TSI Assay Utilization: Impact on Costs of Graves' Hyperthyroidism Diagnosis

Amy McKee, PhD; and Fred Peyerl, PhD

Graves' disease (GD) is one of the most common autoimmune diseases, affecting approximately 3.45 million people in the United States alone.[1,2] In these individuals, thyroid-stimulating immunoglobulins (TSIs) are produced and directly contribute to GD pathology.[3-5] It is estimated that up to 80% of hyperthyroid cases are caused by GD and, by inference, TSI; the remaining 20% of hyperthyroid cases are attributable to other non-autoimmune etiologies.[6] Accurate diagnosis and treatment of GD early in the disease process improves patient quality of life by limiting many of the manifestations of GD including heart palpitations, irritability, anxiety, fatigue, and insomnia.

Differential diagnosis of hyperthyroidism, a systematic process of elimination to determine the underlying cause, can be an especially challenging and lengthy process. Many patients with hyperthyroidism present with atypical symptoms or have subclinical hyperthyroidism with no apparent symptoms, low to borderline-low thyroid-stimulating hormone (TSH), and normal free triiodothyronine (FT3) and free thyroxine (FT4) levels.[7] In these patients, diagnosis of GD may be delayed for months to years and this delay may adversely impact patient quality of life and productivity.[8,9] Not surprisingly, the diagnosis of patients with atypical symptoms usually centers on management of presenting symptoms; whereas, the underlying cause is neither diagnosed nor treated. Patients undergoing this process often migrate between physician providers in search of a definitive diagnosis of their troublesome symptoms. Interviewed physicians estimate that 30% of subclinical hyperthyroid patients have borderline-low TSH levels that present additional diagnostic challenges given the high degree of variation in existing definitions of normal, low, and borderline-low TSH levels (**Table 1**) per published clinical ranges.[10,11] Evidence-based clinical guidelines for management of subclinical hyperthyroidism are lacking.[12,13] Furthermore, modest excess of thyroid hormone can have detrimental effects on cardiac function, bone turnover, and cognitive function, and is associated with increased all-cause and cardiovascular-related mortality,[14-18] which may suggest that certain subclinical hyperthyroid patients may benefit from thyroid-regulating therapy.

Given the inherent complexities and diagnostic challenges outlined above, a patient may spend months being evaluated and treated by specialists other

Objectives: Thyroid-stimulating immunoglobulins (TSIs) are autoantibodies that bind to the thyroid-stimulating hormone (TSH) receptor on thyroid cells, resulting in Graves' disease (GD), the most common cause of hyperthyroidism. Recently published guidelines recognize the value of anti-TSH receptor antibodies, and a TSI test with high sensitivity and specificity for GD, recently cleared by the US Food and Drug Administration, is now available. Despite this, existing diagnostic algorithms for hyperthyroidism do not currently include TSI testing except in specific cases like pregnancy. The objectives of this analysis are to understand whether incorporating a test that specifically detects TSIs into existing algorithms results in cost savings and reduces time to diagnosis for payers and managed care organizations.

Study Design: An evidence-based economic model was developed to determine the average time to diagnosis and annual costs associated with various diagnostic algorithms for GD in a population of 100,000 managed care enrollees. Diagnostic algorithms used in current practice and hypothetical algorithms that include the TSI test were identified using published clinical guidelines and interviews with practicing endocrinologists. The model estimates costs of current and TSI test–based diagnostic algorithms using payment amounts for laboratory tests, procedures, and physician visits.

Results: Compared with non-TSI algorithms, 100% use of algorithms that include the TSI test result in 46% faster time to diagnosis and generate 47% overall cost savings due in large part to reductions in costly procedures and specialist office visits.

Conclusions: Incorporation and early utilization of the TSI in vitro diagnostic test into current diagnostic algorithms confers cost savings and shortens time to diagnosis.

(Am J Manag Care. 2012;18(1):e1-e14)

In this article
Take-Away Points / e2
Published as a Web exclusive
www.ajmc.com

Take-Away Points

Inclusion of a thyroid-stimulating immunoglobulin test earlier in the diagnostic pathway of patients with low thyroid-stimulating hormone indicative of hyperthyroidism results in significant cost and time savings to payers and at-risk managed care organizations.

■ Net direct costs of diagnosis are reduced by up to 43%.

■ Net cost of avoiding misdiagnosis and treatment of unexplained symptoms is reduced by up to 85%.

■ Overall net cost is reduced by up to 47% and time to diagnosis is reduced by as much as 46%.

than endocrinologists, which may result in an increase in otherwise avoidable office visits, laboratory tests, and symptom management.

The most commonly used test for diagnosis of GD is the relatively expensive thyroid radioactive iodine uptake and scan (RIUS).[19] Thyroid RIUS tests are used to differentiate GD from other causes of hyperthyroidism and can be important for determining a course of action in patients who will undergo radioablation or surgical removal of the thyroid. Recently published guidelines have promoted the value of measuring anti-TSH receptor antibodies as an alternative way to diagnose GD when thyroid scintigraphy is not available or is contraindicated.[20] The US Food and Drug Administration recently cleared a commercially available reporter bioassay (Thyretain) that specifically detects TSI,[21] which is the functional type of anti-TSH receptor that causes GD. Taken together, these reports suggest that TSI testing may provide a more streamlined diagnostic algorithm that could reduce the dependence on thyroid RIUS, and substantially shorten the time to GD diagnosis.

The aim of the current study is to determine whether utilization of the TSI bioassay test will reduce overall costs of diagnosis to payers and shorten the time to diagnosis of GD. We use a budget impact model to assess the impacts of early TSI testing on costs and time to diagnosis.

METHODS

Perspective and Target Audience

The model was designed from a managed care payer perspective, specifically managed care organizations (MCOs) that have assumed financial risk for the care of their members. The target audiences are decision and policy makers of health plans, health systems, and other MCOs.

