

# Cost-effectiveness of Adding Magnetic Resonance Imaging to Rheumatoid Arthritis Management

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**Background:** Early, aggressive treatment of rheumatoid arthritis (RA) improves outcomes but confers increased risk. Risk stratification to target aggressive treatment of high-risk individuals with early RA is considered important to optimize outcomes while minimizing clinical and monetary costs. Some advocate the addition of magnetic resonance imaging (MRI) to standard RA risk stratification with clinical markers for patients early in the disease course. Our objective was to determine the incremental cost-effectiveness of adding MRI to standard risk stratification in early RA.

**Methods:** Using a decision analysis model of standard risk stratification with or without MRI, followed by escalated standard treatment protocols based on treatment response, we estimated 1-year and lifetime quality-adjusted life-years, RA-related costs, and incremental cost-effectiveness ratios (with MRI vs without MRI) for RA patients with fewer than 12 months of disease and no baseline radiographic erosions. Inputs were derived

from the published literature. We assumed a societal perspective with 3.0% discounting.

**Results:** One-year and lifetime incremental cost-effectiveness ratios for adding MRI to standard testing were \$204 103 and \$167 783 per quality-adjusted life-year gained, respectively. In 1-way sensitivity analyses, model results were insensitive to plausible ranges for every variable except MRI specificity, which published data suggest is below the threshold for MRI cost-effectiveness. In probabilistic sensitivity analyses, most simulations produced lifetime incremental cost-effectiveness ratios in excess of \$100 000 per quality-adjusted life-year gained, a commonly cited threshold.

**Conclusion:** Under plausible clinical conditions, adding MRI is not cost-effective compared with standard risk stratification in early-RA patients.

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**A**FFECTING 1.5 MILLION Americans during their most productive years, rheumatoid arthritis (RA) has a mean age at onset of between 45 and 55 years, depending on sex and ethnicity, and results in an excess of \$19.3 billion in direct and indirect costs each year.<sup>1-5</sup> Early aggressive treatment has been shown to improve outcomes and increase clinical remission<sup>6</sup>;

## See Invited Commentary at end of article

however, early RA is also more likely to remit spontaneously,<sup>7</sup> and aggressive treatment confers clinical and financial costs.<sup>8</sup> Therefore, accurate risk stratification of early-RA patients is important to enable initiation of aggressive treatment in those at high risk for developing severe disease while sparing those at reduced risk from unnecessary treatment.

Standard risk stratification tools include clinical, laboratory, and radiographic evidence of disease activity and/or damage. Magnetic resonance imaging (MRI) provides supplementary informa-

tion to standard risk stratification.<sup>9,10</sup> Magnetic resonance imaging identifies bone erosions earlier than conventional radiography<sup>9</sup> and can detect bone marrow edema and synovitis, possible erosion precursors.<sup>11,12</sup> Therefore, MRI has been proposed as a more sensitive method of risk-stratifying RA patients to optimize treatment.<sup>13</sup> However, few studies, to our knowledge, have directly compared it to standard risk-stratification tools. No randomized clinical trials, to our knowledge, have sought to determine the optimal role for MRI in the management of early RA. It would be preferential to use MRI only in scenarios that offer detectable clinical benefit at an acceptable cost.

It is unlikely that a trial to define the optimal risk-stratification approach could be undertaken because too many plausible MRI specifications and RA therapeutics exist to make exhaustive testing feasible, it would be difficult to enroll sufficient early-RA patients, and it would require many years of follow-up to capture clinically significant outcome differences. Decision analytic methods provide a rational, evidence-based, and updatable framework to inform clinical, research, and policy decisions. De-

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cision analysis also enables assessment of giving aggressive treatment to all patients at baseline (ie, no risk stratification), given the benefits of early treatment and reduced sensitivity and specificity of risk stratification in early RA. Our objective was to determine the incremental benefits and costs of adding MRI to standard risk stratification in early RA and to compare each of these strategies to a no-risk stratification strategy (“treat all”).

## METHODS

We created a decision analysis model to examine differential outcomes achieved using standard risk stratification only vs with MRI vs a “treat all” strategy. Ours was a hypothetical population of individuals with recent-onset RA ( $\leq 12$  months) and no baseline radiographic erosions (eAppendix; available at <http://www.archinternmed.com>).

### MODEL STRUCTURE AND OUTPUT

The hypothetical patient population contained individuals at high risk for developing severe disease (ie, those who would develop plain radiographic erosions within 12 months, known as having a poor prognosis) and those at lower risk (ie, those who would not develop radiographic erosions, labeled as having a good prognosis). Risk stratification, using standard tests (ie, rheumatoid factor and/or anti-cyclic citrullinated peptide antibody positivity and disease activity assessment) only or with MRI, was used to discriminate between poor-prognosis and good-prognosis patients (**Figure 1**; “risk stratification”). On the basis of the results of testing, a treatment regimen was assigned. Treatment regimens in the model consisted of 3 tiers that represent accepted clinical practice in the United States and are consistent with recent practice guidelines<sup>14</sup>: optimized methotrexate monotherapy, escalated as needed; combination therapy of 2 or more traditional disease-modifying antirheumatic drugs (eg, triple therapy with hydroxychloroquine sulfate, sulfasalazine, and methotrexate)<sup>15</sup>; and biologic therapy (in combination with methotrexate). In response to initial risk stratification, patients could receive tier 1 (negative test result) or tier 2 (positive test result) therapy. Lack of treatment response led to treatment escalation (from tier 1 to 2 and tier 2 to 3). To explore the value of risk stratification in and of itself, we included the “treat all” strategy, in which we eliminated all risk stratification (ie, all patients received tier 2 therapy at baseline without testing having been performed).

