Cost Effectiveness of Routine Surveillance Endomyocardial Biopsy Beyond 12 Months Post Heart Transplantation

Lampert et al: Cost Effectiveness of Endomyocardial Biopsy

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Abstract

**Background**—Despite low risk of late rejection after heart transplant (HT), surveillance endomyocardial biopsies (EMB) are often continued for years. We assessed the cost-effectiveness of routine EMB beyond 12 months post-HT.

**Methods and Results**—Markov model compared the following surveillance EMB strategies to baseline strategy of stopping EMB 12 months post-HT: 1.) q 4 months during year 2 post-HT, 2.) q 6 months during year 2; 3.) q 4 months for years 2-3, and 4.) q 6 months for years 2-3. Patients entered the model 12 months post-HT and were followed until 36 months. In all strategies, patients had EMB with symptoms; in biopsy strategies beyond 12 months, EMB was also performed as scheduled regardless of symptoms. One-way and Monte Carlo sensitivity analyses were performed. Stopping EMB at 12 months was dominant (more effective, less costly), saving $2884/patient compared to the next best strategy (q 6 months for year 2) and gaining 0.0011 QALYs. Increasing the annual risk of asymptomatic rejection in years 2-3 from previously reported 2.5% to 8.5% resulted in the biopsy q 6 months for year 2 strategy gaining 0.0006 QALYs, but cost $4,913,599/QALY gained. EMB for 12 months was also no longer dominant when mortality risk from untreated asymptomatic rejection approached 11%; competing strategies still cost >$200,000/QALY as that risk approached 99%.

**Conclusions**—Surveillance EMB for 12 months post-HT is more effective and less costly than EMB performed beyond 12 months, unless risks of asymptomatic cellular rejection and its mortality are strikingly higher than previously observed.

**Key Words:** cost-effectiveness, heart transplantation, biopsy, rejection
Improved patient and donor selection and long term care of heart transplant (HT) recipients has resulted in one year survival of approximately 90%.1 Advances in immunosuppressive therapies, such as calcineurin inhibitors and mycophenolate mofetil, have decreased the incidence of significant treated rejection from nearly 70% to approximately 30%, with most episodes occurring during the first year after transplantation.2,3,4 While most rejection is asymptomatic or minimally symptomatic at the time of diagnosis, it is still associated with an increased risk of allograft vasculopathy and loss.5,6,7 Therefore, though the risk of rejection after one year is substantially lower than during the first six months post-HT, many centers continue routine rejection surveillance for up to 5 years following transplantation.3

Endomyocardial biopsy (EMB) remains the gold standard for rejection monitoring. However, EMB is costly, associated with patient discomfort and inconvenience, and carries a small risk of potentially serious complications such as pericardial tamponade and severe tricuspid regurgitation.8,9,10 Several transplant centers have retrospectively demonstrated the safety of symptom driven biopsies only after the first post-transplant year, but in absence of a prospective trial confirming this many centers remain reluctant to adopt this approach. Subsequently, the usefulness of routine surveillance EMB in all patients beyond 1 year remains a subject of debate and considerable variation exists between institutions in the frequency and duration of surveillance biopsies.11 Current guidelines recommend surveillance EMB (every 4 – 6 months) for an extended period of time in transplant recipients at higher risk for late acute rejection, but do not comment on the routine use in all patients.12

The low yield of EMB beyond one year post-HT, its cost, and the small but real risk associated with the procedure, call into question the cost-effectiveness of this strategy. This is an ever more
important consideration in an era of increased focus on health care cost containment. Here we assess the cost-effectiveness of various EMB strategies beyond one year post-HT to 1.) demonstrate whether we could model any potential clinical benefit to prolonged surveillance and 2.) define the cost associated with prolonged surveillance biopsy strategies, which has not previously been reported.