Time Horizon

The model is used to estimate the impact of costs on the MCO's annual budget. Analyses of cost per patient are estimated on a cost-per-diagnosis basis.

Patient Population

The model uses a theoretical population of 100,000 enrollees in an MCO. The percentage of patients in an MCO presenting for TSH testing for hyperthyroidism is estimated at 14.6% per year and is based upon the percentage of the US population that is tested for TSH each year. This estimate was based on a published estimate that 45 million first-time TSH tests are performed in the United States each year per 300 million people[22,23]; 6.3% of patients were estimated to have low or borderline-low TSH levels based on primary research interviews. An occurrence rate of 0.644% for suspected GD was estimated based upon the average estimate that 70% of those with hyperthyroidism have GD (Table 1).[6,22-24]

Model Design

Laboratory and office visit costs associated with currently used and theoretical TSI test–based algorithms were calculated and compared (**Table 2**) to determine direct cost savings. Misdiagnosis costs associated with current and TSI test-based algorithms were estimated and compared to determine additional cost savings (Table 2). Total costs to the payer were determined as the sum of direct and misdiagnosis costs and were compared between current and TSI algorithms to determine total cost savings to the payer (Table 2).

MCO Inputs and Assumptions

Cost savings discussed here are based on fee-for-service contracts only for Medicare, Medicaid, and commercial health plan enrollees, or covered lives. General findings also hold true for capitated contracts. Based upon known demographics of GD patients, a mix of plan types was assumed. The theoretical distribution of enrollees receiving TSH testing as percentage of total enrollment is: 20% Medicare, 18% Medicaid, and 62% commercial (Table 1). Reimbursement rates for Current Procedural Terminology (CPT) codes assigned to each laboratory test and office visit were obtained from the Centers for Medicare and Medicaid Services (CMS) 2010 fee schedules and the 2010B CMS physician fee schedule, which were used to estimate Medicare costs for each code.[25] For office visit–related costs, the average of non-facility and facility costs for each code was used. For RIUS test costs we used 75% of published hospital rate charges from a commercial payer to estimate the cost to Medicare.[26] Based on industry averages, Medicaid reimbursement rates were estimated at 80% of Medicare reimbursement rates and commercial payer

■ **Table 1.** Model Inputs

Patients in a Population of 100,000 Enrollees		
Patients	**Occurrence Rate[a] (%)**	**Total Number**
Patients undergoing TSH testing	14.6	14,600
Patients with low to borderline-low TSH	0.920	920
Patients with GD	0.644	644
Payer mix undergoing TSH testing		
Medicare	20	
Medicaid	18	
Commercial insurance	62	
Rates of clinical and subclinical hyperthyroidism[b]		
Clinical[c]	30	
Subclinical[d]	70	
Low TSH[e]	70	
Borderline-low TSH[f]	30	
Rate of GD patients incorrectly diagnosed with another condition[b]		
Current diagnostic algorithms	5	
TSI test–based algorithms	0.75	

Direct Cost Inputs		
	Medicare ($)	**Medicaid ($)**	**Commercial ($)**
Laboratory tests			
TSH (84443)	24	19	29
T3RU/THBR (84479)	9	7	11
FT4 (84439)	13	10	16
FT3 (84481)	24	19	29
TRAb (83519)	19	15	23
TPO (86376)	21	17	25
TSI (84445)	73	58	88
RIUS (26)	1255	1004	904
Office visits			
PCP initial (99203)	87	70	104
PCP follow-up (99213)	58	46	70
Specialist initial (99204)	141	113	169
Specialist follow-up (99214)	88	70	106

Misdiagnosis Cost Inputs		
	Misdiagnosed Patients (%)	**Average Treatment Cost per Yr ($)**	**Average Duration of Treatment (yrs)[b]**
Anxiety	10	6400	0.5
Arrhythmia	8	6053	0.5
Depression	10	13,500	0.5
Diabetes	14	15,702	0.5
Fatigue/malaise	17	5923	0.5
Hyperlipidemia	27	2832	0.5
Hypertension	14	1394	0.5

FT3 indicates free triiodothyronine; FT4, free thyroxine; GD, Graves' disease; PCP, primary care physician; RIUS, radioactive iodine uptake and scan; THBR, thyroid hormone–binding ratio; TPO, thyroid peroxidase antibody; TRAb, thyroid receptor antibody; TSH, thyroid-stimulating hormone; TSI, thyroid-stimulating antibody; T3RU, triiodothyronine resin uptake.
[a]Sources used for determination of prevalence rates.[22-24]
[b]Estimates from a panel of expert endocrinologists.
[c]Clinical hyperthyroidism: patients that have overt symptoms of hyperthyroidism.
[d]Subclinical hyperthyroidism: patients with no symptoms.
[e]Low TSH = <0.3 mIU/L.
[f]Borderline-low TSH = 0.3 mIU/L – 0.5 mIU/L.

■ **Table 2.** Impact of 100% TSI Algorithm Utilization on Costs and Time of GD Diagnosis