Patients were assessed at 3-month intervals for survival, drug toxic effects, disease activity, and treatment response for the initial 12 months (Figure 1; “treatment”) based on data suggesting that clinical and radiographic progression is evident after 12 months.<sup>16</sup> Drug-related adverse events (AEs) were divided into mild, which conferred a small decrement in quality of life but no associated costs or mortality effect, and moderate to severe (eg, infections requiring antibiotic therapy and/or hospitalization), which conferred more substantial but reversible decrements in quality of life, survival, and associated direct and indirect costs. To reflect the response of the physician to severe AEs, treatment was withheld for individuals experiencing moderate to severe AEs during the next 3-month interval, resulting in decreased treatment-related costs and clinical response at the next assessment.

Our model assessed disease activity at 3-month intervals to determine whether the patient had achieved remission. In the base case, remission was defined as a Disease Activity Score of 2.6 or less.<sup>17,18</sup> Although it does not represent a complete lack of disease activity, this level of activity would likely prompt continu-

ation of the existing treatment rather than escalation. Alternative definitions were explored in sensitivity analyses. For individuals whose conditions did not achieve remission, we assessed the American College of Rheumatology (ACR) criteria for a 50% improvement in disease activity (ACR50). Individuals whose conditions showed an ACR50 response were maintained with the same treatment, and those whose conditions did not show an ACR50 response were advanced to the next treatment tier.

Total (direct and indirect) RA-related costs and quality-adjusted life-years (QALYs) were tallied at the end of 12 months. These values were then extrapolated to estimate lifetime costs and quality of life using published life tables. Lifetime estimates considered the disease activity level (and associated productivity cost) and treatment assignment at the end of the first year. Poor-prognosis RA conferred an additional cost to allow for the inclusion of greater anticipated direct costs over time. Individuals with no treatment response at the end of 12 months of treatment were assumed to obtain an ACR50 response during the following cycle.

### TARGET POPULATION AND DATA SOURCES

The hypothetical patient population consisted of individuals 45 years old with a new diagnosis of RA per the ACR 1987 consensus criteria of 12 months or less of disease and no evidence of plain radiographic erosions at baseline. We searched the published literature for the following input variables: *RA-related costs, mortality, treatment response, and AE rates* for each treatment tier, *MRI and standard risk stratification sensitivity and specificity, and quality of life*. Input assumptions for the base case analysis and ranges used in sensitivity analyses are listed in **Table 1**, described herein, and detailed in the eAppendix. Whenever plausible equivalent options existed for input assumptions, we selected those most favorable for MRI to evaluate a best-case scenario for MRI. To acknowledge limitations in available input data and ensure that our analysis captured the full spectrum of possible clinical values, we used estimate ranges in excess of published values for sensitivity analyses.

### TREATMENT RESPONSE AND TREATMENT-RELATED AEs

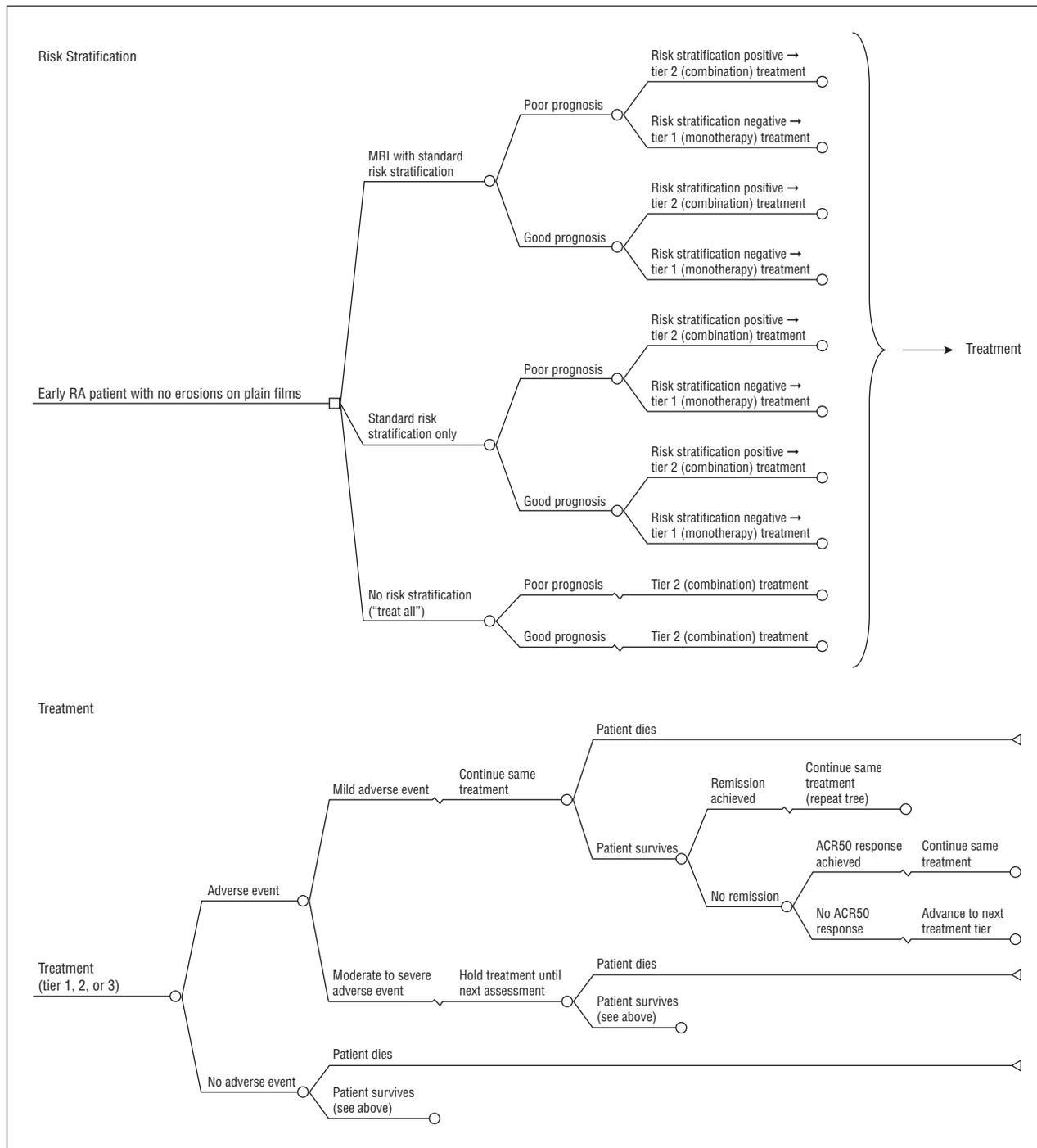
Treatment responses were derived from the published literature and stratified by poor-prognosis vs good-prognosis RA, treatment duration (3 vs 6 or more months of treatment duration), and the need to temporarily withhold treatment after a severe AE. To use the broadest plausible ranges for sensitivity analyses, AE rates were drawn from randomized clinical trials and prospective, observational cohort studies. Mild AE estimates included AEs described as “mild” and “any AE” estimates. Moderate to severe AE estimates included published data reported for “serious AEs” or “serious infections.”