**Methods**

**Model Design and Structure**

A Markov model was constructed comparing various surveillance EMB strategies to a baseline strategy of stopping routine EMB at 12 months post-HT. Four alternative strategies were examined: continued routine EMB every 4 months during year 2 post transplant (i.e., EMB 16, 20, and 24 months post-HT), routine EMB every 6 months during year 2 post HT, routine EMB every 4 months during years 2 and 3 post HT, and routine EMB every 6 months during years 2 and 3 post HT. Markov analysis was performed with TreeAge Pro 2013 Software (Williamstown, MA). No IRB approval was required for this study, since we used only literature data sources.

Patients entered the model after 12 months of routine post-HT clinic visits. The Markov model cycle length was 1 month. In all strategies, patients had an EMB for any signs or symptoms associated with rejection (dyspnea on exertion or at rest, paroxysmal nocturnal dyspnea, orthopnea, palpitations, and syncope or near-syncope), instances in which graft function could be compromised (i.e., infection), or an absolute decrease in left ventricular ejection fraction (LVEF) of more than 10% from baseline. In addition, patients received routine scheduled surveillance biopsies regardless of symptoms based on the strategy modeled.
Transitions during each monthly cycle for patients included remaining well, developing acute cellular rejection (ACR), developing hemodynamically significant ACR, developing antibody mediated rejection (AMR), or death. Patients transitioned to other states based on the monthly relative likelihood of those events (Figure). The model cycled until 36 months post HT. For example, “patient A” presents for their routine 24 month post-transplant clinic visit. In the baseline strategy, “patient A” would be evaluated clinically. If “patient A” reports symptoms of worsening dyspnea, orthopnea, palpitations or was found to have decrease in left ventricular systolic function, he would undergo an EMB. In the absence of any signs or symptoms of rejection, “patient A” would not undergo a biopsy. In the prolonged biopsy strategies, “patient A” would undergo a biopsy regardless of symptoms. If a biopsy was performed and demonstrated rejection, “patient A” would be treated accordingly. At the next monthly cycle, “patient A” would then either transition to another state or remain in his current state based on the relative probabilities of each event. If a biopsy was performed and did not demonstrate rejection, “patient A” would remain in the “well” state.

Costs

Costs, in 2010 US dollars, used in the model and ranges examined in sensitivity analyses are shown in Table 1. In our baseline model, patients with ACR without hemodynamic compromise were not hospitalized. Their treatment costs included methylprednisolone (1 gram IV x 3 days), IV infusion center cost, follow up echocardiogram, and follow up office visit. Since practice and resources available vary among transplant centers regarding inpatient or outpatient treatment of patients with ACR without hemodynamic compromise, sensitivity analysis included the possibility of hospitalization and its associated costs. Treatment costs for hemodynamically significant ACR included hospitalization, thymoglobulin (1.5 mg/kg IV x 3 days), T-cell subset
labs, follow up echocardiogram, and a follow up office visit. Hospitalization costs for
hemodynamically significant ACR were based on Healthcare Cost and Utilization Project
(HCUP) median costs for ICD-9 Code 996.83 (complications of transplanted heart) with a
median length of stay of 5 days.
Antibody mediated rejection treatment costs included hospitalization, plasmapharesis, catheter
for plasmapharesis, IVIG (2 grams/kg IV over 2 days), donor specific antibody testing, follow up
echocardiogram, and follow up office visit. Because AMR management typically involves more
intensive and a longer duration of care, costs of hospitalization for its treatment were estimated
using HCUP data on the mean charges for ICD-9 code 996.83 (complications of transplanted
heart) with a mean length of stay of 8.4 days. Follow up office visits for all types of rejection
were billed as a Level 4 established patient visit (CPT 99214).

