple aneurysms forming in a single patient, nor have we considered a model in which the risk of rupture increases over time. Under both of these scenarios, screening is likely to be beneficial.

Our recommendation for screening is based on our belief that the gains attributable to screening under a constant rupture rate model outweigh the losses attributable to screening under a rapidly decreasing rupture rate model. Table 5 compares the losses, benefits, and cost of screening employing four natural history models: a constant 2% annual risk of rupture (the scenario where screening has the greatest potential), a constant 1% annual risk of rupture, a risk of rupture that decreases by 10% annually, and a risk of rupture that decreases by 50% annually (the scenario where screening is detrimental at any age). Based on this comparison, we recommend a single screening for patients 30 years of age and under. At this early age the

<table>
<thead>
<tr>
<th>Screening Age(s) (yrs)</th>
<th>Constant Risk Scenario</th>
<th>Decreasing Risk Scenario</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age(s) (yrs)</td>
<td>Rupture Rate</td>
<td>Rupture Rate</td>
</tr>
<tr>
<td>20</td>
<td>+ 10.9 mo</td>
<td>+ 6.2 mo</td>
</tr>
<tr>
<td></td>
<td>(+ 4.5)</td>
<td>(+ 4.8 mo)</td>
</tr>
<tr>
<td></td>
<td>$1475</td>
<td>$2123</td>
</tr>
<tr>
<td>30</td>
<td>+ 11.0 mo</td>
<td>+ 6.2 mo</td>
</tr>
<tr>
<td></td>
<td>(+ 4.8 mo)</td>
<td>(+ 4.9 mo)</td>
</tr>
<tr>
<td></td>
<td>$1934</td>
<td>$2929</td>
</tr>
<tr>
<td>40</td>
<td>+ 9.0 mo</td>
<td>+ 4.8 mo</td>
</tr>
<tr>
<td></td>
<td>(+ 4.3 mo)</td>
<td>(+ 4.6 mo)</td>
</tr>
<tr>
<td></td>
<td>$2500</td>
<td>$3844</td>
</tr>
<tr>
<td>50</td>
<td>+ 5.9 mo</td>
<td>+ 2.9 mo</td>
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<tr>
<td></td>
<td>(+ 3.0 mo)</td>
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<tr>
<td></td>
<td>$3217</td>
<td>$4883</td>
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<tr>
<td>20 and 40</td>
<td>+ 16.6 mo</td>
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<tr>
<td></td>
<td>(+ 7.2 mo)</td>
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</tr>
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<td></td>
<td>$3308</td>
<td>$4664</td>
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</table>

* D = average cost of diagnostic testing per patient; W = average work up cost per patient of managing detected aneurysms that would never rupture. Prevalence of intracranial aneurysms at age 40 years is 20%. Screening sensitivity = 95%, specificity = 95%. Dollar amounts are estimated D + W costs. Data in parentheses indicate 5% discount for future effects (see Discussion for definitions of discount).
potential benefits of screening are large, at a cost comparable to the cost of annual mammographic screening. Beyond age 30 years the costs of screening are much higher, and there is a loss in life expectancy even under the slower declining risk model. As for two screenings per patient, the benefits are ample under the constant rupture rate model, but the cost is high, particularly under the decreasing rupture rate model; thus, at this time we do not believe a second screening is justifiable.

This work further supports the need for research that will determine: 1) the mechanism of aneurysm rupture; 2) factors impacting the risk of intracranial aneurysm formation, including the pattern of familial inheritance and the association of other disorders such as polycystic kidney disease; and 3) aneurysm characteristics predictive of the likelihood of rupture. Multicenter collaborations utilizing newly available noninvasive diagnostic tools such as MR angiography will be necessary to answer these questions.

Appendix

The Fortran program used the following formulas to calculate risks.

**Notation:**

Let X denote the screening age;

\( p(An)_X \) = the probability of an aneurysm by age Y;

\( p(An)_{Y/Z} \) = the probability of an aneurysm by age Y, given no aneurysm by age Z;

\( p(\text{Rup})_Y \) = the probability of rupture within Y years after formation;

\( p(\text{Rup})_{Y/Z} \) = the probability of rupture within Y years after formation, given no rupture within the first Z years;

\( I_Y \) = the annual incidence rate at age Y;

\( R_Y \) = the annual rupture rate Y years after formation;

SE = the sensitivity of the screening test; and

SP = the specificity of the screening test.