### PROGNOSTIC TEST CHARACTERISTICS

Performance characteristics for standard risk stratification and MRI were derived from the published literature. We defined sensitivity and specificity as the ability of either testing approach to predict the likelihood of radiographic progression at 12 months.

### QUALITY OF LIFE

The quality-of-life estimates in the model represented remitted RA, moderate to severe disease activity, and a partially treated state (ie, ACR50 response). To reflect our definition of remission (Disease Activity Score  $\leq 2.6$ ), we assumed a utility score



**Figure 1.** Model decision trees. Risk-stratification tree represents risk stratification (standard testing with and without magnetic resonance imaging [MRI]) and “treat all” arms. Positive test result leads to baseline combination therapy. Treatment tree represents treatment regimens including optimized methotrexate monotherapy, escalated as needed; combination therapy of 2 or more traditional disease-modifying drugs (eg, triple therapy with hydroxychloroquine sulfate, sulfasalazine, and methotrexate); and biologic therapy (with methotrexate). Lack of treatment response (see text) leads to treatment escalation (from tier 1 to 2 and tier 2 to 3). ACR50 indicates American College of Rheumatology criteria for a 50% improvement in disease activity; RA, rheumatoid arthritis.

of 0.95 for remitted RA and varied this assumption in sensitivity analyses.

### COSTS

All costs were converted to 2010 US dollars using the Bureau of Labor Statistics’ Consumer Price Index for March 2010.<sup>81</sup> Costs were assigned from the societal perspective and, where available, drawn from the published literature. Additional cost es-

timates were derived from Medicare reimbursement data and 2006 Agency for Healthcare Research and Quality Healthcare Cost and Utilization Project data.<sup>58</sup>

Productivity costs related to RA disability and work losses were derived from the published literature<sup>68-73</sup> using a fractional estimate of the US national mean hourly wage for nonfarm workers and assuming a 40-hour workweek, 50 weeks per year. A broad range of productivity costs were tested in sensitivity analyses, including no RA-related and/or AE-related productivity costs.

**Table 1. Model Input Variables**

Variable	Base Case (Range), %	References
Population and test characteristics		
Prevalence of poor-prognosis RA	30.0 (0-100)	19-25
Standard risk stratification specificity	76.5 (56.5-96.5)	26-28
Standard risk stratification sensitivity	81.1 (62.2-100)	26-28
MRI specificity	57.9 (37.9-77.9)	11,12,19,23,24,29-32
MRI sensitivity	90.0 (80.0-100.0)	11,12,19,23,24,29-32
Treatment response <sup>a</sup>		
Probability of ACR50		
After withholding treatment for AE	0 (0-10.0)	...
With tier 1 treatment	11.4-50.0 (6.4-60.0)	33-35
With tier 2 treatment	25.0-60.0 (15.0-70.0)	34-36
With tier 3 treatment	30.0-60.0 (20.0-70.0)	33-35
Probability of remission		
After withholding treatment for AE	0 (0-5.0)	...
With tier 1 treatment	0-45.6 (0-55.6)	34,35,37
With tier 2 treatment	8.3-70.0 (0-70.0)	34,35,37,38
With tier 3 treatment	8.3-70.0 (0-70.0)	34,35,37,38
Probability of treatment response persistence	98.8 (95.0-100)	39,40
Decrease in treatment response persistence for poor- (vs good-) prognosis RA	5.0 (0-20.0)	40
AE rates		
Probability of mild AE		
With tier 1 treatment	24.6 (9.6-39.6)	41-46
With tier 2 treatment	45.2 (30.2-60.2)	43,44,46-48
With tier 3 treatment	30.0 (15.0-45.0)	49-53
Probability of moderate to severe AE		
With tier 1 treatment	1.5 (0.5-2.5)	33,34,38,42,45,54-56
With tier 2 treatment	3.4 (2.4-4.4)	34,55
With tier 3 treatment	1.2 (0.2-2.2)	33,34,38,56,57
Temporary incremental increase in mortality due to moderate to severe AE <sup>b</sup>	0.2 (0-10.0)	58
QALY		
Decrement for mild AE <sup>c</sup>	0.1 (0.05-0.15)	59
Decrement for moderate to severe AE <sup>c</sup>	0.45 (0-0.75)	59-62
For remitted RA	0.95 (0.90-1.00)	10
For active good-prognosis RA	0.82 (0.79-0.97)	63-66
For active poor-prognosis RA	0.69 (0.40-0.97)	63-66
For individuals achieving ACR50 improvement in good-prognosis RA	0.885 (0.79-0.97)	63-66
For individuals achieving ACR50 improvement in poor-prognosis RA	0.82 (0.40-0.97)	63-66
Costs, \$ <sup>d</sup>		
Standard risk stratification <sup>e</sup>	140 (40-240)	Medicare reimbursement <sup>67</sup>
MRI testing	456 (356-556)	Medicare reimbursement <sup>67</sup>
Direct cost of moderate to severe AE	27 503 (0-48 000)	HCUP net data <sup>58</sup>
Ongoing total cost of poor-prognosis RA	1000 (0-5000)	68-73
Tier 1 treatment	1109 (309-1909)	74,75
Tier 2 treatment	3002 (1002-5002)	74,75
Tier 3 treatment	8291 (6291-22 000)	75,76
12-Month US wage	38 428 (28 428-48 428)	77
Productivity cost attributable to RA <sup>f</sup>	1921 (0-3800)	68-73
Productivity cost due to moderate to severe AE	12 796 (0-23 000)	58,77
Mortality rates		
Annual	0.19 (0.17-0.21)	CDC data <sup>78</sup>
Incremental increase in annual mortality due to RA	0.00029 (0-0.00035)	78-80
Life expectancy for good-prognosis RA, y <sup>g</sup>	37.7 (30.7-44.7)	78-80
Life expectancy for poor-prognosis RA, y	28.7 (18.7-38.7)	78-80
Miscellaneous		
Discount rate	3 (0-6)	...