Probabilities
The probabilities used in the baseline analysis and ranges examined in sensitivity analysis are
shown in Table 2. The annual risk of developing asymptomatic ACR has previously been
demonstrated to be approximately 2.5%\(^\text{16}\) and this value was used in the baseline analysis. An
additional analysis was done using an annual risk of asymptomatic ACR of 8.5% to evaluate the
model under the greater pressure of increased undetected rejection risk.
The probability of having ACR given symptoms (dyspnea on exertion or at rest, paroxysmal
nocturnal dyspnea, orthopnea, palpitations, and syncope or near-syncope) has previously been
noted to be approximately 12%.\(^\text{16}\) However, patients are occasionally treated for ACR in the
absence of an abnormal EMB based on symptoms and/or a change in graft function seen on
noninvasive imaging. In order to capture the costs associated with symptomatic patients who
may be treated despite a negative EMB, we used a rate of 25% for the probability of having ACR
given symptoms. There is limited data available quantifying the risk of death with untreated asymptomatic rejection. One prior analysis of the natural history of moderate rejection showed no increased risk of short or long term mortality. To assume that untreated asymptomatic rejection carries some mortality risk, we used a 5% risk in the baseline model with a wide range in sensitivity analysis.

**Utilities (i.e. Calculation of QALYs)**

The utilities used in the baseline analysis and ranges examined in sensitivity analysis are shown in Table 3. Utilities for patients having a biopsy or with illness were calculated as the utility of the well state multiplied by the utility weight of the biopsy or illness state. The utility of asymptomatic heart failure was used to represent non-hemodynamically significant rejection. The utility of NYHA Class II-III heart failure was used as a surrogate for symptoms of rejection.

**Sensitivity Analysis**

One way and multiway sensitivity analyses were performed. In the one-way analyses all variables were individually tested through the ranges shown in Table 1 to 3. Monte Carlo (probabilistic) sensitivity analysis was performed for the multiway analysis. Monte Carlo analysis simultaneously varies all uncertain parameters over a range of values and probability distributions within that range producing a relative likelihood of resulting incremental cost effectiveness ratios. Parameters were chosen randomly for 10,000 iterations of each biopsy strategy. Probability distributions were chosen based on the level of certainty of each parameter’s distribution. Generally, these distributions were triangular with the baseline value used as the likeliest value, minimum value equal to 0.5 times the baseline, and the maximum value equal to 1.5 times the baseline. To evaluate greater uncertainty in the Monte Carlo
analysis about the utility states and the frequency of rejection resolving with or without treatment, wider triangular distributions were used as shown in Table 4.

Results

In the baseline analysis, stopping EMB at 12 months was dominant (more effective and less costly), saving $2884 per patient compared to the next least costly strategy (every 6 months for year 2 post-HT) and gaining 0.0011 QALYs when using the previously reported 2.5% annual risk of asymptomatic ACR. When compared to a prolonged strategy of biopsies every six months for five years post-transplant, the baseline strategy would save $22.5 million annually in the United States. More frequent and longer durations of continued surveillance biopsies were associated with higher costs and lower effectiveness (Table 5). To ensure that the model was not biased by an underestimate of the risk of asymptomatic ACR, a second baseline analysis was done using an 8.5% annual risk. In doing so, the extended surveillance EMB strategies for 24 months were no longer dominated. The strategy of EMB every 6 months for year 2 now gained 0.0006 QALYs compared to baseline, but cost $4,913,599 per QALY gained (Table 5). Using the 8.5% annual risk of asymptomatic ACR, scheduled surveillance EMB strategies beyond 24 months remained less effective and more costly.

Sensitivity analysis

Individually varying all parameters through the ranges described in Tables 1 – 3 resulted in only two parameters that significantly impacted model results. As the annual risk of asymptomatic ACR approaches 7%, the year 2 post-HT biopsy strategies are no longer dominated. Yet, even with an implausible 50% annual risk of asymptomatic ACR, the strategy of EMB every 6 months
for year 2 post-HT gained 0.0132 QALYs compared to baseline, but still cost $170,249/QALY gained. EMB for 12 months was also no longer dominant when mortality risk from untreated asymptomatic rejection approached 11%. Using an 11% rate of death from untreated asymptomatic rejection created a model where EMB every 6 months for year 2 post-HT gained 0.0001 QALY, costing $28 million per QALY. Competing strategies continued to cost $200,000 per QALY even when that risk approached 99%. In general, medical interventions costing $>100,000 per QALY gained are considered an expensive use of health care resources.28,29

Monte Carlo sensitivity analyses were done using both the 2.5% and 8.5% annual risks of asymptomatic ACR. With the baseline 2.5% annual risk of asymptomatic ACR, stopping EMB at 12 months was favored in 98.3% of model iterations with a willingness to pay threshold of $250,000. Using the higher 8.5% annual risk of asymptomatic cellular rejection still resulted in over 97% of model iterations favoring stopping EMB at 12 months.