	Direct Costs								
	0% TSI Algorithm Utilization				**100% TSI Algorithm Utilization**				
	Total per 100,000 Enrollees ($)	**Per Patient ($)**	**PMPM ($)**	**Direct Costs (%)**	**Total per 100,000 Enrollees ($)**	**Per Patient ($)**	**PMPM ($)**	**Direct Costs (%)**	**Change (%)**
Lab test	64,110	70	0.0534	5	105,280	114	0.0877	14	64
PCP office visit	140,290	152	0.117	11	149,697	163	0.125	20	7
Endo office visit	216,794	236	0.181	16	70,419	77	0.0587	9	−68
RIUS	907,944	987	0.757	68	432,844	471	0.361	57	−52
Total	132,820	1445	1.11	100	758,240	824	0.632	100	−43
	Misdiagnosis Costs								
	0% TSI Algorithm Utilization				**100% TSI Algorithm Utilization**				
	Total per 100,000 Enrollees ($)	**Per Patient ($)**	**PMPM ($)**	**MD Costs (%)**	**Total per 100,000 Enrollees ($)**	**Per Patient ($)**	**PMPM ($)**	**MD costs (%)**	**Change (%)**
Anxiety	14,727	16	0.0122	10	2209	2	0.00184	10	−85
Depression	31,065	34	0.0259	21	4660	5	0.00388	21	−85
Arrhythmia	11,143	12	0.00929	7	1671	2	0.00139	7	−85
Hypertension	4491	5	0.00374	3	674	1	0.00056	3	−85
Diabetes	49,140	53	0.0410	32	7371	8	0.0409	32	−85
Hyperlipidemia	17,726	19	0.0148	12	2659	3	0.00614	12	−85
Fatigue/malaise	22,898	25	0.0191	15	3435	4	0.00286	15	−85
Total	151,190	164	0.126	100	22,679	25	0.0189	100	−85
	Total Payer Costs								
	0% TSI Algorithm Utilization				**100% TSI Algorithm Utilization**				
	Total per 100,000 Enrollees ($)	**Per Patient ($)**	**PMPM ($)**	**Total Costs (%)**	**Total per 100,000 Enrollees ($)**	**Per Patient ($)**	**PMPM ($)**	**Total Costs (%)**	**Change (%)**
Total costs	1,480,328	1609	1.23	100	780,918	849	0.65	100	−47
	Time to Diagnosis								
	0% TSI Algorithm Utilization				**100% TSI Algorithm Utilization**				
Time (weeks)	11.7				6.4				−46%

Endo indicates endocrinologist; GD, Graves' disease; MD, misdiagnosis; PCP, primary care physician; PMPM, per member per month; RIUS, radioactive iodine uptake and scan; TSI, thyroid-stimulating antibody.
Based on a population of 100,000 enrolled patient lives, the table shows impacts on costs and time as a result of % TSI utilization. An inverse linear relationship exists between cost savings and percentage utilization for each parameter. Total costs of GD diagnosis per 100,000 enrollees are shown as well as costs per patient with low to borderline-low TSH (patient with hyperthyroidism) as rounded to the nearest dollar. PMPM costs are shown and were used to determine percent change.

reimbursement rates were estimated at 120% of Medicare reimbursement rates.

Data Sources

The occurrence or prevalence rate for the percentage of patients that test low for TSH is based on the incidence rates for hyperthyroidism in the United States.[1] The percentage of patients with subclinical versus clinical hyperthyroidism, per- centage of patients with low to borderline-low TSH levels, and the misdiagnosis rates (Table 1) were established through in-depth, third-party interviews with practicing endocrinolo- gists (detailed below). The percentage of hyperthyroidism patients with an underlying etiology of GD was estimated at 70% based on published estimates.[6] De-identified records of thyroid function assays performed between January 1, 2007, and June 30, 2008, were analyzed by Management Science

Associates, Pittsburgh, Pennsylvania, to identify *International Classification of Diseases, 9th Revision, Clinical Modification* (*ICD-9-CM*) codes for conditions that are commonly misdiagnosed in patients with hyperthyroidism.

Physician Interviews

Five physicians were selected to provide expert feedback on the diagnostic process because they were familiar with the TSI test and were key opinion leaders in endocrinology. They were located in California, New York, New Jersey, and Florida. The interviews were conducted individually using a questionnaire to guide the discussions. Experts were asked to estimate the average time that it currently takes to arrive at a GD diagnosis; all 5 agreed, on average, that it was 2 to 3 months from the time the patient sees a primary care physician (PCP) to being diagnosed by an endocrinologist. They were asked to describe currently used diagnostic algorithms for hyperthyroidism and GD. The consensus was that the type of algorithm used can vary and depends upon whether patients have overt symptoms of GD. A variety of diagnostic algorithms were discussed and a representative range of these different algorithms was used in the model. When asked to estimate the percentage of patients that present with obvious symptoms of hyperthyroidism, the average response was 70% (range 65%-75%). We also asked physicians to estimate the percentage of patients that have GD and are misdiagnosed, what diseases GD is mistaken for, and how long it takes for a misdiagnosis to be identified. Three of the 5 physicians estimated the misdiagnosis rate at around 5%, while 2 estimated that it was close to 20% of patients. Because these estimates varied by more than 20%, we used the more conservative estimate of 5% in the model, which would lead to a more conservative estimate of cost savings. All physicians estimated that misdiagnosed patients spend 6 months undergoing treatments for the wrong disease before being correctly diagnosed with hyperthyroidism. Finally, we asked physicians how the TSI test could impact this rate of misdiagnosis, which was estimated at 85% based on the sensitivity and specificity of the TSI test. With the exception of the estimated rate of misdiagnosis, the answers varied less than 20%.

Definition of Diagnostic Algorithms

Clinical practice guidelines and in-depth primary research interviews with 5 key opinion leaders in endocrinology were used to identify and validate the mix of current GD diagnostic algorithms. Algorithms that capture current diagnostic practice were outlined for varying TSH results and clinical presentation (**Figure 1A**). Hypothetical algorithms that include TSI testing were similarly defined in order to compare costs with current algorithms (**Figure 1B**).

Model Assumptions

The model assumes that physicians presently utilize a set number of highly structured algorithms, and that they would utilize similarly structured algorithms as they adopt the TSI test. In clinical practice, however, physician behavior likely draws upon a wider variety of less formally structured algorithms; such behavior would likely continue even as they adopt the TSI test. The model uses non-weighted averages to determine costs for all current algorithms and TSI test-based algorithms for patients with clinical disease; in practice, some algorithms may be more heavily utilized than others. The model assumes that patients with clinically overt Graves' disease do not have borderline-low TSH levels, always exhibit TSI, and that all patients with subclinical hyperthyroidism go through the diagnostic process. In the model, treatment costs for misdiagnosed patients are experienced at a constant rate; however, in front-line clinical practice, these costs will likely vary based on several factors including stage of disease progression, type and location of service provider, and terms of payer contracts.