Abbreviations: ACR50, American College of Rheumatology criteria for a 50% improvement in disease activity; AE, adverse event; CDC, Centers for Disease Control and Prevention; ellipses, not applicable; HCUP, Healthcare Cost and Utilization Project; MRI, magnetic resonance imaging; QALY, quality-adjusted life-year; RA, rheumatoid arthritis.

<sup>a</sup>Values include the range of base probabilities of remission (Disease Activity Score  $\leq$ 2.6) and ACR50 response for each treatment tier, for poor-prognosis and good-prognosis RA, and for 3 months and 6 months or greater of treatment.

<sup>b</sup>Derived from HCUP data for in-hospital deaths related to infections and/or complications of medical treatment. No continued mortality effect from moderate to severe AE existed after the first year of therapy.

<sup>c</sup>Represents annual utility decrement.

<sup>d</sup>Reported in 2010 US dollars.

<sup>e</sup>Based on Medicare reimbursement data for bilateral hand and wrist plain radiographs, rheumatoid factor, anti-cyclic citrullinated peptide antibodies, and erythrocyte sedimentation rate. The cost of the physician visit was not considered in the base case analysis but was included in sensitivity analyses.

<sup>f</sup>Individuals with high disease activity incurred 50.0% greater productivity costs than those with ACR50 responses.

<sup>g</sup>Life expectancy after the first year was estimated using National Vital Statistics Report life tables by years of age.

**Table 2. One-Year and Lifetime RA-Related Costs, QALYs, and ICERs for All Risk-Assessment Arms<sup>a</sup>**

Variable	Standard Risk Stratification		"Treat All" Strategy
	By Itself	With MRI	
<b>One-year analysis</b>			
RA-related costs, \$	7450	8246	8622
QALYs	0.8259	0.8298	0.8404
ICER, compared with standard testing, \$	...	204 103	80 828
ICER, compared with MRI, \$	...	...	35 472
<b>Lifetime analysis</b>			
RA-related costs, \$	132 206	135 914	146 510
QALYs	20.1594	20.1815	20.2357
ICER, compared with standard testing, \$	...	167 783	187 397
ICER, compared with MRI, \$	...	...	195 390

Abbreviations: ellipses, not applicable; ICER, incremental cost effectiveness ratio (in dollars per QALY gained); MRI, magnetic resonance imaging; QALY, quality-adjusted life-year; RA, rheumatoid arthritis.

<sup>a</sup>All costs reported in 2010 US dollars.

## MORTALITY

We used standard life table methods derived from the Centers for Disease Control and Prevention's 2007 National Vital Statistics Report<sup>78</sup> to estimate base mortality rates by age. The mortality increment due to moderate to severe AEs was derived from Healthcare Cost and Utilization Project data for in-hospital deaths related to infections and/or complications of medical treatment.<sup>58</sup> Alternative assumptions were considered in sensitivity analyses.

## MODEL VALIDATION

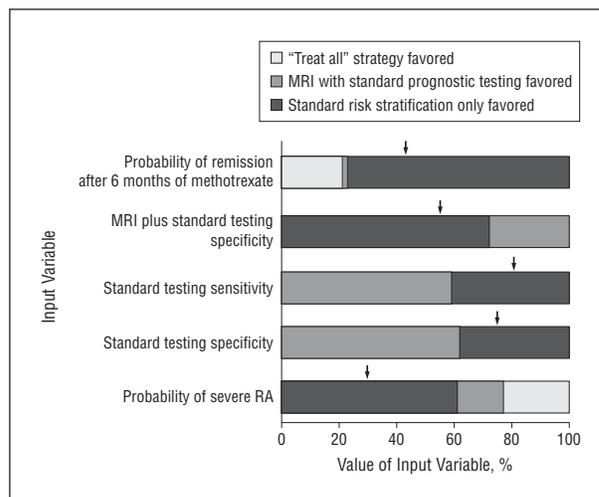
Internal validation was achieved using quantitative and graphic representation of 1-way sensitivity analyses of all input variables across extreme ranges in which the expected outcome was obvious. External validity was demonstrated by comparing the model output to published data; our model estimated the mean unadjusted life expectancy for the populations to be 35.6 years compared with published estimates of 36.9 years.<sup>79</sup>

## BASE ANALYSIS

In the base analysis, we estimated 12-month and lifetime total RA-related costs and QALYs using the input assumptions in Table 1. The incremental cost-effectiveness ratios (ICERs) (in dollars per QALY gained) were calculated for all strategies compared with standard risk stratification only. The lifetime analysis used a 3.0% discount rate for costs and quality of life. Further details of the analysis are presented in the eAppendix.