**Discussion**

This study demonstrates that when using typical rates of ACR, surveillance EMB for 12 months post-HT is more effective and less costly than strategies where EMB is performed beyond 12 months. As would be expected, increasing the risk of asymptomatic ACR and risk of dying from untreated asymptomatic rejection resulted in a net improvement in effectiveness of the longer surveillance EMB strategies, but at considerable costs per QALY gained. Using an 8.5% annual risk of asymptomatic ACR, which is more than three times higher than previously published reports, resulted in a small benefit of surveillance biopsy strategies extending to 24 months. However, this was at a cost of almost $5 million per QALY gained. Additionally, when the risk
of death from untreated asymptomatic rejection approached 11% the longer surveillance biopsy strategies provided a small benefit but at a cost of over $28 million per QALY gained. Even as this risk approached 99%, the cost per QALY gained remained greater than $200,000. Introduced in the early 1970’s by the Stanford group, the modern use of routine EMB for monitoring cardiac allograft rejection has been adopted by nearly all heart transplant centers.30 There are small, but real, procedural risks associated with repeated EMB. Potential complications of EMB include severe tricuspid regurgitation, cardiac tamponade, arrhythmias, accidental arterial puncture and bleeding.8-10 Additionally, in patients requiring anticoagulation for other medical conditions, there are risks associated with interruption or bridging of this therapy to allow for biopsies. The rationale for surveillance biopsies and accepting this small risk is that early recognition and treatment of high-grade rejection (ISHLT Grade 2R or higher) will decrease the risk of future allograft dysfunction or mortality. However, this practice was established in an era of less effective immunosuppression. With current immunosuppression regimens, the risk of significant rejection is approximately 30% in the first year. This risk peaks at one month after transplant and then rapidly declines over the subsequent five months reaching a low near-constant rate by the end of the first year.15 Therefore, the mean number of rejection episodes per patient decreases from 1.2 to 1.8 in the first year to 0.18, 0.13, and 0.02 in the second, third, and fourth years post HT, respectively.31 Additionally, between 60 and 85% of moderate grade rejection episodes (i.e. ISHLT 1990 Grade 2 and some Grade 3A or ISHLT 2004 Grade 1R and some 2R) resolve spontaneously without intensified immunosuppression and those that progress to higher grades of rejection generally occur within the first 6 months post-HT.17,21 Untreated asymptomatic cellular rejection has also not been associated with an increase in mortality17 and previous studies have demonstrated no difference in mortality using a symptom
driven biopsy strategy.\textsuperscript{16} In the setting of previously described low rates of asymptomatic rejection beyond 12 months post-HT, our model illustrated that prolonged EMB strategies are more costly and less effective than a symptom driven approach. To demonstrate any effectiveness of a routine surveillance biopsy strategy beyond one year with our model required using rates of asymptomatic cellular rejection and an attendant mortality that are significantly higher than have been reported in published series.