Comparison of Direct Costs of GD Diagnosis: Current Versus TSI Algorithms

An Excel-based budget impact calculator model was designed to assess the cost of current GD diagnostic algorithms (Figure 1A) compared with the cost of theoretical algorithms utilizing TSI testing (Figure 1B).

The cost of each diagnostic algorithm shown in Figure 1A is driven by costs of the following: 1) laboratory tests (TSH, triiodothyronine resin uptake [T3RU]/thyroid hormone–binding ratio [THBR], FT4, FT3, thyroid receptor antibody, thyroid peroxidase antibody, and TSI), 2) RIUS test and interpretation, and 3) number of PCP and endocrinologist/specialist office visits (Figure 1, Table 1). For TSI diagnostic algorithms in subclinical hyperthyroid patients, a weighted average was used because endocrinologists predicted that 20% of subclinical GD patients would not exhibit detectable levels of TSI; for all other patient types, a flat average was taken across the diagnostic algorithms. A weighted average of the diagnosis cost for current and TSI algorithms was taken across patient types based on the percentages of clinical and subclinical hyperthyroid patients with low or borderline-low TSH (Table 1). The estimated GD diagnosis cost associated with current algorithms was compared with the estimated GD diagnosis cost associated with TSI algorithms to establish overall cost savings.

Comparison of GD Misdiagnosis Costs: Current Versus TSI Algorithms

De-identified claims data were used to quantify the most common *ICD-9-CM* codes and related misdiagnoses in GD patients (Table 1). The model assumes that misdiagnosed patients

■ Figure 1. Current Diagnostic Algorithm Mix
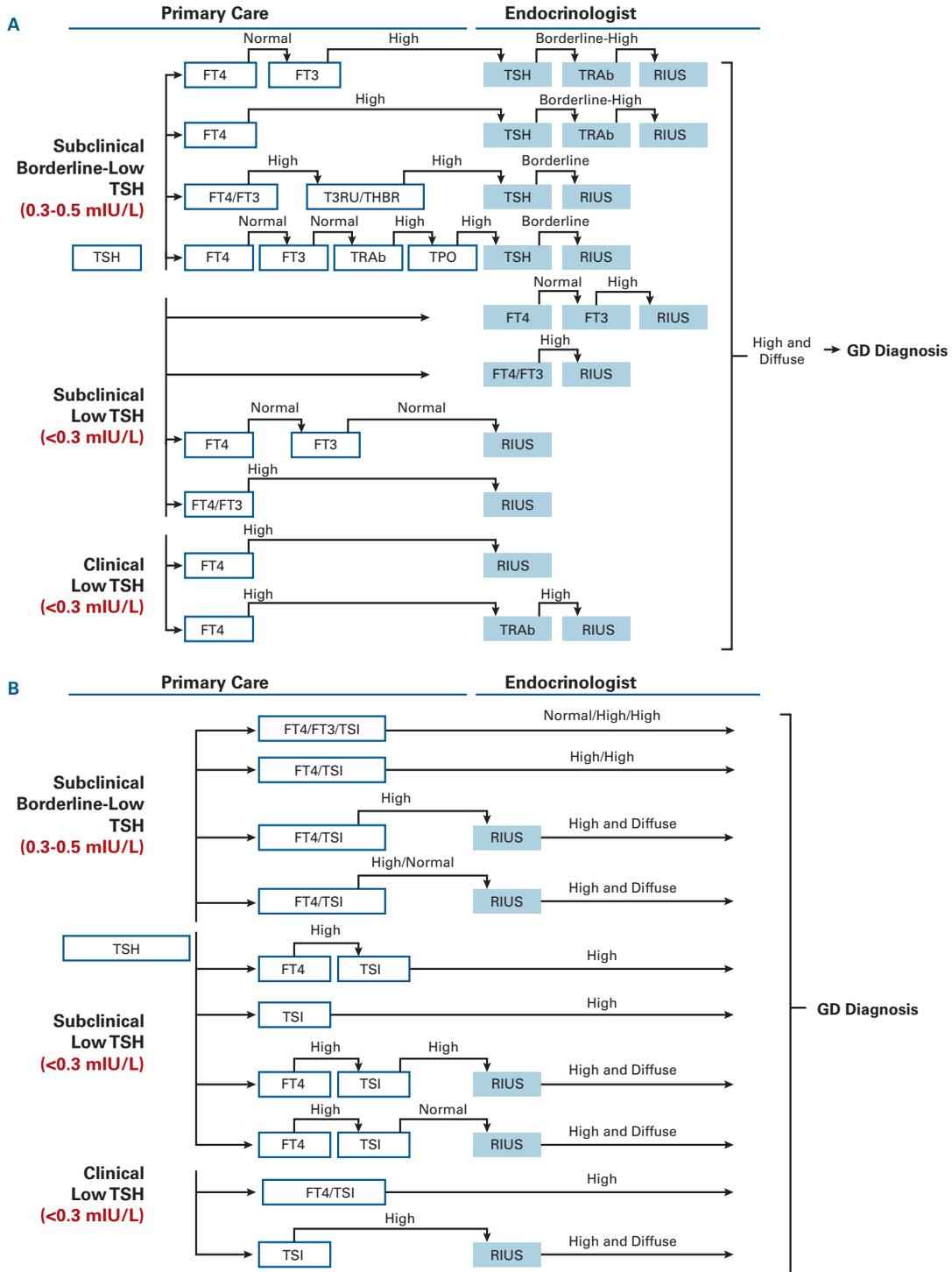
FT3 indicates free triiodothyronine; FT4, free thyroxine; PCP, primary care physician; RIUS, radioactive iodine uptake and scan; THBR, thyroid hormone binding ratio; TPO, thyroid peroxidase antibody; TRAb, thyroid receptor antibody; TSH, thyroid-stimulating hormone; TSI, thyroid-stimulating immunoglobulin; T3RU, triiodothyronine resin uptake.
A. Currently used diagnostic algorithms for GD.
B. Hypothetical diagnostic algorithms that utilize the TSI test at different stages of the diagnostic process are shown. Average costs were generated using the mix of algorithms shown, using lab test and office visit costs as outlined in methods.
Diagnostic algorithms used to determine costs associated with diagnosis of GD. Each white box represents a separate office visit to a PCP and each blue box represents an office visit to an endocrinologist.