## SENSITIVITY ANALYSIS

One-way sensitivity analyses of all input variables were performed across the broadest range of clinically possible estimates for the 12-month and lifetime models. Additional multiway and threshold analyses (to determine when the favored strategy changed) were performed for key variables identified in 1-way analyses. Running the decision model as a Monte Carlo simulation, we performed a probabilistic sensitivity analysis, which traces the experiences (and thus costs and quality of life) of 10 000 hypothetical individuals through the model, and the values for each input variable were simultaneously varied using predefined distributions. Because the data for this model were limited and to



**Figure 2.** Threshold analysis for variables to which model output was sensitive in 1-way sensitivity analysis. Each horizontal bar represents the complete range of values for the variables listed on the vertical axis. Shaded areas represent those values that produced favorable (ie, <\$100 000 per quality-adjusted life-year gained) incremental cost-effectiveness ratios (in dollars per quality-adjusted life-year gained) for a given strategy. For example, when the probability of remission after 6 months of methotrexate therapy is greater than 23.0%, standard risk stratification only is favored over the other strategies. Arrows indicate base case assumptions. MRI indicates magnetic resonance imaging; RA, rheumatoid arthritis.

provide the most conservative analysis, we report the results using uniform distributions for each variable (see the eAppendix for additional sensitivity analyses using alternative distributions). In addition, we adjusted our cost related to moderate to severe AEs using a cost-to-charge ratio (eAppendix).

## RESULTS

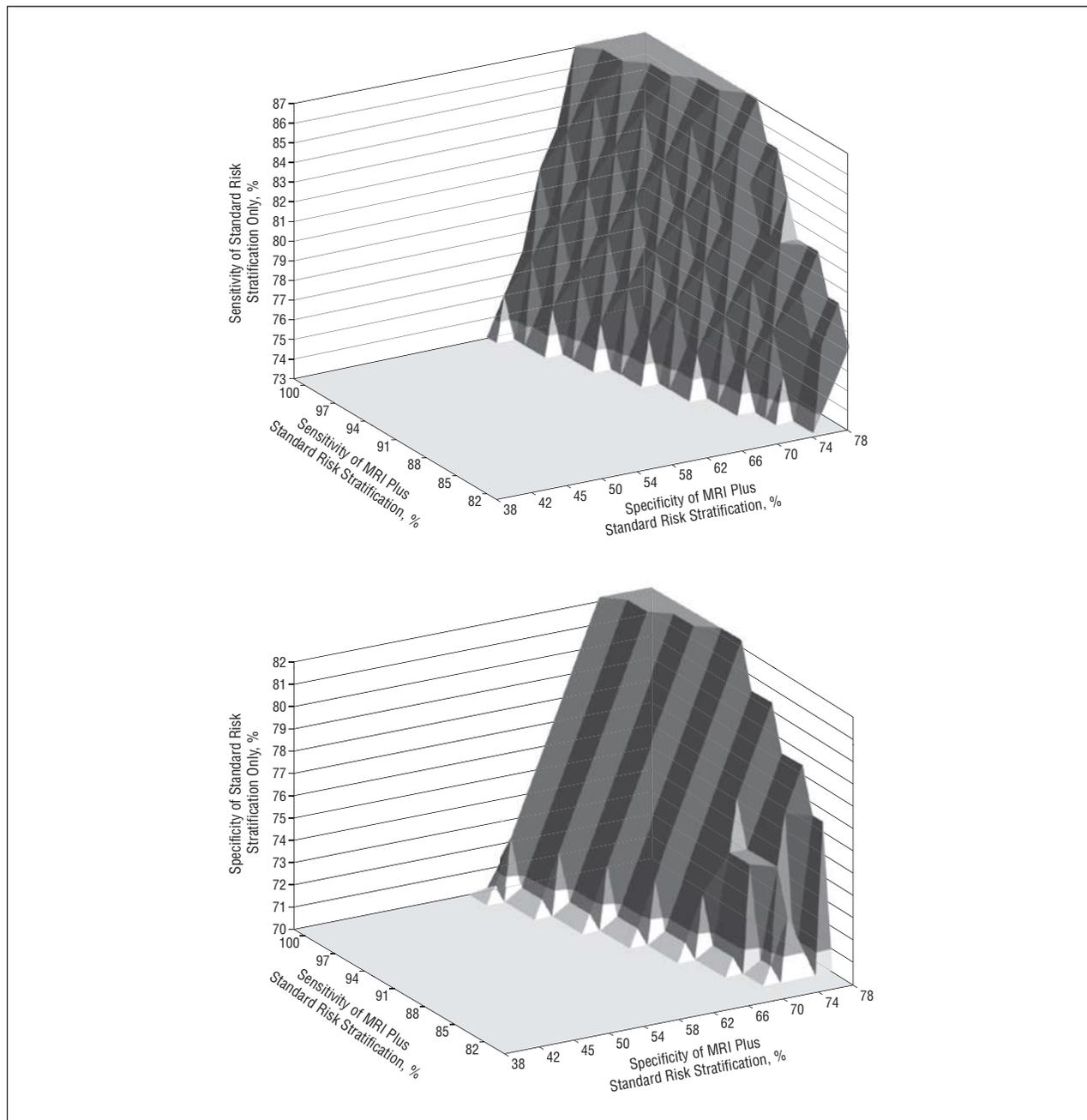
### BASE ANALYSIS

In a hypothetical population of RA patients with no baseline radiographic erosions and disease duration of less than 12 months, estimated 1-year and lifetime ICERs for the MRI strategy compared with the standard risk stratification only were \$204 103 and \$167 783 per QALY gained, respectively.

