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Brief Communication

The Economic Implications of Noninvasive Molecular Testing for Cardiac Allograft Rejection

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Endomyocardial biopsy is the mainstay for monitoring cardiac allograft rejection. A noninvasive strategy—peripheral blood gene expression profiling of circulating leukocytes—is an alternative with proven benefits, but unclear economic implications. Financial data were obtained from five cardiac transplant centers. An economic evaluation was conducted to compare the costs of outpatient biopsy with those of a noninvasive approach to monitoring cardiac allograft rejection. Hospital outpatient biopsy costs averaged $3297, excluding reimbursement for professional fees. Costs to Medicare and private payers averaged $3581 and $4140, respectively. A noninvasive monitoring test can reduce biopsy utilization. The savings to health care payers in the United States can be conservatively estimated at approximately $12.0 million annually. Molecular testing using gene expression profiling of peripheral circulating leukocytes is a new technology that offers physicians a noninvasive, less expensive alternative to endomyocardial biopsy for monitoring allograft rejection in cardiac transplant patients.

Key words: Endomyocardial biopsy, cost, heart transplantation, gene expression profiling, reimbursement, economics

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Introduction

Heart transplantation is established therapy for end-stage cardiac disease. Today, approximately 2200 persons receive heart transplants each year in the United States (1). The long-term outcomes of cardiac transplantation have steadily improved. However, death typically accompanies graft failure which, in turn, is often due to rejection (2). Heart retransplantation is rarely an option and, therefore, graft retention is essential.

Monitoring for acute rejection is critically important and remains a major challenge. Endomyocardial biopsy is the mainstay for detecting allograft rejection in heart transplantation. Unfortunately, it is far from ideal (3–10). It can only detect rejection after cellular infiltration and/or graft damage has occurred, the pathological interpretation is subjective and variable and the procedure is invasive, associated with discomfort, inconvenience and low but definite risks of complications and death.

Alternative noninvasive monitoring technologies have been tested in hopes of overcoming the foregoing problems (9). While several technologies have shown promise, either their performance has been poor or their implementation has been difficult. As a result, no viable alternative to biopsy has emerged.

A new approach may fulfill this promise. The Cardiac Allograft Rejection Gene Expression Observational (CARGO) study has demonstrated the feasibility and established the utility of peripheral blood gene expression profiling of circulating leukocytes for acute rejection management (11–14). Molecular testing now offers clinicians a noninvasive management (NIM) strategy for acute rejection monitoring and tailored immunosuppressive management. The first such test, based on the CARGO study, has recently been made commercially available (AlloMap™ test, XDx Reference Laboratory, South San Francisco, CA, USA).

The initial clinical results for this new technique for immunological monitoring have been impressive. Its

economic implications, based on reduced resource utilization, fewer complications and improved patient management, are expected to lower costs to payers and hospitals/transplant centers.

Methods

This economic evaluation has been performed in conjunction with the CARGO study. Supplemental data were collected to permit a straightforward comparison of invasive and noninvasive cardiac allograft rejection monitoring.

No previous attempt has been made to systematically examine the actual cost of endomyocardial biopsy. Therefore, in order to assess the economic impact of NIM strategies, such as molecular testing, endomyocardial biopsy costs must be quantified as well.

Below, various features of the CARGO study are presented first, followed by a description of the supplemental data. Next, the accounting procedures required for the cost analysis are reviewed. Finally, the approach used to analyze the data is summarized.

The cardiac allograft rejection gene expression observational study

The CARGO study began in August 2001, and enrolled over 650 cardiac transplant recipients at eight U.S. transplant centers (11–14). Over 6000 biopsies were performed and analyzed.

The participating centers—Stanford University, the University of California at Los Angeles, Ochsner Clinic, Temple University, Columbia University, Cleveland Clinic, the University of Pittsburgh and the University of Florida—are responsible for over 20% of the cardiac transplants performed each year in the United States.