are treated for 6 months before receiving an accurate diagnosis. Costs associated with treatment of each of these conditions per year were calculated using published literature.[27-31] The number of patients impacted by misdiagnosis was based on the expert interviews and indicated misdiagnosis rates of 5% and 0.75% for currently used algorithms and TSI algorithms, respectively. Costs of misdiagnosis were calculated per patient and multiplied by the number of patients with low to borderline-low TSH per year in a population of 100,000 enrollees to determine annual total costs associated with misdiagnosis (Table 1).

Total costs to the payer were determined by adding the total direct costs and the costs of misdiagnosis. The impact on a budget of 100,000 enrollees was determined by using the occurrence rate to determine the number of patients undergoing testing for hyperthyroidism.

Time to Diagnosis: Current Versus TSI Algorithms

Average time to diagnosis assumes 1 week for each patient procedure or diagnostic test, and an additional 8 weeks before a patient sees an endocrinologist (based on endocrinologist interviews). These estimates were used to calculate the time to diagnosis associated with each algorithm.

Sensitivity Analysis

A 1-way sensitivity analysis was performed by increasing or decreasing key inputs by 20% and determining the impact on payer cost per patient.

RESULTS

Impact of TSI Algorithm Utilization on Direct Payer Costs of GD Diagnosis

Comparing current and hypothetical GD diagnostic algorithms shows that TSI algorithms require fewer tests, thereby facilitating more rapid referral to endocrinologists and reduced dependence on the RIUS tests compared with non-TSI algorithms (Figure 1). Direct costs comprise lab test costs, office visit costs, and RIUS costs. Because TSI testing is likely to be incorporated with current algorithms, costs associated with incremental increases in the percentage of TSI utilization were calculated. We identified an inverse linear relationship between direct cost savings and percentage utilization of TSI algorithms (Appendix A). As a result of increasing TSI utilization, the net direct payer costs decreased up to 43% with 100% TSI test utilization.

Costs associated with laboratory testing increase by 64% from $0.0534 per member per month (PMPM) to $0.0877 PMPM when TSI test utilization grows from 0% to 100%. Costs associated with PCP office visits increase by 7% from $0.117 PMPM to $0.125 PMPM when TSI test utilization in-

creases from 0% to 100% (Table 2). Costs associated with endocrinologist office visits decrease by 68% from $0.181 PMPM to $0.0587 PMPM when TSI testing grows from 0% to 100% (Table 2). Costs associated with RIUS decrease by 52% from $0.757 to $0.361 when TSI test utilization grows from 0% to 100%. Because RIUSs alone are the greatest contributors (68%) of total payer diagnostic costs under current algorithms (Table 2), the cost reduction in RIUS testing by utilizing 100% TSI imparts the greatest impact on cost savings.

Accounting for all factors included in the direct costs of GD, 100% TSI algorithm utilization reduces annual GD diagnosis costs by 43%, representing a $0.48 PMPM savings from $1.11 with 0% TSI utilization to $0.632 with 100% utilization of TSI algorithms.

Impact of Increasing TSI Algorithm Utilization on Payer Costs Associated With the Treatment of Misdiagnosed GD

The expert interviews indicated that TSI-based algorithms would reduce the rate of incorrect diagnoses of GD patients from 5% with current algorithms to 0.75% due to the TSI test's high sensitivity and high positive-predictive value. Conditions were identified for which GD patients with unexplained symptoms are most commonly diagnosed, and published studies were used to estimate the average annual cost for treating these conditions in a population of 100,000 enrollees (Table 2, Appendix C).[27-31]

A 100% utilization of TSI-based algorithms results in an 85% net decrease in misdiagnosis cost from $0.126 PMPM to $0.0189 PMPM (Table 2), representing a $0.11 PMPM cost savings.

Impact of Increasing TSI Algorithm Utilization on Total Payer Costs and Time to Diagnosis of GD

The total estimated cost of GD diagnosis borne by a payer is the sum of direct costs and costs associated with the misdiagnosis of GD patients. In a population of 100,000 enrollees, total payer costs decrease by 47% from $1.23 PMPM to $0.651 when TSI test utilization increases from 0% to 100% (Table 2), representing a $0.58 PMPM cost savings. A 100% utilization of TSI-based algorithms in patients with low to borderline-low TSH results in a 46% net decrease in time to diagnosis from 11.7 weeks to 6.4 weeks (Table 2). Total time to diagnosis is reduced by 5.3 weeks per patient.