One-year and lifetime RA-related costs, QALYs, and ICERs for standard risk stratification only and with MRI and the "treat all" strategy are listed in **Table 2**. Herein, we report the results of sensitivity analyses for the lifetime analysis; results of the 12-month analyses are provided in the eAppendix.

### SENSITIVITY ANALYSIS

Model results were insensitive to wide variation in input variables. In 1-way sensitivity analyses (eAppendix), only 5 of 70 variables produced ICERs below the commonly accepted threshold of \$100 000 per QALY gained<sup>82</sup>: the underlying prevalence of poor-prognosis RA in the population, standard testing sensitivity, standard testing specificity, MRI specificity, and the probability of remission after 6 months of methotrexate monotherapy. Threshold values in which the favored strategy (ie, the particular strategy producing ICERs <\$100 000 per QALY gained) changed for each of these 5 variables are illustrated in **Figure 2**. Mag-

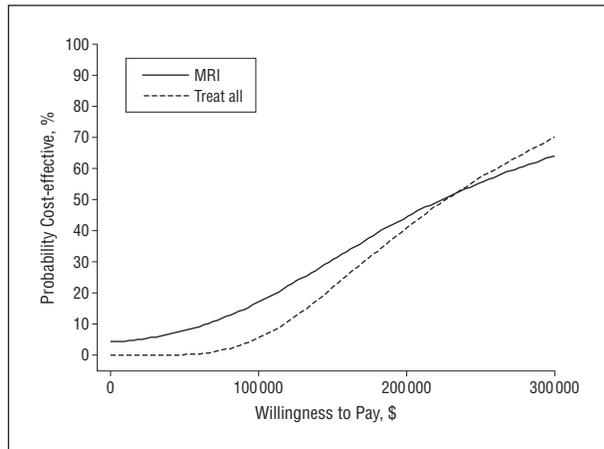


**Figure 3.** Graphic depiction of test performance assumptions under which magnetic resonance imaging (MRI) plus standard risk stratification is the favored strategy (gray volume). Axes display plausible ranges for MRI sensitivity (horizontal) and specificity (depth) and standard risk stratification sensitivity (vertical, top) and specificity (vertical, bottom). Gray volume represents assumptions under which MRI is favored (ie, yields incremental cost-effectiveness ratios <\$100 000 per quality-adjusted life-years gained [in dollars per quality-adjusted life-years gained]); the remaining space reflects assumptions under which standard risk stratification only is preferred.

netic resonance imaging was favored over standard risk stratification only and the “treat all” scenario when the probability of remission after 6 months of methotrexate monotherapy was 21% to 23% (<21%, “treat all” favored; >23%, standard risk stratification favored); standard risk stratification sensitivity and specificity were less than 59% and less than 62%, respectively; the specificity of MRI plus standard risk stratification was 72% or higher; or the underlying prevalence of poor-prognosis RA in the population was 61% to 77%. The “treat all” strategy was favored compared with that of adding MRI when the probability of re-

mission after 6 months of methotrexate monotherapy was less than 21% or the prevalence of poor-prognosis RA was greater than 77%. Data<sup>19-25</sup> suggest that the prevalence of poor-prognosis RA ranges from 1% to 34%. Therefore, none of these thresholds represents a clinically probable or consistently achievable value.

The lifetime model output was insensitive to simultaneously varying the definition of remission, occurrence of AEs, costs, and/or quality-of-life assumptions. The MRI strategy produced favorable ICERs when MRI sensitivity approached 100%, even if MRI specificity was lower than



**Figure 4.** Acceptability curve of the cost-effectiveness of adding magnetic resonance imaging (MRI) to standard risk stratification according to willingness to pay. The vertical axis represents the probability of cost-effectiveness, defined as producing an incremental cost-effectiveness ratio (ICER) below the willingness-to-pay threshold (in dollars per quality-adjusted life-years gained) listed on the horizontal axis for the MRI (solid line) and “treat all” (dotted line) strategies, respectively. For example, at an ICER threshold of \$100 000 per quality-adjusted life-year gained, less than 10.0% of simulations yielded ICERs below \$100 000 for the “treat all” strategy and less than 20.0% for the MRI strategy compared with standard risk stratification only.

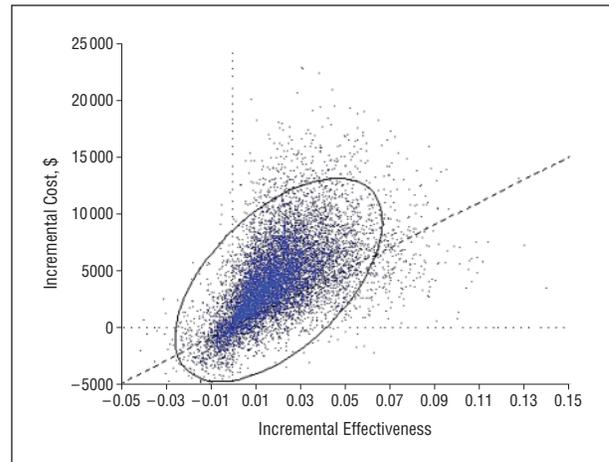
that of standard risk stratification only (**Figure 3**). Further sensitivity analyses are reported in the eAppendix.