Despite tremendous progress over the past three decades in the care of the transplant patient, there still is a lack of consensus on how to risk-stratify patients and hence tailor post-transplant surveillance for rejection and graft dysfunction. Beyond the presence of histological evidence for rejection on an endomyocardial biopsy, there are numerous other factors which programs consider when devising a post-transplant surveillance strategy. Our analysis did not include individual risk factors for rejection such as a shorter time since transplant, history of rejection, younger age, and African-American ethnicity. Patients with a higher risk of rejection therefore may derive greater benefit from routine surveillance EMB and biopsy strategies may need to be individualized or modified based on the patient demographics of a particular transplant center. In particular, African-American patients are at risk for hemodynamically significant rejection and worsened mortality and may benefit from continuing biopsy surveillance for up to five years post-transplant.\textsuperscript{3,12} However, though non-African-Americans with risk factors are at a higher risk of late rejection, it may take at least 200 biopsies to prevent one hemodynamically significant episode without any clear survival benefit\textsuperscript{3} and our analysis may assist centers in deciding which surveillance strategy to employ.
The diagnosis of rejection and the decision to treat often is made in the face of negative or inconclusive biopsies. Such patients may be treated for rejection if they have profound hemodynamic perturbations or worsening systolic dysfunction. This is particularly evident with AMR, where only recently have consensus diagnostic pathology criteria been published. The routine assessment of donor specific antibodies (DSA) is becoming more commonplace and hence the interpretation of DSA and the decision to alter therapy could potentially be affected by the findings on biopsy. Lastly, the management of some patients may be affected by the invasive hemodynamics that are typically obtained in conjunction with the endomyocardial biopsy. Hemodynamic perturbations can heighten the suspicion for rejection, but may also suggest restrictive physiology or aid in the management of patient’s volume status. While an invasive surveillance strategy may take all of this data into account, the bulk of patients who present for routine surveillance biopsies are asymptomatic, have normal hemodynamics, bland biopsy findings and no DSA. Our data would suggest that continuing such an invasive strategy is not cost effective for the vast majority of transplant patients, but our knowledge of how to delineate the truly high-risk patient remains incomplete and will likely continue to evolve over time.

Cardiac transplantation remains the treatment of choice for patients with end-stage heart failure. It results in improved survival and quality of life. Current 1-year post-HT survival approaches 90% and the median survival is over 10 years, making cardiac transplantation a critical therapeutic option for select patients. However, heart transplantation is inherently costly. The billed charges for the heart transplantation procedure alone are approximately $780,000 and they have increased disproportionately relative to inflation since 1983. Charges for the first year post-HT approach $1,000,000. Additionally, long-term costs of post-transplant care such as careful monitoring of immunosuppression, screening for rejection and transplant vasculopathy,
and treating episodes of rejection can be as high as $70,000 per year.\textsuperscript{35} Consequently, heart transplantation cannot be fairly evaluated using a $50,000 or $100,000 per QALY gained benchmarks that are generally used in cost-effectiveness analyses.\textsuperscript{28,29} Society has largely accepted heart transplantation despite the high costs due to the lack of alternative treatments for generally young patients with a life limiting illness. With the considerable initial costs associated with transplantation, it is sensible to continue significant investments in post-HT care and surveillance. However, with increasing pressures to contain costs, we must still attempt to minimize unnecessary or extreme costs. While the incidence of serious complications related to EMB are less than 1\%\textsuperscript{11}, its diagnostic yield beyond 12 months post-HT is low, it results in patient discomfort, and adds to the significant costs associated with transplantation. In our model, prolonged surveillance EMB was less effective than shorter duration surveillance, due to the loss of QALYs associated with repeated EMB outweighing the gains associated with the procedure. In the setting of higher than previously demonstrated rates of asymptomatic cellular rejection and death from untreated asymptomatic rejection, routine surveillance EMB was only minimally effective for up to 24 months. Even then, its costs were well beyond what would be considered economically reasonable, millions of dollars per QALY gained. Therefore, routine surveillance EMB beyond one year post-HT are not cost-effective and their use should be reconsidered.