Cost Sensitivity to Changes in Model Inputs

A 1-way sensitivity analysis was conducted to understand how increasing and decreasing model inputs impact the cost-savings outcomes (Figure 2). The model shows that 100%

TSI algorithm utilization results in estimated cost savings of $760 per patient per year (Table 2). Varying each input by 20% never decreased cost savings by more than $760 (total cost savings per patient per year) and therefore did not reverse the finding of cost savings. Cost is most sensitive to changes in reimbursement rates for RIUS testing (Figure 2). Increasing the reimbursement rate for these tests by 20% further improved per-patient cost savings by $107. Alternatively, decreasing the reimbursement rate by 20% reduced cost savings by only $23 per patient. Of the 3 payer types included in the model (Medicare, Medicaid, and commercial), changes in commercial reimbursement rates for lab tests had the most impact on cost savings. Increasing or decreasing reimbursement rates associated with other inputs in the model, including lab test and office visits costs, impacted the cost savings by less than $20 per patient. Increasing or decreasing the estimated cost of treating misdiagnosed conditions by 20% impacted cost savings by less than $10 per patient. Increasing or decreasing the conservative estimate of 5% misdiagnosed patients by 20% impacted the cost savings by $32. We used the conservative estimate because there was a wide range of estimates for the percentage of GD patients that were misdiagnosed. If the higher estimate of 20% were used, the cost savings per patient would be increased to $1179.

DISCUSSION

In an environment of rising healthcare costs, cost-containment measures allow payers the opportunity to provide value-based benefits to patients. The model described here shows that utilization of TSI testing in the primary care setting early in the diagnostic process results in improved patient care by more rapid diagnosis and an overall cost savings to the payer by 1) reducing the cost of diagnosis and 2) reducing costs associated with misdiagnosis through multiple, avoidable office visits.

Reduced Costs of Diagnosis

The model described here utilizes cost estimates to understand how increasing utilization of TSI algorithms together with presently used diagnostic algorithms leads to overall cost and time savings to payers. Interviews with an endocrinology panel suggest that utilization of the TSI test reduces the number of other diagnostic tests and office visits required as part of the differential diagnosis of hyperthyroidism. In addition, these interviews suggest that utilization of the TSI test is likely to reduce dependence on expensive RIUS testing, will provide more streamlined referral from PCPs to endocrinologists, and will result in fewer specialist office visits.

Reimbursement for TSI test is higher than that for other laboratory tests currently used to diagnose GD; however, the TSI tests offer a definitive diagnosis in GD patients and fewer visits with the endocrinologist, while other lower reimbursement cost test options (eg, TSH, FT3, FT4) often provide ambiguous diagnostic results, which must be confirmed using a more invasive and expensive RIUS test and require more visits to the endocrinologist. Thus, in a hypothetical population of 100,000 members, the added costs of TSI laboratory testing ($0.034 PMPM) are more than offset by reducing the reliance on the RIUS test (decrease of $0.396 PMPM) and shifting physician office visits to lower-cost PCPs (decrease of $0.115 PMPM).

### Reduced Costs Associated With Misdiagnosis

Adverse outcomes are associated with undiagnosed or misdiagnosed subclinical hyperthyroidism.[32-34] Hyperthyroidism patients experience troubling symptoms such as palpitations or racing heart, restlessness, sleeplessness, irritability, and fatigue that impact their quality of life. As diagnosis can take months, it is not uncommon for patients to "doctor shop" for symptom relief.

A recent study of TSH test results in a population of individuals undergoing health fair screening found that 2.1% of individuals had subclinical hyperthyroidism, defined by the authors as having a level of TSH between 0.01 and 0.3 mIU/L and normal FT3 and/or FT4, and 41% of these patients were not on thyroid medication at the time of testing,[35] suggesting that subclinical hyperthyroidism is relatively common in the general population. There is a lack of understanding of how improved detection of subclinical hyperthyroidism might improve patient quality of life or impact costs. Accordingly, a study of the utility of TSI testing in subclinical hyperthyroid patients is warranted. Identification of GD in such patients may lead to an improved quality of life by alleviating symptoms and subsequently reducing costs related to lost productivity. According to feedback from endocrinologists, patients today experience roughly a 20% loss in productivity during the process of differential diagnosis of hyperthyroidism. Earlier utilization of TSI testing in the diagnostic process may also reduce loss of patient productivity.

Use of TSI algorithms offers more efficient differential diagnosis of GD and reduces the likelihood of misdiagnoses of subclinical patients. Physicians estimate that the TSI test will reduce the misdiagnosis rate of GD by 85%, based on the high sensitivity and positive predictive value of the test. In a hypothetical population of 100,000 enrollees, this model shows that utilization of TSI algorithms reduces annual misdiagnosis costs by $0.107 PMPM.

