Original article

Budget impact analysis of a novel gene expression assay for the diagnosis of malignant melanoma

David S. Cassarino
Department of Pathology, Southern California Permanente Medical Group, Los Angeles, CA, USA

Nicolas Lewine
Doria Cole
Brandon Wade
Gary Gustavsen
Health Advances, LLC, Weston, MA, USA

Address for correspondence:
Gary Gustavsen, MS, Health Advances, LLC 9 Riverside Road, Weston, MA 02493, USA. E-mail: ggustavsen@healthadvances.com

Keywords:
Melanoma – Gene expression – Cost-effectiveness – Health economics – Myriad myPath Melanoma – Dermatology – Pathology

Accepted: 25 July 2014; published online: 11 September 2014
Citation: J Med Econ 2014; 1–10

Abstract

Background:
Traditional pathology techniques alone can be insufficient to reliably distinguish between malignant melanoma, dysplastic nevi, and benign nevi in biopsies of suspicious pigmented lesions. Numerous studies have shown high rates of ambiguity when assessing such samples. A novel gene expression assay has been developed to objectively differentiate malignant melanoma from benign nevi.

Objective:
The purpose of this study was to quantify the economic impact of the gene expression assay on a US commercial health plan.

Methods:
The clinical paradigm of care was modeled for a hypothetical cohort of patients with suspicious pigmented lesions that are difficult-to-diagnose. Costs were assigned to each unit of care provided based on 2013 Medicare fee-for-service rates. Patients were followed for 10 years and were modeled to progress according to the natural history of their disease. The total cost of care was calculated for two scenarios: a Reference Scenario, representing current clinical practice, and a Test Scenario, in which each lesion was tested with the gene expression assay and diagnosed. Total cost of care was compared between the two scenarios to determine overall budget impact. Sensitivity analyses were performed to test the robustness of the model.

Results:
The gene expression assay reduces costs by $1268 per patient tested over 10 years, a decrease of 8.3%, after accounting for the cost of the assay. For a health plan with 10 million members, this would translate to over $8 million in savings. The largest portion of this saving comes from reducing the number of missed melanomas, which would otherwise progress to advanced disease. In sensitivity analyses, no single model input changed within a reasonable range of values caused the model to show that the assay was not cost-saving.

Conclusion:
In addition to improving the diagnosis of melanoma, this gene expression assay would likely reduce costs for health plans that choose to cover it.

Introduction

Melanoma affects over 76,000 people per year in the US and nearly 10,000 will die of their disease. Early detection is crucial; over 98% of patients with localized melanoma survive 5 years after their diagnosis, compared to only 16% of patients with metastatic disease. Although the treatment of metastatic...
melanoma has improved significantly in recent years due to the approval of several novel therapies, the majority of patients with metastatic disease still typically progress within 10 months.3–5

Early detection of melanoma relies on patients or physicians identifying a pigmented lesion that displays worrisome characteristics.6 Once identified, these suspicious pigmented lesions (SPLs) are biopsied and sent to a pathologist for analysis. Approximately 2 million SPL biopsies occur per year in the US, less than 5% of which are actually diagnosed as melanoma.7,8 Although this illustrates the frequency of potentially unnecessary biopsies of non-malignant lesions, the more troubling aspect of melanoma diagnosis is the uncertainty pathologists often encounter when attempting to distinguish melanoma from non-melanoma.