Limitations

Our analysis has several limitations. First, although most of our data inputs were based on prior studies of heart transplantation, these studies are generally small to moderate in size consisting of at most only a few hundred patients. Because of limited data in certain instances, such as the rate of acute cellular rejection given symptoms of rejection and the risk of death given untreated...
rejection, expert opinion was utilized. In particular, the 2.5% risk of asymptomatic ACR was based on a series of patients who were treated during a different era of maintenance immunosuppression.\(^\text{13}\) These patients were typically maintained with cyclosporine, azathioprine, and prednisone. With improved maintenance immunosuppression, it is possible that the risk of asymptomatic ACR is even lower and our analysis underestimated the cost associated with prolonged surveillance EMB. Second, treatment patterns for rejection (and therefore costs) vary amongst transplant centers. Less costly treatments, such as oral prednisone for ACR may result in a more favorable cost-effectiveness analysis. Third, many centers now use gene expression profiling tests to monitor for rejection beyond 12 months post-HT. We did not evaluate the use of these tests and only assessed the cost of biopsy surveillance compared to no routine surveillance. However, gene expression profiling may not offer any cost benefit over endomyocardial biopsies for prolonged surveillance.\(^\text{36}\) Finally, our model did not account for outcomes beyond 36 months and therefore may underestimate any delayed benefits of detecting asymptomatic rejection beyond 12 months post-HT. There may be a relationship between asymptomatic rejection and coronary artery vasculopathy, however the impact of discontinuing surveillance biopsies after one year on the rates of vasculopathy could not be determined with this study and would require much longer term follow up. However, asymptomatic rejection beyond 3 years remains rare and there continues to be controversy about whether rejection that occurs this late after HT has long-term negative effects.\(^\text{37}\)

**Conclusions**

Given currently accepted rates of rejection, using surveillance EMB for only the first 12 months post-HT is more effective and less costly than strategies where surveillance EMB is performed beyond 12 months. Even in the setting of improbably high rates of asymptomatic rejection and
mortality, the costs per QALY remain exceedingly high for performing surveillance EMB beyond one year. The role of surveillance EMB for cardiac transplant patients beyond one year should be reassessed.

**Disclosures**

None.

**References**

Table 1.

<table>
<thead>
<tr>
<th>Costs (US$ 2010) used in baseline analysis and ranges examined in sensitivity analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>Endomyocardial biopsy(^\text{13})</td>
</tr>
<tr>
<td>AMR Hospitalization(^\text{14})</td>
</tr>
<tr>
<td>AMR Treatment(^\text{13})</td>
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<tr>
<td>Hemodynamic ACR Hospitalization(^\text{14})</td>
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<tr>
<td>Hemodynamic ACR Treatment(^\text{13})</td>
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<td>ACR Treatment(^\text{13})</td>
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### Table 2.

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<th>Event</th>
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<th>Range</th>
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<tr>
<td>Developing rejection symptoms each month</td>
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<td>0.001 – 0.1</td>
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<td>Acute cellular rejection</td>
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<tr>
<td>Annual risk of asymptomatic ACR</td>
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<td>0.02 – 0.50</td>
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<td>Likelihood of ACR given symptoms</td>
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<td>Probability of death with treated ACR</td>
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<td>0.01 – 0.9</td>
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<td>Probability ACR resolves with treatment</td>
<td>0.95</td>
<td>0.1 – 0.95</td>
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<tr>
<td>Hemodynamic acute cellular rejection</td>
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<td>Likelihood of hemodynamic ACR given symptoms</td>
<td>0.15</td>
<td>0.01 – 0.5</td>
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<tr>
<td>Probability of death with treated hemodynamic ACR</td>
<td>0.06</td>
<td>0.01 – 0.9</td>
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<td>Probability hemodynamic ACR resolves with treatment</td>
<td>0.80</td>
<td>0.1 – 0.95</td>
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<td>Antibody Mediated Rejection</td>
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<tr>
<td>Annual risk of asymptomatic AMR</td>
<td>0.052</td>
<td>0.01 – 0.20</td>
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<tr>
<td>Likelihood of AMR given symptoms</td>
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<td>0.005 – 0.1</td>
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<td>Probability of death with treated AMR</td>
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<td>0.01 – 0.8</td>
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<td>Probability AMR resolves with treatment</td>
<td>0.76</td>
<td>0.1 – 0.95</td>
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<tr>
<td>Untreated</td>
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<td>Probability of death with untreated asymptomatic rejection</td>
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<td>0.01 – 0.9</td>
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<td>0.0005 – 0.5</td>
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<td>Condition</td>
<td>Baseline</td>
<td>Range</td>
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<tr>
<td>Well state (in a post-transplant patient)</td>
<td>0.76</td>
<td>0.1 – 0.99</td>
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<td>Endomyocardial biopsy</td>
<td>0.97</td>
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<tr>
<td>Acute cellular rejection</td>
<td>0.865</td>
<td>0.1 – 0.99</td>
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<td>Hemodynamic acute cellular rejection</td>
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<td>0.1 – 0.9</td>
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<td>Antibody mediated rejection</td>
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<td>0.1 – 0.9</td>
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<td>Hospitalization</td>
<td>0.65</td>
<td>0.1 – 0.9</td>
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<tr>
<td>Symptoms of rejection</td>
<td>0.8</td>
<td>0.1 – 0.99</td>
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Table 4.