■ **Figure 2.** Sensitivity Analysis
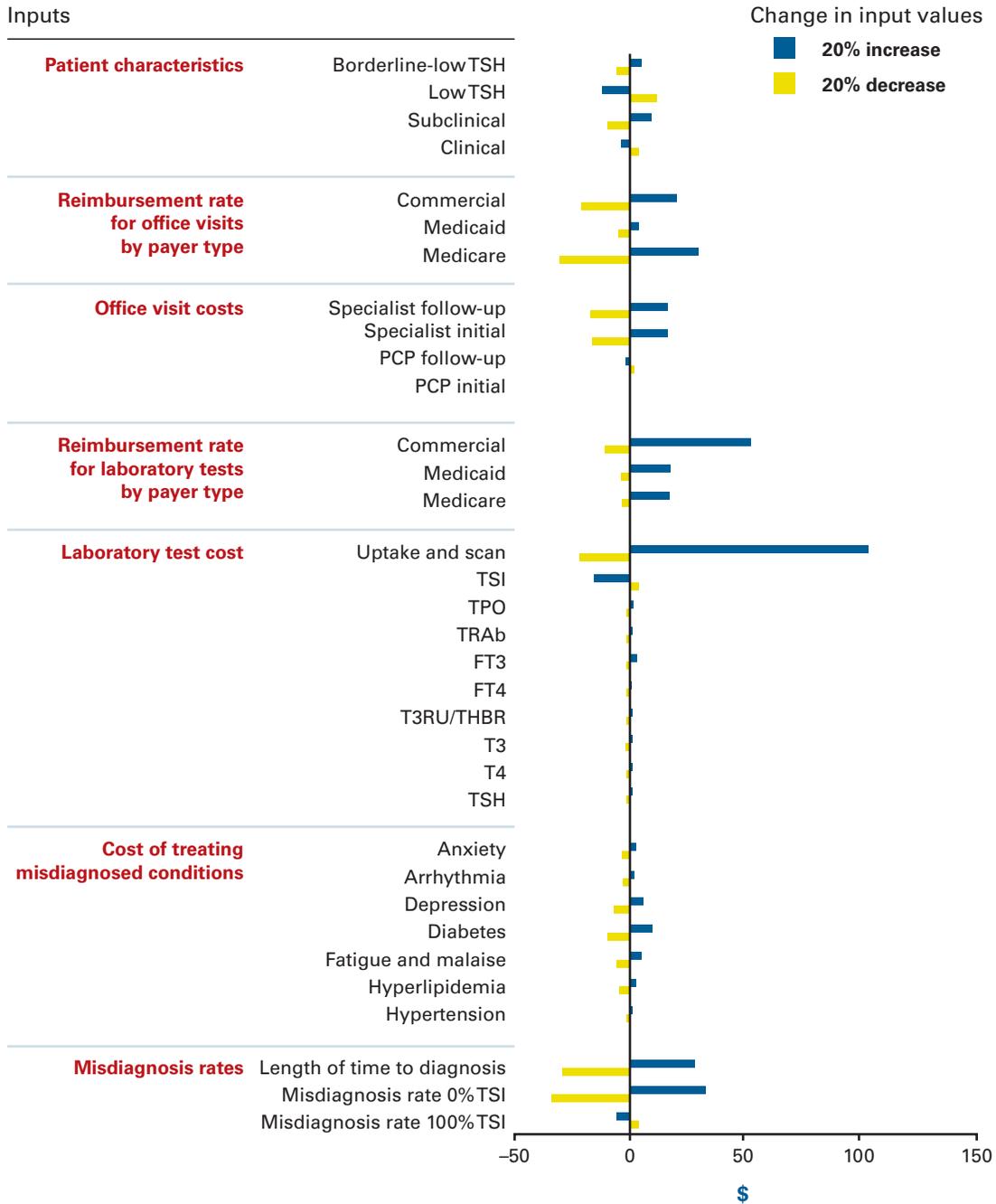
FT3 indicates free triiodothyronine; FT4, free thyroxine; PCP, primary care physician; RIUS, radioactive iodine uptake and scan; THBR, thyroid hormone binding ratio; TPO, thyroid peroxidase antibody; TRAb, thyroid receptor antibody; TSH, thyroid-stimulating hormone; TSI, thyroid-stimulating immunoglobulin; T3RU, triiodothyronine resin uptake.
Each model input shown was increased (blue bars) or decreased (yellow bars) by 20% and the change in the average payer cost savings per patient is shown relative to the total cost savings per patient of total payer costs with 100% utilization of TSI algorithms.
Change in cost savings (US$) per patient compared with base case cost savings per patient.

Reduction in Total Costs to Payers

The impact of TSI algorithms in a population of 100,000 enrollees reduces total annual payer costs by 47%, or $698,892; these findings translate into payer cost savings of $760 per patient, or $0.58 PMPM. A 100% utilization of TSI-based al- gorithms also results in a 46% average reduction in time to diagnosis, or 5.3 weeks, versus current algorithms.

Limitations

Limitations of this model include use of observational

opinion garnered from a panel of expert physicians to inform the modeling of diagnostic algorithms. To understand how physicians use the TSI test and how its introduction impacts actual cost data, further studies will be needed as TSI testing is incorporated into diagnostic algorithms for GD.

CONCLUSIONS

Because it was not available at the time of initial publication of the American Thyroid Association and the American Association of Clinical Endocrinologists guidelines for diagnosis of hyperthyroidism, TSI testing has limited inclusion in currently recommended algorithms.[12,13,20] However, as physicians learn more about the availability of this in vitro diagnostic test and its ability to support a definitive diagnosis for GD that allows them to better manage and treat their patients, TSI testing should become part of future guidelines for differential diagnosis of hyperthyroidism.[21,36] Increased use of TSI-based diagnostic algorithms decreases time to diagnosis and reduces both the costs of differential diagnosis and costs resulting from misdiagnosis and associated symptom management from GD-driven hyperthyroidism. Faster, more efficient diagnosis can reduce costs while benefiting patient productivity and improving patient care. Payers incorporating the TSI bioassay into existing diagnostic algorithms may reduce time to diagnosis, thereby retaining covered lives and decreasing the economic burden of GD diagnosis.

REFERENCES

1. **Golden SH, Robinson KA, Saldanha I, Anton B, Ladenson PW.** Clinical review: prevalence and incidence of endocrine and metabolic disorders in the United States: a comprehensive review. *J Clin Endocrinol Metab.* 2009;94(6):1853-1878.

2. **Vanderpump MP, Tunbridge WM, French JM, et al.** The incidence of thyroid disorders in the community: a twenty-year follow-up of the Whickham Survey. *Clin Endocrinol (Oxf).* 1995;43(1):55-68.

3. **Kriss JP, Pleshakov V, Chien JR.** Isolation and identification of the long-acting thyroid stimulator and its relation to hyperthyroidism and circumscribed pretibial myxedema. *J Clin Endocrinol Metab.* 1964;24:1005-1028.

4. **Michalek K, Morshed SA, Latif R, Davies TF.** TSH receptor autoantibodies. *Autoimmun Rev.* 2009;9(2):113-116.

5. **McIver B, Morris JC.** The pathogenesis of Graves' disease. *Endocrinol Metab Clin North Am.* 1998;27(1):73-89.

6. **Weetman AP.** Graves' disease. *N Engl J Med.* 2000;343(17):1236-1248.

7. **Braverman LE, Utiger RD, eds.** *The Thyroid: A Fundamental and Clinical Text.* 8th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2000.