Numerous studies have illustrated that pathologists arrive at different diagnoses for the same samples in a small percentage of cases. For example, on 478 consecutive cases referred to the Massachusetts General Hospital Pigmented Lesion Clinic, expert pathologists documented a change from the original pathologist’s diagnosis in 35% of cases, nearly two-fifths of which led to a change in recommended treatment.9 Another study showed that, in 143 difficult-to-diagnose cases, two Columbia University pathologists agreed only 55% of the time; in 36% of cases, one pathologist called the lesion definite or probable melanoma, while the other called it definite or probable benign nevus.10 Piepkorn et al.11 showed that concordance was only 56% between six dermatopathologists, while Farmer et al.12 showed that 38% of tested samples had at least two discordant interpretations. Alarmingly, Brochez et al.13 found that pathologists on average missed 13% of melanomas, and 25% of samples diagnosed as melanomas were actually false-positives. Numerous other studies show similar levels of discordance.7,14–20 Although certain factors pre-dispose a sample to misdiagnosis—such as originating from a punch biopsy or being a dysplastic nevus or a Spitz nevus—misdiagnosis is found across all lesion types.13,14,16,18

The over-diagnosis of melanoma is concerning because it not only causes patients to undergo unnecessary procedures and years of close clinical follow-up, but can also cause significant psychological and emotional stress for patients.21–23 Missed melanomas, on the other hand, can be clinically and financially devastating because untreated melanomas are likely to progress to more advanced—and potentially incurable—disease. In both cases, physicians risk litigation; one notable analysis found that misdiagnosis of melanoma was the second-most common cause of pathology malpractice claims.24

It is clear from this evidence that pathologists would benefit from improved tools to clearly distinguish melanoma from non-melanoma. Many pathologists commonly use immunohistochemical stains for markers such as Ki-67 to attempt to make a more informed diagnosis, but misdiagnosis persists.25–27 Some pathologists have begun using various types of genetic investigations such as fluorescence in situ hybridization (FISH)28–31 or array comparative genomic hybridization (aCGH)32. However, these assays are largely investigational and require time and particular expertise to develop, perform, and interpret.33–35 Therefore, pathologists still have an unmet need for an objective melanoma diagnostic that is broadly accessible and provides a clear, actionable result.

Myriad myPath Melanoma is a gene expression assay that was developed to address this unmet need. Using formalin-fixed, paraffin-embedded (FFPE) SPL biopsy tissue as a sample, this real time PCR-based assay measures the expression levels of 23 genes from various independent biological pathways and combines it into a diagnostic 'score' that is used to distinguish melanoma from non-melanoma.36 The assay was developed on a training cohort of 595 samples and validated on an independent cohort of 571 samples from four leading US institutions. In the validation cohort, the assay was able to identify melanoma with 90% sensitivity and 91% specificity.36 In addition, early data on the assay’s clinical utility suggests that it improves concordance between pathologists and causes pathologists to change their treatment recommendations in some cases.37

However, in order to impact patient care in real-world clinical practice, the test must be covered by healthcare payers such as commercial insurance companies and government health plans. These payers are increasingly concerned with the cost of molecular tests due to the growing number of high-cost molecular diagnostic and prognostic tests currently being developed and launched.38,39 In particular, the economic impact of this melanoma diagnostic test has not yet been evaluated.

The objective of this study was to model the economic impact of Myriad myPath Melanoma (‘the assay’) on a hypothetical US commercial payer.

Methods

Model design and modeled population

A deterministic, decision-analytic model was developed to project the cost of using the gene expression assay compared to standard clinicopathologic evaluation. The assay is intended for use in ambiguous, difficult-to-diagnose SPL biopsy samples. Accordingly, the model included only patients with difficult-to-diagnose SPLs. The model followed a single cohort of patients, each with a difficult-to-diagnose SPL biopsy in the first year of the model. The clinical care given to these patients was modeled over 10 years, including natural progression to more advanced stages of melanoma as appropriate. Costs were
assigned to each unit of care according to the reimbursement rates paid by a typical US commercial health plan. The clinical paradigm and total costs were calculated for two parallel scenarios: the Reference Scenario, designed to reflect current clinical practice in the absence of the assay, and the Test Scenario, in which all of the patients were assumed to receive the assay in the first year of the model and the subsequent clinical paradigm was adjusted accordingly. Costs were compared between the Reference Scenario and the Test Scenario in order to determine the assay’s economic impact.