The results of the CARGO study have been presented and published elsewhere (11–14). In brief, the study has demonstrated that molecular expression testing after cardiac transplantation distinguishes the quiescent state from acute rejection, and that a noninvasive clinical algorithm incorporating molecular testing in conjunction with clinical and graft function assessment can identify 65–85% of outpatient encounters as quiescent—not requiring biopsy.

A validation study has recently been completed. This study, along with regulatory certification of the reference laboratory, has resulted in the commercial offering of a molecular test for distinguishing cardiac allograft rejection and quiescence (AlloMap^{TM} test).

Supplemental financial data and cost accounting procedures

Financial and resource utilization data were obtained from five of the CARGO centers. Centers provided the following data: (i) full costs of endomyocardial biopsy (including direct and indirect costs), (ii) average Medicare and private payer reimbursement (based on their largest 3–5 contracts) for endomyocardial biopsy, including reimbursement amounts for the center, the pathologist and the cardiologist, (iii) case rate duration (for centers with private payer managed care contracts) and (iv) endomyocardial biopsy protocols and schedules.

As expected, cost accounting procedures and practices differed across the participating hospitals/transplant centers. Some centers used decision support systems for cost accounting, while others provided their cost data in the more traditional manner, using cost-to-charge ratios. This well-documented variability in approaches to cost accounting is a common difficulty encountered when conducting economic evaluations (15–18).

Three methods can be used to allocate costs (15,16). They are as follows: responsibility costing, full costing and differential costing. Centers provided full costing for this analysis. Under this system, full costs consist of the direct costs related to the production process, plus an allocated share of the indirect costs that the hospital incurs as overhead.

This study examines the costs and reimbursement of *outpatient* biopsies. Data on inpatient biopsies performed either during the perioperative period or as a result of transplant complications are not analyzed. It is assumed that the performance of inpatient biopsies will not be immediately affected in a molecular testing-based protocol.

Right-heart catheterization/invasive hemodynamics and noninvasive echocardiography are variably performed with biopsy procedures. The right heart catheter adds to the overall cost of the invasive approach and would not be performed in a molecular testing-based protocol.

Subject to the foregoing considerations, biopsy costs were estimated and reimbursement data were obtained from each of the participating centers.

General data analysis procedures

Descriptive statistics, including averages and volume-weighted averages, were computed for the cost and reimbursement data. Additionally, at this early stage in the development of molecular testing, when outcomes are considered to be equivalent under the null hypothesis, a cost-minimization analysis is appropriate (19,20). In the future, as outcome data become available and any significant variations are identified, a cost-effectiveness analysis with outcomes expressed in common natural units and valued accordingly is preferable (20).

With respect to the above, the overall effectiveness of molecular testing relative to endomyocardial biopsy is in the process of being firmly established in the ongoing Invasive Monitoring Attenuation through Gene Expression (IMAGE) trial. Based on the initial clinical results, molecular testing has been shown to have performance characteristics that equal those of endomyocardial biopsy when distinguishing acute rejection from quiescence. However, other outcomes are expected to have economic implications. Eventually, the results of the IMAGE trial will serve as the basis for a formal cost-effectiveness analysis.

Results

The results of this study are presented in two parts.

First, the data relevant to the cost-minimization analysis are aggregated across transplant centers and then summarized in tabular form (19). The data are averaged and the ranges for all centers identified. This approach assures the confidentiality of the data provided by each of the individual transplant centers—an essential condition for participation in the study.

Next, the data are analyzed according to multiple perspectives, including those of the hospital/transplant center, the Medicare program and private payers. Financial impacts are then calculated at both a patient-specific and at an aggregate level.