<table>
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<tr>
<th>Specific Probabilities used in Monte Carlo Sensitivity Analysis</th>
<th>Likeliest</th>
<th>Min - Max</th>
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<tr>
<td>Probability ACR resolves with treatment</td>
<td>0.95</td>
<td>0.60 – 0.98</td>
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<tr>
<td>Probability hemodynamic ACR resolves with treatment</td>
<td>0.9</td>
<td>0.4 – 0.95</td>
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<tr>
<td>Probability AMR resolves with treatment</td>
<td>0.75</td>
<td>0.25 – 0.99</td>
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<tr>
<td>Probability asymptomatic rejection resolves without treatment</td>
<td>0.25</td>
<td>0.1 – 0.5</td>
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<tr>
<td>Utility of well state</td>
<td>0.76</td>
<td>0.5 – 0.95</td>
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<td>Utility of endomyocardial biopsy</td>
<td>0.997</td>
<td>0.5 – 0.999</td>
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<td>Utility of ACR</td>
<td>0.865</td>
<td>0.5 – 0.95</td>
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<td>Utility of hemodynamic ACR</td>
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<td>0.3 – 0.9</td>
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<tr>
<td>Utility of AMR</td>
<td>0.5</td>
<td>0.3 – 0.9</td>
</tr>
<tr>
<td>Utility of hospitalization</td>
<td>0.65</td>
<td>0.3 – 0.9</td>
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<tr>
<td>Utility of symptoms of rejection</td>
<td>0.8</td>
<td>0.4 – 0.9</td>
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Table 5.

<table>
<thead>
<tr>
<th>Biopsy Strategy</th>
<th>ICER – 2.5% annual risk asymptomatic cellular</th>
<th>ICER – 8.5% annual risk asymptomatic cellular</th>
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</thead>
<tbody>
<tr>
<td>Baseline (stop 12 months post-HT)</td>
<td></td>
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</tr>
<tr>
<td>q 4 months for 12-24 months post HT</td>
<td>Dominated*</td>
<td>$4,913,599†</td>
</tr>
<tr>
<td>q 6 months for 12-24 months post HT</td>
<td>Dominated*</td>
<td>$4,975,254†</td>
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<tr>
<td>q 4 months for 12-36 months post HT</td>
<td>Dominated*</td>
<td>Dominated*</td>
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<tr>
<td>q 6 months for 12-36 months post HT</td>
<td>Dominated*</td>
<td>Dominated*</td>
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ICER = incremental cost-effectiveness ratio
*More costly and less effective than the baseline strategy.
†Per quality adjusted life year gained
Figure Legends

**Figure.** Markov model. Patients remain in a health state (circular arrows) or move from one health state to another (straight or curved arrows) on the basis of transition probabilities. As patients cycle through the model, they accumulate costs and utilities expressed as QALYs. The Markov cycle length is 1 month. Patients enter the model in either the “well” state or with signs or symptoms of rejection. During each cycle, patients can remain well, develop acute cellular rejection (ACR), develop hemodynamically significant ACR, developing antibody mediated rejection (AMR), or die. For simplicity, the Dead state is not shown in the figure. All states can transition to death.
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Brent C. Lampert, Jeffrey J. Teuteberg, Michael A. Shullo, Jonathan Holtz and Kenneth J. Smith

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