Within the modeled population, patients were followed in separate cohorts according to their diagnosis: conventional nevus, dysplastic/atypical nevus, or malignant melanoma. The distribution of samples in the Reference Scenario was determined by combining the current distribution of all SPLs among these three cohorts with the varying rates of ambiguity in each (Supplemental Table 1)\textsuperscript{17,19–20}. Within the dysplastic cohort, mild, moderate, and severe dysplasia were modeled separately due to differences in recommended treatment for each\textsuperscript{40,41}. Although severe dysplasia is more rare than mild/moderate dysplasia among all SPLs, it accounts for a larger portion of the modeled population due to its significantly higher rate of ambiguity\textsuperscript{13,18}. Within the malignant melanoma cohort, localized, regional, and distant melanoma were modeled separately due to their significantly different treatment and prognosis. The majority of melanoma diagnoses in the model were of localized disease, since there is significantly less ambiguity in diagnosis of regional or distant melanoma.

### Cost inputs

Table 1 displays the unit costs employed in the model. Unless otherwise specified, costs were based on 2013 Medicare fee-for-service rates\textsuperscript{42}. To determine which Current Procedural Terminology (CPT) codes were most commonly used in real-world practice, interviews were conducted with professional coders in the fields of dermatology, dermatopathology, and surgical oncology. CPT codes were then mapped to national payment rates using 2013 Medicare fee schedules. For each code, the total Medicare reimbursement (combining both professional fees and facility fees, as appropriate) was calculated for four separate Place of Service settings: physician office, ambulatory surgical center, hospital outpatient, and hospital inpatient. The payment amounts for each setting were then combined in a weighted average according to the number of times the relevant CPT code was billed to Medicare from each of the four settings in 2012. This data was sourced from the 2012 PhysicianSupplier Procedure Summary (PSPS) database, which contains data on all fee-for-service claims billed to Medicare Part B.

For certain types of care, a variety of CPT codes are used to describe similar services; in these cases, a single payment amount was calculated by performing a weighted average of the different codes according to their real-world billing frequency using the PSPS database. Finally, based on interviews with several commercial health plans, all Medicare payment rates were inflated by 25% to better reflect the rates paid by commercial insurers (with the exception of payment rates for pharmaceuticals).

If Medicare costs were unavailable for a certain type of care, its cost was determined from an alternative source. The cost of aCGH ($1650) was sourced from commercial laboratories’ advertised prices\textsuperscript{43,44}. The cost of the gene expression assay ($1500) was sourced from the assay manufacturer. Costs for oral pharmaceuticals were sourced from published Wholesaler Acquisition Cost (WAC) prices\textsuperscript{45}.

For pharmaceuticals, the cost per milligram was translated into the cost of a full course of treatment according to the dosing schedule specified in the drug’s FDA label, clinical guidelines, or the most relevant clinical trials\textsuperscript{36–53}. For dosing schedules dependent on body weight or surface area, an average body weight of 70 kg and body surface area of 1.73 m\textsuperscript{2} were used.

### Clinical paradigm

In order to calculate the total cost incurred by a payer in the Reference Scenario, a clinical paradigm was mapped that specified exactly what units of care were received by each patient. This paradigm was determined using clinical guidelines, clinical literature, and interviews with expert physicians. Fourteen physician interviews were conducted, comprising four dermatologists, eight dermatopathologists, and two surgical oncologists. Within each specialty, interviewees were geographically varied and from a mix of community and academic practices. The clinical paradigm in the Reference Scenario, along with associated costs, is displayed in Figure 1.

The clinical paradigm and costs were modeled according to each patient’s diagnosis and were separated into three distinct categories: diagnostic pathology costs, to be incurred in the first year of the model (Figure 1A), initial treatment costs, to be incurred in the year that the patient is diagnosed (Figure 1B), and follow-up and monitoring costs, to be incurred each year after the patient is diagnosed (Figure 1C).