#### PROBABILISTIC SENSITIVITY ANALYSIS

Probabilistic sensitivity analysis of lifetime RA-related costs and QALYs yielded a mean ICER estimate of \$302 251 (95% interpercentile range, \$17 044-\$697 006) per QALY gained for MRI compared with standard risk stratification only (**Figure 4** and **Figure 5**), excluding the 11.1% of simulations in which MRI produced lower QALY estimates at a greater cost than standard risk stratification only. Most runs (83% and 79%) yielded ICERs (for adding MRI compared with standard risk stratification only) greater than commonly used willingness-to-pay thresholds (ie, \$100 000 and \$150 000 per QALY gained, respectively). We explored a wide range of alternative scenarios for our probabilistic sensitivity analyses (eAppendix). One scenario (assuming nonuniform distributions, using a cost-to-charge ratio for moderate to severe AE costs, and inversely correlating sensitivity and specificity) lowered the mean ICER for adding MRI to \$22 868 per QALY gained, but 63.3% of runs still produced ICERs greater than \$100 000 per QALY gained. For the “treat all” strategy, the lifetime probabilistic sensitivity analysis yielded a mean ICER estimate (compared with standard risk stratification only) of \$268 263 (95% interpercentile range, \$97 448-\$563 513) per QALY gained, and 94.6% of runs yielded ICERs greater than \$100 000 per QALY gained.

#### CONCLUSIONS

Using a decision analytic model of early-RA risk assessment, we found that the lifetime ICER for adding MRI to standard prognostic assessments was generally unfavor-



**Figure 5.** Incremental cost-effectiveness ratio (ICER) scatterplot of adding magnetic resonance imaging (MRI) to standard risk stratification. Incremental effectiveness (in quality-adjusted life-years [QALYs]) and lifetime rheumatoid arthritis-related costs are plotted on the horizontal and vertical axes, respectively. Each dot represents the ICER for 1 simulation. The ellipse represents a 95% confidence ellipse around the ICERs (dots) for the MRI strategy compared with standard risk stratification only. The dashed line represents the commonly cited cost-effectiveness threshold of \$100 000 per QALY gained, and every dot above this line exceeds this threshold. Therefore, only the dots located on the lower right of this diagonal dashed line represent cost-effective simulations for MRI compared with standard risk stratification at a threshold of \$100 000 per QALY gained. These dots correlate with the less than 20.0% of simulations producing cost-effective ICERs for the MRI strategy in Figure 4. Data presented are for the lifetime analysis.

able, at \$167 783 per QALY gained, and offered an incremental gain of fewer than 2 quality-adjusted days. Probabilistic sensitivity analysis suggested that this result was robust. Most simulations in probabilistic sensitivity analyses yielded ICERs for MRI above the commonly cited ICER threshold of \$100 000 per QALY gained. Although decision analytic models are not designed to estimate the number needed to treat or harm as primary outcome measures, we can estimate that 37 patients would need to undergo MRI to identify 1 additional poor-prognosis RA patient. However, in performing these 37 MRIs, 5 additional good-prognosis RA patients would be inappropriately treated with baseline combination therapy and 4 additional patients would experience moderate to severe AEs from combination therapy during a 5-year period.

Although thresholds for acceptable health care value are controversial, most contemporary estimates of willingness to pay for health benefits in the United States range from \$50 000<sup>82</sup> to 3 times the per-person US gross domestic product (approximately \$144 000) per QALY gained.<sup>83</sup> Our data suggest MRI is unlikely to be a cost-effective addition to standard prognostic assessments in early RA, despite using highly conservative assumptions (that is, those biased in favor of MRI), including assumptions regarding the quality-of-life effect of RA or complications of its treatments. Although the cost-effectiveness of MRI was sensitive to the performance characteristics of MRI and standard risk stratification, our findings suggest that MRI must provide significantly greater sensitivity, and at least equal specificity, as standard testing only to deliver acceptable value in a population of early-RA patients. Although MRI provides greater sensitivity than standard testing, it is un-

clear how large an incremental increase in specificity it offers, if any. The specificity of MRI and standard risk stratification are reduced in very early RA<sup>84</sup> and are likely to be further reduced with office-based extremity MRIs or in the hands of less-experienced readers.

It is noteworthy that our model included the option of not performing risk stratification (ie, the “treat all” strategy). The “treat all” strategy was preferred in comparison with adding MRI to standard risk stratification in the 12-month analysis. In the *lifetime* analysis, the “treat all” strategy was preferred when MRI sensitivity approached 100% and when the underlying prevalence of poor-prognosis RA in the population was sufficiently high (>77.0%) that most patients would benefit from aggressive treatment. Although such a high prevalence of poor-prognosis RA is unlikely, the incremental risk of serious AEs is small with combination or biologic treatment compared with methotrexate monotherapy, suggesting that overtreatment confers little additional health risk, particularly in the short term. Our finding that the “treat all” strategy was cost-effective in the first year of treatment supports alternative approaches to early-RA treatment, including induction and withdrawal or induction and maintenance strategies, which may offer economic in addition to clinical<sup>85</sup> value and deserve further evaluation. In this setting, our work suggests it may be appropriate to shift focus away from risk stratification per se toward optimizing early diagnosis and early-RA treatment.