Table 1: Summary of the aggregated endomyocardial biopsy-related financial data

Variable	Average	Range
Biopsy cost		
Hospital only*	$3297	$642–$4628
Hospital (w/professional reimbursement)†	$4002	$1157–$5594
Total biopsy reimbursement		
Private payer	$4140	$1886–$5065
Medicare	$3581	$2919–$3934
Medicare reimbursement		
Hospital only	$2876	$2369–$3116
Cardiologist	$459	$423–$470
Pathologist	$246	$93–$497
Private payer reimbursement		
Hospital only	$3250	$1490–$4500
Cardiologist	$626	$284–$804
Pathologist	$264	$72–$557

*This is a fully allocated accounting cost estimate based on the volume-weighted average. It includes direct and indirect hospital costs, but excludes the fees for professional services associated with the biopsy. The hospital component or facility fee is often referred to as Part A, while Part B consists of the excluded professional fees.

†This is the functional cost of biopsy for the case rate period, during which the hospital/transplant center pays for professional services, typically at the Medicare rate. Because Medicare is a cost-based payment system, Medicare fees for professional services are considered to be a reasonable proxy for actual costs.

Cost analysis of endomyocardial biopsy

The participating centers performed an average of 58 heart transplant procedures per year (range: 31–95). The payer mix was similar across all centers, with 54% of the patients being privately insured (range: 35–67%), 33% covered by Medicare (range: 25–45%) and 13% being classified as 'other' (range: 8–20%).

Table 1 summarizes the aggregated endomyocardial biopsy-related financial data compiled for this analysis.

An estimated total accounting cost, including direct and indirect components, was derived for a typical hospital biopsy encounter (often referred to as Part A, or facility costs), excluding professional fees (often referred to as Part B). The average *cost* across all centers was $3297. Including professional reimbursement at the Medicare rate, the average biopsy cost was $4002 (Part A + Part B). This amount is the functional cost of biopsy during the case rate period, when the center is responsible for the professional reimbursement. Because the Medicare program consists of a cost-based payment system, Medicare fees for professional services are considered to be a reasonable proxy for costs.

Under a case rate contract, all services for a defined period of time are covered on the basis of a negotiated global price (18). There is no additional fee-for-service reimbursement during this period. The hospital/transplant center effectively bears the expense for all patient management during this period (e.g. transplantation, biopsies, laboratory tests, etc.) including professional fees. Once the period covered by the global contract expires, the hospital/transplant center and physicians are paid on a fee-for-service or per biopsy basis. The average duration of the case rate contract among the participating centers was 59 d (range: 14–104). It should also be pointed out that Medicare does not pay on a case rate basis for professional services (Part B), although hospital services (Part A) are covered under a diagnosis-related group.

Institutional *costs* must be distinguished from third party *reimbursement*, which often varies by payer source (17,18). Given the foregoing considerations, reimbursement information was obtained for Medicare and private insurers. In both cases, hospital and professional reimbursement were individually documented.

Total reimbursement from private payers and Medicare for the biopsy procedure, including professional fees and facility reimbursement, averaged $4140 and $3581, respectively. Note that while the distinction between *cost* and *reimbursement* is a significant consideration for hospitals/transplant centers, it is largely irrelevant for payers whose costs are functionally equivalent to what they pay for a service.

As shown in Table 1, on average, for all centers, the hospital-only (Part A) portion of the biopsy *cost* exceeds Medicare *reimbursement* by $421 ($3297–$2876). For private payers, this difference is only $47 ($3297–$3250). Thus, regardless of payer source, these results indicate that some hospitals are inadequately reimbursed for their biopsy-related costs.

As expected, the total biopsy reimbursement associated with private payers exceeds that of Medicare by $559 ($4140 vs. $3581, respectively).