Diagnostic pathology costs did not vary by diagnosis, since they are incurred before a diagnosis is made. All patients were assumed to receive the ‘standard pathology’ evaluation (i.e., H&E stain and visual sample examination). Within the modeled population (which consists only of difficult-to-diagnose samples), all samples received immunohistochemistry and a second opinion. In addition, half received some form of advanced molecular testing in
the Reference Scenario (40% FISH, 10% aCGH). In the Test Scenario, the gene expression assay replaced any use of FISH and aCGH.

Initial treatment costs varied significantly by diagnosis. Few benign lesions receive wide local excision (WLE), although most dysplastic and malignant lesions do. In the model, a high percentage of dysplastic lesions received WLE because over 75% of the modeled dysplastic population is composed of lesions with severe dysplasia due to their greater ambiguity (Supplemental Table 1). Not all malignant lesions receive WLE, because some are sufficiently excised with the original biopsy. After WLE, patients with Breslow thickness >1 mm are recommended to receive a sentinel lymph node biopsy (SLNB) to test for regional disease. Approximately 60–70% of melanoma lesions have a depth of ≤1 mm, and therefore do not get a SLNB. Of those who do receive a SLNB, 15–25% have detectable disease in the sentinel node and are, therefore, upstaged to regional disease. Patients with regional disease receive a complete lymph node dissection (CLND) and a minority (15%) also receive adjuvant therapy with high-dose interferon alpha-2b.

Finally, all patients who progress to metastatic melanoma were assumed to receive systemic drug therapy, while ~40% receive radiation therapy as well. The cost of systemic drug therapy was calculated using a hypothetical sequential drug regimen based on clinical guidelines and Table 1. Unit costs.

<table>
<thead>
<tr>
<th>Category</th>
<th>Unit</th>
<th>Unit cost*</th>
<th>Primary codes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>(CPT unless otherwise specified)</td>
</tr>
<tr>
<td>Diagnostic pathology</td>
<td>Surgical Pathology/H&amp;E</td>
<td>$78</td>
<td>88305</td>
</tr>
<tr>
<td></td>
<td>Immunohistochemistry, per stain</td>
<td>$134</td>
<td>88321–88325</td>
</tr>
<tr>
<td></td>
<td>Second Opinion</td>
<td>$134</td>
<td>88367</td>
</tr>
<tr>
<td></td>
<td>FISH</td>
<td>$1425</td>
<td></td>
</tr>
<tr>
<td></td>
<td>aCGH</td>
<td>$2063</td>
<td></td>
</tr>
<tr>
<td></td>
<td>myPath™ Melanoma</td>
<td>$1500</td>
<td></td>
</tr>
<tr>
<td>Initial treatment</td>
<td>Wide Local Excision - Benign Lesion</td>
<td>$330</td>
<td>11400–11446</td>
</tr>
<tr>
<td></td>
<td>Wide Local Excision - Malignant Lesion</td>
<td>$468</td>
<td>11600–11646</td>
</tr>
<tr>
<td></td>
<td>Repair</td>
<td>$463</td>
<td>12031–13153</td>
</tr>
<tr>
<td></td>
<td>Graft</td>
<td>$1543</td>
<td>15200–15261</td>
</tr>
<tr>
<td></td>
<td>Tissue Transfer</td>
<td>$1513</td>
<td>14000–14060</td>
</tr>
<tr>
<td></td>
<td>WLE Pathology</td>
<td>$103</td>
<td>88305</td>
</tr>
<tr>
<td></td>
<td>Sentinel Lymph Node Biopsy</td>
<td>$3500</td>
<td>38500–38530</td>
</tr>
<tr>
<td></td>
<td>Sentinel Lymph Node Biopsy Pathology</td>
<td>$299</td>
<td>88307</td>
</tr>
<tr>
<td></td>
<td>Complete Lymph Node Dissection</td>
<td>$7098</td>
<td>38724, 38745, 38760, DRG 581</td>
</tr>
<tr>
<td></td>
<td>Complete Lymph Node Dissection Pathology</td>
<td>$1363</td>
<td>88307 x10</td>
</tr>
<tr>
<td>Laboratory testing</td>
<td>Comprehensive metabolic panel</td>
<td>$18</td>
<td>80053</td>
</tr>
<tr>
<td></td>
<td>Lactate dehydrogenase</td>
<td>$10</td>
<td>83615</td>
</tr>
<tr>
<td></td>
<td>Complete blood count</td>
<td>$11</td>
<td>85027</td>
</tr>
<tr>
<td></td>
<td>Liver function panel</td>
<td>$14</td>
<td>80076</td>
</tr>
<tr>
<td>Drugs</td>
<td>Adjuvant high-dose IFN alfa-2b</td>
<td>$59,944</td>
<td>J9214</td>
</tr>
<tr>
<td></td>
<td>High-dose Interleukin 2</td>
<td>$59,148</td>
<td>DRGs 837–838</td>
</tr>
<tr>
<td></td>
<td>Ipilimumab</td>
<td>$106,680</td>
<td>J9228</td>
</tr>
<tr>
<td></td>
<td>Vemurafenib</td>
<td>$132,013</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dabrafenib</td>
<td>$92,462</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Trametinib</td>
<td>$105,850</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dacarbazine</td>
<td>$1525</td>
<td>J9130</td>
</tr>
<tr>
<td></td>
<td>Temozolomide</td>
<td>$50,593</td>
<td>J8700</td>
</tr>
<tr>
<td></td>
<td>Paclitaxel</td>
<td>$926</td>
<td>J9626</td>
</tr>
<tr>
<td>Imaging</td>
<td>X-Ray</td>
<td>$55</td>
<td>71020</td>
</tr>
<tr>
<td></td>
<td>CT</td>
<td>$389</td>
<td>71260</td>
</tr>
<tr>
<td></td>
<td>MRI (Brain)</td>
<td>$643</td>
<td>70552</td>
</tr>
<tr>
<td></td>
<td>PET/CT</td>
<td>$1469</td>
<td>78816</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>Office Visit - Min</td>
<td>$53–$293</td>
<td>99201–99205, 99211–99215</td>
</tr>
<tr>
<td></td>
<td>Chemotherapy administration</td>
<td>$202</td>
<td>96413–96415</td>
</tr>
</tbody>
</table>