**Probability of an Aneurysm:**

**Constant Incidence Rate**

\[ p(An)_Y = 1.0 - (1.0 - I_Y)^Y \]

<table>
<thead>
<tr>
<th>I</th>
<th>( p(An)_{40} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.00128</td>
<td>0.05</td>
</tr>
<tr>
<td>0.00265</td>
<td>0.10</td>
</tr>
<tr>
<td>0.00564</td>
<td>0.20</td>
</tr>
<tr>
<td>0.00890</td>
<td>0.30</td>
</tr>
</tbody>
</table>

\[ p(An)_{Y/Z} = 1.0 - (1.0 - I_{Y-1}) (1.0 - I_Y) \cdots (1.0 - I_Z) \]

**Increasing Incidence Rate**

\[ p(An)_Y = 1.0 - [(1.0 - I_0) (1.0 - I_1) \cdots (1.0 - I_{Y-1})] \]

where \( I_Y = I_{Y-1} + CI_{Y-1} \), and C is a constant = 0.01 (1% increase in rate per year)

**Probability of Rupture:**

**Constant Rupture Rate**

\[ p(\text{Rup})_Y = 1.0 - (1.0 - R)^Y \]

\[ R \quad p(\text{Rup})_0 \quad p(\text{Rup})_5 \quad p(\text{Rup})_{10} \]

\[ 0.02 \quad 0.0200 \quad 0.09608 \quad 0.18293 \]

\[ p(\text{Rup})_{Y/Z} = 1.0 - (1.0 - R)^{Y-Z} \]

**Decreasing Rupture Rate**

\[ p(\text{Rup})_Y = 1.0 - [(1.0 - R_0) (1.0 - R_1) \cdots (1.0 - R_{Y-1})] \]

where \( R_Y = R_{Y-1} - DR_{Y-1} \)

and D is a constant = decrease in rupture rate per year

\[ D \quad p(\text{Rup})_0 \quad p(\text{Rup})_5 \quad p(\text{Rup})_{10} \]

\[ 0.50 \quad 0.09773 \quad 0.17807 \quad 0.18293 \]

\[ 0.10 \quad 0.03068 \quad 0.11951 \quad 0.18293 \]

\[ p(\text{Rup})_{Y/Z} = 1.0 - [(1.0 - R_Z) (1.0 - R_{Z+1}) \cdots (1.0 - R_{Y-1})] \]

**Probability of a True-Positive Result:**

\[ p(\text{TP}) = p(An)_X (1.0 - p(\text{Rup})_{X-Yx}) \cdot \text{SN} \]

where Yx is the mean age at which an aneurysm forms, given that an aneurysm has formed by age X.

**Probability of a False-Positive Result:**

\[ p(\text{FP}) = (1.0 - p(An)_X) (1.0 - \text{SP}) \]

**Probability of SAH Before Screening:**

\[ p(\text{SAH})_B = p(An)_X p(\text{Rup})_{X-Yx} \cdot \text{SN} \]

**Probability of SAH After Screening:**

\[ p(\text{SAH})_A = p(An)_X (1.0 - p(\text{Rup})_{X-Yx}) (1.0 - \text{SN}) \]

\[ p(\text{Rup})_{80-Yx/X} + (1.0 - p(An)_X) p(An)_{80/X} p(\text{Rup})_{80-Zx} \]

where Zx is the mean age at which an aneurysm forms, given that no aneurysm has formed by age X.

**Average Life Expectancy:**

**Without Screening**

\[ \text{LE}_{w/o} = 80.0 - \left( p(An) \cdot p(\text{Rup}) \cdot \text{mortality/morbidity discounted from SAH} (80 - \text{age at SAH}) \right) \]

**With Single Screening at Age X**

\[ \text{LE}_{w/ scren} = 80.0 - \left( \{ [p(\text{SAH})_B p(\text{mortality/morbidity discounted from SAH}) (80 - \text{age at SAH})] \right) \]

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\[ p(\text{FP}) \times p(\text{arteriography complication}) \times (80 - X) + p(\text{TP}) \times p(\text{arteriography complication or mortality/morbidity discounted from surgery}) \times (80 - X) + p(\text{SAH}) \times p(\text{mortality/morbidity discounted from SAH}) \times (80 - \text{age at SAH}) \]