This analysis has several limitations. Because published data for our input variables were limited, we used some assumptions that relied on expert opinion. However, we chose estimates with strong clinical face validity, and we tested wide ranges of possible values for each input variable. We used data from patients with later-stage disease than our target population; as many as 62.0% of participants in studies included in the model had baseline plain radiographic erosions, likely representing populations with greater disease severity. However, this likely overestimated the favorability of MRI, because using MRI increases the proportion of the population receiving aggressive treatment at baseline due to the high sensitivity of MRI in identifying individuals at risk for progression. We did not consider the consequences of AEs after the first year of treatment and we did not include spontaneous remission in our model because data suggest it occurs in less than 8% of early-RA patients,<sup>7</sup> both of which are reasons for possibly overestimating the favorability of MRI. Removing these biases would make the cost-effectiveness of MRI even less favorable. We did not use a cost-to-charge ratio in the calculation of costs related to moderate to severe AEs but found that adjusting for this resulting bias in sensitivity analyses did not qualitatively alter our results except in combination with other modifications. We used clinical rather than radiographic outcomes because we believe these correlate with quality-of-life measures and are in accordance with recommendations for RA clinical trials.<sup>86-88</sup>

To our knowledge, ours is the first study to evaluate the cost-effectiveness of MRI for early-RA risk stratification. Other data examining the cost-effectiveness of MRI as a risk-stratification tool have found inconsistent results. A randomized clinical trial<sup>89</sup> in early breast cancer

demonstrated no reduction in subsequent operation rates in the MRI vs the no-MRI group, but a study<sup>90</sup> of knee MRI after acute injury in patients with normal plain radiographs found reduced costs and improved clinical outcomes in the MRI group compared with the no-MRI group. Although the use of MRI in RA in the United States is unknown, an unpublished national survey of rheumatologists demonstrated that more than a third of respondents had used MRI in the treatment of their RA patients within the last year (Marissa Blum, MD, written communication, June 2010).

Our data suggest that adding MRI to standard risk stratification is unlikely to be a cost-effective alternative to standard testing only under commonly found clinical conditions and accepted willingness-to-pay thresholds. Given our findings in combination with the fact that non-radiologist MRI facility ownership is increasing,<sup>91</sup> our data support a prudent approach to technology adoption in RA risk stratification. Data clearly defining the clinical benefit of MRI in early-RA treatment are urgently needed.

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## INVITED COMMENTARY

# What We Can Learn From a Decision Model

*All models are wrong, but some are useful.*

George Box

Only a few of the many clinical problems in medicine can be addressed by performing a randomized clinical trial. Consequently, we need additional tools to identify the optimal clinical management strategies for patients. One set of tools is the analyses of clinical registries and databases to assess diagnostic tests or to compare treatments—activities now termed *comparative effectiveness research*. Another powerful tool is the use of a model, or simulation, of a clinical decision to examine the likely consequences of alternative choices. A model is particularly useful in scenarios with multiple clinical options because it is difficult to study several strategies in a single clinical trial.

A strong model boils down the problem at hand to its basic components, thus displaying the fundamental structure of the decision. The model should identify and retain the critical elements of the problem while ignoring its less important and irrelevant aspects. In other words, the challenge is to make the model simple enough but not too simple. The model lays out the relevant alternatives (eg, treatment A vs treatment B), and the consequences—clinical and economic—of each alternative. Once the model has been structured, the key model variables (eg, percentage of patients responding to each treatment, the ability of a test to predict treatment response or mortality) need to be quantified using reasonable, unbiased, and internally consistent estimates. A hypothetical cohort of patients can then be followed up through the model during the course of their lifetimes to project the outcomes and costs of each strategy and thus to help identify the optimal approach to the clinical problem. The effect on the decision of uncertainties in the model variables can be assessed by systematically varying those factors through plausible ranges and determining whether the optimal decision would change—an exercise termed a *sensitivity analysis*.

Simple, well-constructed models can provide many insights and lead to fundamentally correct decisions. More than 30 years ago, Pauker and Kassirer<sup>1</sup> applied decision analysis to 2 prototypical clinical decisions: whether to begin treatment when one is uncertain of the diagnosis and whether to treat, perform a test, or do neither when faced with a patient with an uncertain diagnosis.<sup>2</sup> This classic work provided key insights into these basic clinical problems using the simple yet elegant framework of a decision tree. Since their pathbreaking work, thou-

sands of decision models have been published regarding many different clinical problems. These articles use more sophisticated modeling tools than did Pauker and Kassirer, but the fundamental issues are the same: the need to structure the model properly, to estimate the variables correctly, and to identify the turning points for the decision. One of the main goals of building a model is to gain insights into the decision, not just obtain the “right answer.”

In this issue of the *Archives*, Suter and associates have applied modeling techniques to analyze the optimal management of a patient with early RA. The uncertain factor in this clinical problem is whether the patient has an aggressive underlying disease, which has a poor prognosis and requires multidrug treatment, or less aggressive underlying disease, which has a good prognosis and is likely to respond to single-drug treatment (or even remit spontaneously). Clinical indicators of the aggressiveness of early RA exist, but they are imperfect. Some evidence suggests that MRI might provide more information regarding disease prognosis, but risk stratification based on the MRI findings is also imperfect, and testing is expensive. So, should the patient (1) be treated with a simple drug regimen, (2) be treated with an aggressive drug regimen, or (3) be tested via MRI and the results used to decide between a simple or an aggressive drug regimen? Notice that the clinical problem stated in this way is general—we face similar decisions in caring for patients with cancer, infections, or heart disease. More aggressive treatment may be more effective, but it also confers more risk of AEs. No certainty exists that the treatment will work, even when it is given based on the test results. The insight from decision models is that testing makes more sense when the test is more informative, especially if the test can identify patients who are more (or less) likely to respond to aggressive treatment. This is, of course, the holy grail of “personalized medicine”—finding just the right treatment for an individual. Unfortunately, few tests specifically predict treatment response. Nevertheless, a test that can identify high- and low-risk patients may be favorable enough to use in targeting therapy, giving more aggressive treatment to the high-risk patient and less aggressive treatment to the low-risk patient.

As with all models, the optimal strategy depends on the precise values of the model variables: the likely response of the disease to treatment, how that response varies according to the underlying prognosis, the perfor-