*Where possible, costs were based on 2013 Medicare fee-for-service rates weighted by the billing frequency in each setting (e.g., physician office vs hospital outpatient). All Medicare rates except drug costs were inflated by 25% to account for a commercial payer’s perspective.

**Cost sourced from prices advertised by commercial laboratories.

†Cost sourced from test manufacturer.

Includes cost of IHC for a minority of samples.

Cost sourced from published WAC price.

††Costs represent a full course of treatment according to the dosing schedule specified in the FDA label or most current guidelines/trials. For dosing schedules dependent on patient characteristics, an average body weight of 70 kg and body surface area of 1.73 m² were used.
For each drug in the regimen, the cost of a full course of therapy was pro-rated according to the drug's published progression-free survival. These pro-rated costs were summed to determine the overall cost of systemic drug therapy (see Table 1).

Follow-up and Monitoring protocols were based on published literature and guidelines. Only incremental costs directly attributable to the original SPL were modeled. Patients with dysplastic or malignant lesions received incrementally more SPL biopsies in subsequent years since their original lesion would cause them to be considered higher-risk. These subsequent biopsies of unrelated lesions were all assumed to be unambiguously benign, and therefore incurred no costs beyond the biopsy itself and initial pathology. Patients with melanoma received annual imaging exams, increasing from X-Rays for localized melanoma to CT or PET/CT for regional or distant melanoma.