Modeling the effects of a noninvasive management protocol

For purposes of this analysis, a straightforward financial model of posttransplant biopsy management was constructed, and the financial impact of modifying current protocols through the use of noninvasive testing was calculated taking into consideration multiple perspectives (i.e. hospital/transplant center and payer). This was accomplished using Microsoft© Excel spreadsheet software. Multiple formulas and functions were incorporated within the spreadsheet to depict the relationships among and between the relevant variables and assumptions (the functions and formulas are available upon request). While the intent of this analysis is to assess the financial impact of molecular testing using the AlloMap™ test, the modeling would apply to any NIM protocol that allowed for a

Table 2: Changes in biopsy utilization with noninvasive management (NIM)

Variables	Assumptions	
Year 1 Utilization	Current practice	With NIM adoption
Total biopsies	13	6.6
NIM tests	0	8
Years 2 through 5 utilization	Current practice*	With NIM adoption
Total biopsies (per year)	3	0.6
NIM tests (per year)	0	3
NIM test assumptions		
Biopsy follow-up rate	20%	
NIM test cost†	$2950	
NIM test cost, Medicare, 'other payers'†	$2655	

*While the majority of U.S. transplant programs indicate 2–4 protocol biopsies for cardiac allograft recipients in years 2–5 posttransplant, recently some centers have begun to reduce or eliminate biopsies in this >1 year posttransplant population. The analysis of biopsy reduction through NIM testing would be different in these centers. Currently they represent the minority, however.

†The list price of the AlloMap™ test is $2950. This price is essentially the cost of the test to payers with a 10% discount for Medicare (as is typical).

reduction of protocol biopsies and their replacement with an alternative test.

The NIM financial model makes several key assumptions about the utilization of the NIM test (Table 2). The key assumption is that the test will allow for a reduction of protocol or routine biopsies and their substitution with a NIM test.

Importantly, it is assumed that a positive NIM test, indicating rejection, may result in a follow-up or confirmatory biopsy. The 'biopsy follow-up frequency' is estimated to be 20% based on data from the CARGO validation study and the assumption that the majority of positive tests will result in a follow-up biopsy.

This financial model assumes a reduction of eight protocol-scheduled biopsies and substitution with eight NIM tests during the first year posttransplant. Due to the follow-up biopsies triggered by NIM tests indicating rejection, total biopsies are reduced by 6.4, from 13 to 6.6 (5 protocol scheduled biopsies plus 1.6 follow-up biopsies triggered by the assumption of 20% follow-up rate on 8 NIM tests).

It is assumed that year 2–5 protocol biopsies are reduced from three per year to zero per year, and substituted by three NIM tests. Total biopsies are reduced from three per year to 0.6 per year during years 2–5 posttransplant (0 protocol scheduled biopsies plus 0.6 follow-up biopsies triggered by the assumption of 20% follow-up rate on three NIM tests).

Table 3: Financial modeling results showing the impact of the NIM test according to the perspectives of hospitals/transplant centers and payers

Per patient savings for hospitals/transplant centers and payers* ($ per patient over 5 years of management)	
Hospitals/transplant centers	3741
Payers	
Medicare	4193
Private insurers	6511
Hospital/transplant center case study: total annual savings ($ per year)	
Hospital/transplant center	187 064
Payers	
Medicare	69 181
Private insurers	175 784
Total annual savings to hospitals/transplant centers and and payers*‡ ($ per year)	
Hospitals/transplant centers	8 230 832
Payers (all)	11 977 621
Medicare	3 043 973
Private insurers	7 734 507
Other payers (e.g. Medicaid)	1 199 141

*All figures exclude expenses associated with biopsy-related complications.

†Hospital/transplant center case study assumptions are as follows: (i) 50 heart transplants per year, (ii) 250 heart transplant recipients being managed long-term, (iii) 33% of patients covered by Medicare and (iv) 54% of patients covered by private insurers.

‡Calculations are based on per-patient savings extrapolated to the U.S. cardiac transplant population (estimated at 2200 new transplants per year and 11 000 total patients actively managed).

For purposes of financial modeling, the price of the currently available NIM test is used (i.e. $2950, with a 10% Medicare discount). This represents the cost of molecular testing to the payers.

In three successive steps, Table 3 presents the results of the financial model used in the cost analysis.

First, the table shows per patient savings from both a hospital/transplant center and a payer perspective. Savings impacts are shown per patient over 5 years of management (with NIM testing assumptions as per Table 2). Over 5 years, per patient savings to hospitals/transplant centers will be $3741, while per patient savings to Medicare and private insurers will be $4193 and $6511, respectively.