Disease progression

Over the 10-year duration of the model, patients were shifted between diagnosis categories according to the natural progression rate of their disease. For benign and dysplastic lesions, no lesions progressed to melanoma except 'False Negative' lesions (i.e., missed melanomas). The percentage of false negative lesions that progressed to melanoma varied according to the diagnosis the patient actually received, since a missed melanoma can be cured by WLE (Supplemental Figure 1B). Therefore, false negatives had a greater chance of progressing to melanoma if they were initially diagnosed as benign (which do not typically receive WLE) vs dysplastic (which commonly receive further excision). All disease progression was modeled according to the rate specified by published Kaplan-Meier curves for similar disease.

For patients with melanoma, progression to later stages of disease was based on published survival statistics (Supplemental Figure 1A).

Test impact

In the Test Scenario, modeled samples were tested with the gene expression assay. To determine its impact on patients' diagnoses, the assay's sensitivity (90%) and specificity (91%) were applied to the modeled population so that it correctly identified 90% of Condition Positives (i.e., true positives + false negatives) and 91% of...
Table 2. False result rate.

<table>
<thead>
<tr>
<th>Lesion type</th>
<th>False result rate in overall SPL biopsy population</th>
<th>Percentage of all SPLs that are ambiguous (i.e., modeled population)</th>
<th>False result rate in modeled population**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign</td>
<td>0.5%</td>
<td>5%</td>
<td>10%</td>
</tr>
<tr>
<td>Dysplastic</td>
<td>2.5%</td>
<td>20%</td>
<td>12.5%</td>
</tr>
<tr>
<td>Malignant</td>
<td>5%</td>
<td>19%</td>
<td>33%</td>
</tr>
<tr>
<td>Total</td>
<td>1.3%</td>
<td>10%</td>
<td>13%</td>
</tr>
</tbody>
</table>

*see Supplemental Table 1.
**False Result Rate in Overall SPL divided by percentage of all SPLs that are ambiguous; Assumes all false results are ambiguous and would, therefore, be tested.

Condition Negatives (i.e., true negative + false positives). The rates of misdiagnosis (i.e., false positives and false negatives) in the Reference Scenario were calculated by dividing the overall misdiagnosis rate in the whole SPL population by the percentage of samples that are ambiguous (and therefore modeled) (Table 2).

### Cost savings and sensitivity analysis

To determine the economic impact of the assay on a hypothetical commercial payer, total and per-patient costs were compared between the Test Scenario and the Reference Scenario. One-way sensitivity analyses were conducted for each major assumption to test the model’s robustness. For this analysis, the assay’s cost impact was re-assessed after changing each assumption to its minimum and maximum plausible value.

### Results

#### Impact on diagnostic accuracy

The net effect of the assay was to increase diagnostic accuracy from 87% of tested samples to 91% (Table 3). More specifically, the assay drastically reduced the rate of missed melanomas in the modeled population from 11% to 2%, while increasing the false positive rate from 3% to 8%.

The cumulative 10-year cost of managing patients with inaccurate diagnoses is much higher than the cost if they had been diagnosed accurately (Table 3). Benign lesions cost less than $2800 over 10 years if they are diagnosed accurately, but cost $14,600 if they are misdiagnosed as melanoma. Melanomas cost, on average, $43,000 over 10 years if diagnosed accurately, but cost anywhere from $58,000 to $104,000 if they are misdiagnosed as benign or dysplastic, respectively, due to progression to more advanced disease. On the whole, the assay re-allocates patients from the more expensive missed melanoma categories to less expensive categories.

#### Source of savings

The largest portion of the savings came from a reduction in treatment for advanced disease (due to reducing the number of missed melanomas) and from a reduction in the use of other advanced molecular pathology methods such as FISH and aCGH. Figure 2 shows the assay’s cost impact for each type of care.

The assay reduces missed melanomas from 10% of the benign tested population and 13% of the dysplastic tested population to 1% of each (Table 3). This leads to an increase in spending on initial treatment and annual follow-up, since these missed melanomas are now accurately diagnosed as melanoma. However, this increase is offset by significant savings on downstream treatment for advanced disease, since many of these lesions would have progressed to regional or distant disease if left untreated. Combined with the savings on other molecular pathology tools and the cost of the assay itself, net per-patient savings
over 10 years was $3504 for patients originally diagnosed as benign and $210 for patients originally diagnosed as dysplastic (Figure 2).