Second, Table 3 presents a case study of the impact of NIM testing on a hypothetical hospital/transplant center and its payers. In this case, it is projected that a center doing 50 transplants per year and managing 250 total heart transplant recipients would save $187 064 per year upon introduction of NIM testing. With Medicare covering 33% of these patients, the annual savings would be $69 181. Private payers covering 54% of these patients would be expected to save $175 784 per year upon introduction of NIM testing.

Finally, Table 3 provides an estimate of the total annual or aggregate savings associated with the NIM test. The savings to Medicare is approximately $3.0 million, compared with $7.7 million for private insurers and $1.2 million for other payers (e.g. Medicaid, Military Health System, etc.), equaling a total payer savings of approximately $12.0 million annually. Meanwhile, hospitals/transplant centers are projected to experience an annual savings of about $8.2 million.

Discussion

This study documents the costs and reimbursement of endomyocardial biopsy in cardiac transplantation, while also modeling significant savings for payers and hospitals/transplant centers upon introduction of a NIM approach, such as molecular testing.

At this time, it is difficult to estimate the economic impact of molecular testing on physicians. Data collected in this study did not include important inputs into this analysis, such opportunity costs, hospital risk pool distribution methodologies and the contractual relationships between hospitals/transplant centers, physicians and payers.

While it is clear that revenue from biopsy will drop as biopsy usage decreases, physicians and hospitals/transplant centers incur significant opportunity costs in performing biopsies. The biopsy procedure takes a cardiologist approximately 20–40 min to perform and a corresponding amount of time for a nurse or laboratory technician, as well as catheterization laboratory or biopsy suite time. At one major center in this study, a 450 h per year physician facility and support staff timesavings was estimated. Using these timesavings to perform additional revenue generating procedures may offset the decreased physician biopsy revenue.

The cost analysis presented here does not entirely capture the full clinical and economic benefits associated with molecular testing. Significant value-added benefits can be anticipated in three areas. Once the necessary data become available, the value of these added benefits must be firmly established in a formal cost-effectiveness analysis.

First, biopsy-related complications will be reduced as biopsy usage decreases. While endomyocardial biopsy in transplant recipients is generally safe, there are low but definite risks of complications, such as pneumothorax, ventricular perforation, flail tricuspid leaflets, arrhythmias and even death (4–10). The incidence of serious complications is estimated in the literature between 0.3% and 0.7% (5,6,8–10).

Based on resource utilization, the treatment expenditures associated with the more serious complications are predictably substantial, although these have not been documented in financial terms by discrete causes in the published literature.

Second, in addition to reduced complications, biopsy reduction has other patient benefits including diminished pain and suffering, decreased use of an invasive and unpleasant procedure, potential quality of life improvements and increased patient satisfaction.

Third, while not included in this analysis, it is possible that the clinical benefits of molecular testing will exceed simply replacing biopsies. This test has been shown to be predictive of future clinical outcomes and possessing a high negative predictive value for future rejection, which may lead to immunosuppression optimization and improved patient outcomes.

There are several issues associated with this analysis that are currently being addressed in ongoing studies. These include the following: (i) the uncertainty and potential variability in usage patterns and frequency of molecular testing, (ii) the prevalence of heart transplant monitoring protocols with infrequent biopsies greater than 1 year posttransplant and their relationship to molecular testing use and (iii) the cost implications of potential immunosuppression reduction through molecular testing.

In summary, molecular testing using gene expression profiling of peripheral circulating leukocytes is a new technology offering physicians a noninvasive alternative to endomyocardial biopsy. This study demonstrates that biopsy reduction through NIM strategies, such as molecular testing, extends significant economic savings to payers and hospitals/transplant centers. These savings are likely to be even more remarkable once the above-mentioned data become available to conduct a formal cost-effectiveness analysis.

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