For the lesions in the tested population that were originally diagnosed as melanoma, the assay reduces over-diagnosis of melanoma from 33% of this sample of highly ambiguous lesions to only 3% (Table 3). This downgrading leads to savings on initial treatment and annual follow-up, since non-melanomas incur fewer costs than melanomas. The net per-patient savings over 10-years for these samples was $63 (Figure 2). The spending on advanced treatment in this cohort increases due to the assay’s imperfect sensitivity, which leads to some of these melanomas being missed and progressing to advanced disease.

**Sensitivity analysis**

To assess the model’s sensitivity to changes in specific inputs, each input was modified within its range of plausible values and the overall cost savings were re-calculated. Each tested input was changed in a way that lowered the cost savings (‘Conservative’) and in a way that increased it (‘Aggressive’).

No single input, when changed within a reasonable range of values, caused the model to show that the assay was no longer cost-saving (Figure 3). Of the 21 inputs tested, 13 changed the per-patient cost savings by less than 30% in either direction. The eight inputs to which the model was most sensitive are shown in Figure 3. The model was most sensitive to the percentage of samples that are ambiguous and, therefore, sent for testing with the gene expression assay; poor selection of appropriate samples by referring dermatopathologists would lead to reduced cost-effectiveness. The model was also sensitive to the rates of disease progression for localized melanomas and missed melanomas diagnosed as dysplastic lesions. If only 20% of missed melanomas diagnosed as dysplastic lesions progress (vs 35% in the model’s base case), cost savings would decrease by 64%, to $491 per patient. More plausibly, if

<table>
<thead>
<tr>
<th>Type of Care</th>
<th>Cost at 10 years</th>
<th>Per-Patient Cost Impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnostic Pathology</td>
<td>-$776</td>
<td>-$1,500</td>
</tr>
<tr>
<td>Cost of Test</td>
<td>-$1,825</td>
<td>-$496</td>
</tr>
<tr>
<td>Initial Treatment</td>
<td>-$1,261</td>
<td>-$360</td>
</tr>
<tr>
<td>Follow-Up and Monitoring</td>
<td>-$2,383</td>
<td>-$808</td>
</tr>
<tr>
<td>Treatment for Advanced Disease</td>
<td>-$6,046</td>
<td>-$2,358</td>
</tr>
<tr>
<td>Net Impact</td>
<td>-$3,087</td>
<td>-$1,268</td>
</tr>
<tr>
<td><strong>Whole Population</strong></td>
<td><strong>-$6,046</strong></td>
<td><strong>-$1,268</strong></td>
</tr>
</tbody>
</table>

**Figure 2.** Per-patient economic impact by Reference Scenario diagnosis and type of care. Negative numbers indicate cost savings; positive numbers indicate cost increases. The assay is cost-saving in all diagnostic categories. In lesions originally diagnosed as benign or dysplastic, the assay identifies a number of melanomas that would otherwise be missed, which increases initial treatment and follow-up costs while significantly decreasing the costs incurred treating advanced disease. In lesions originally diagnosed as Melanoma, the assay identifies a number of false positives, which reduces initial treatment and follow-up costs.

<table>
<thead>
<tr>
<th>Table 4. Assay economic impact.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of assays</strong></td>
</tr>
<tr>
<td>Per patient tested</td>
</tr>
<tr>
<td>5 M Member Health Plan</td>
</tr>
<tr>
<td>10 M Member Health Plan</td>
</tr>
</tbody>
</table>

*Assumes health plan members receive skin biopsies at the same rate as the national average.

**Cumulative cost in Reference Scenario minus Cumulative Cost in test scenario.**
50% of missed melanomas diagnosed as dysplastic lesions progress, cost savings would increase by 61% to over $2000 per patient.

### Discussion

The diagnosis of malignant melanoma is imperfect. Although routine pathology examination is sufficient to diagnose the majority of suspicious pigmented lesions, discordance rates between different pathologists examining ambiguous samples are alarmingly high. This discordance leads to misdiagnosis in both directions: some nevi are misdiagnosed as melanoma and some melanomas are misdiagnosed as benign or atypica/dysplastic nevi. In both cases, patients suffer, physicians become vulnerable to litigation, and healthcare costs are needlessly increased.

Myriad myPath Melanoma is a gene expression assay designed to serve as an objective, unambiguous tool to differentiate melanoma from non-melanoma. It has been shown to be highly accurate and has demonstrated strong potential for clinical utility. To further assess the assay’s value to the healthcare system, this study modeled its impact on costs incurred by a hypothetical third-party payer.

The analysis demonstrated that this assay could generate significant cost savings for commercial health plans. Even after accounting for the cost of the assay, 10-year cumulative costs decreased by $1268 per patient tested, a drop of over 8%. For a health plan with 10 million covered lives, this would translate to over $8 million in savings ($0.067 per member per month).

The largest contributor to the assay’s economic benefit was a reduction in the incidence of missed melanomas, which are otherwise likely to progress to advanced disease and require expensive interventions such as more extensive surgery, lymph node dissections and systemic drug therapy. However, when used on lesions currently diagnosed as melanoma, the assay would also re-classify many of the false-positive melanoma diagnoses.

The assay’s health-economic benefit depends on it being ordered selectively for the 10% of suspicious pigmented lesion biopsies that are ambiguous and difficult-to-diagnose. If used on all SPL biopsies, the assay would no longer be cost-saving. Health plans could, therefore, consider coverage criteria that would ensure that the assay is ordered for the appropriate population.

Sensitivity analyses demonstrated that the model was not overly sensitive to any one input or assumption, indicating a reasonable degree of confidence in the results. No single input, when modified within a reasonable range, caused the assay to no longer be cost-saving. The quality and reliability of any budget impact model are directly related to the quality and reliability of the data used to generate it. If the clinical paradigm is not reflective of real-world clinical practice, the modeled cost savings may not be realized. Similarly, if the model’s cost inputs are not reflective of true costs, the model will be inaccurate. In this analysis, the extensively sourced clinical paradigm and robustly calculated cost inputs help to instill
further confidence in the results. However, this study is not without limitations.

Limitations

Medicare rates may have changed since this analysis was conducted due to changes in policy (e.g., bundling laboratory tests into OPPS rates) or in individual payment rates (e.g., cuts to pathology rates). In addition, although patients typically owe some out-of-pocket cost-sharing for medical care, this was not taken into account due to its high variation between health plans.

Patients were followed for the duration of the model without regard to turnover in health plan membership, which may affect the proportion of the savings realized by any individual health plan over the model’s time horizon.

Importantly, the model assumes that the treatment patients receive aligns with their gene expression assay result. In the real world, however, it is possible that physicians could disregard the assay result after ordering it. Clinical practice patterns and actual costs may vary by region or by health plan, which would modify the modeled cost savings. Further study using real-world practice and costs is warranted to validate these findings.

Conclusion

This budget impact model shows that use of a novel gene expression assay for the diagnosis of melanoma has the potential to be cost-saving to payers, as patients are diagnosed more accurately and treated more appropriately. Further study is required to validate these findings, particularly in a real-world setting.

Transparency

Declaration of funding
Myriad Genetic Laboratories, Inc.

Declaration of financial/other relationships
David Cassarino has served on an advisory board and received an honorarium from Myriad Genetic Laboratories, Inc. JME peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

References

43. Emory Genetics Laboratory. Informed consent for array CGH Analysis. Decatur, GA: 2010
44. Greenwood Genetic Center. Diagnostic Laboratory Tests, Charges, & CPT Codes 2013
47. U.S. Food and Drug Administration. Full Prescribing Information: YERVOY (ipilimumab). BLA no. 125377 2013