8. **Bunevicius R, Velickiene D, Prange AJ Jr.** Mood and anxiety disorders in women with treated hyperthyroidism and ophthalmopathy caused by Graves' disease. *Gen Hosp Psychiatry.* 2005;27(2):133-139.

9. **Stern RA, Robinson B, Thorner AR, Arruda JE, Prohaska ML, Prange AJ Jr.** A survey study of neuropsychiatric complaints in patients with Graves' disease. *J Neuropsychiatry Clin Neurosci.* 1996;8(2):181-185.

10. **Baskin HJ, Cobin RH, Duick DS, et al; AACE.** American Association of Clinical Endocrinologists Medical Guidelines for Clinical Practice for the Evaluation and Treatment of Hyperthyroidism and Hypothyroidism. *Endocr Pract.* 2002;8(6):457-469.

11. **Surks MI, Ortiz E, Daniels GH, et al.** Subclinical thyroid disease: scientific review and guidelines for diagnosis and management. *JAMA.* 2004;291(2):228-238.

12. **Singer PA, Cooper DS, Levy EG, et al.** Treatment guidelines for patients with hyperthyroidism and hypothyroidism: Standards of Care Committee, American Thyroid Association. *JAMA.* 1995;273(10):808-812.

13. **Arbelle JE, Porath A.** Practice guidelines for the detection and management of thyroid dysfunction: a comparative review of the recommendations. *Clin Endocrinol (Oxf).* 1999;51(1):11-18.

14. **Biondi B, Palmieri EA, Fazio S, et al.** Endogenous subclinical hyperthyroidism affects quality of life and cardiac morphology and function in young and middle-aged patients. *J Clin Endocrinol Metab.* 2000;85(12):4701-4705.

15. **Auer J, Scheibner P, Mische T, et al.** Subclinical hyperthyroidism as a risk factor for atrial fibrillation. *Am Heart J.* 2001;142(5):838-842.

16. **Kumeda Y, Inaba M, Tahara H, et al.** Persistent increase in bone turnover in Graves' patients with subclinical hyperthyroidism. *J Clin Endocrinol Metab.* 2000;85(11):4157-4161.

17. **Greenspan SL, Greenspan FS.** The effect of thyroid hormone on skeletal integrity. *Ann Intern Med.* 1999;130(9):750-758.

18. **Parle JV, Maisonneuve P, Sheppard MC, Boyle P, Franklyn JA.** Prediction of all-cause and cardiovascular mortality in elderly people from one low serum thyrotropin result: a 10-year cohort study. *Lancet.* 2001;358(9285):861-865.

19. **McDermott MT, Woodmansee WW, Haugen BR, Smart A, Ridgway EC.** The management of subclinical hyperthyroidism by thyroid specialists. *Thyroid.* 2003;13(12):1133-1139.

20. **Bahn Chair RS, Burch HB, Cooper DS, et al.** Hyperthyroidism and other causes of thyrotoxicosis: management guidelines of the American Thyroid Association and American Association of Clinical Endocrinologists. *Thyroid.* 2011;21(6):593-646.

21. **Kamijo K, Murayama H, Uzu T, Togashi K, Kahaly GJ.** A novel bioreporter assay for thyrotropin receptor antibodies using a chimeric thyrotropin receptor (mc4) is more useful in differentiation of Graves' disease from painless thyroiditis than conventional thyrotropin-stimulating antibody assay using porcine thyroid cells. *Thyroid.* 2010;20(8):851-856.

22. CLX Medical, Inc. announces new CEO interview with questions regarding planned acquisition of the ThyroTest® Rapid Screening Device [press release]. CLX Medical; 2008. http://equitydigest.com/clx_interview.pdf. Accessed July 7, 2010.

23. US Census. http://2010.census.gov/2010census/data/. Published 2010. Accessed July 7, 2010.

24. **Ogunyemi D.** Autoimmune thyroid disease and pregnancy. http://emedicine.medscape.com/article/261913-overview. Published 2010. Accessed July 7, 2010.

25. Laboratory fee schedule. Centers for Medicare and Medicaid Services; 2010. https://www.cms.gov/ClinicalLabFeeSched/02_clinlab.asp#TopOfPage. Accessed July 7, 2010.

26. Kaiser Foundation Hospital Charges California N Region. http://xnet.kp.org/hospitalcharges/list.html. Published 2010. Accessed July 7, 2010.

27. **Khaykin Y, Wang X, Natale A, et al.** Cost comparison of ablation versus antiarrhythmic drugs as first-line therapy for atrial fibrillation: an economic evaluation of the RAAFT pilot study. *J Cardiovasc Electrophysiol.* 2009;20(1):7-12.

28. Odell TW, Gregory MC. Cost of hypertension treatment. *J Gen Intern Med*. 1995;10(12):686-688.

29. Cost of diabetes care. BJC Healthcare; 2010. http://www.diabetes-busters.com/chdi_wellness.aspx?id=3579. Accessed November 10, 2010.

30. Brandle M, Davidson MB, Schriger DL, Lorber B, Herman WH. Cost effectiveness of statin therapy for the primary prevention of major coronary events in individuals with type 2 diabetes. *Diabetes Care*. 2003;26(6):1796-1801.

31. Causes of fatigue and malaise. WrongDiagnosis.com. http://www.wrongdiagnosis.com/sym/fatigue.html. Published 2010. Accessed November 10, 2010.

32. Ross DS, Neer RM, Ridgway EC, Daniels GH. Subclinical hyperthyroidism and reduced bone density as a possible result of prolonged suppression of the pituitary-thyroid axis with L-thyroxine. *Am J Med*. 1987;82(6):1167-1170.

33. Sawin CT, Geller A, Wolf PA, et al. Low serum thyrotropin concentrations as a risk factor for atrial fibrillation in older persons. *N Engl J Med.* 1994;331(19):1249-1252.

34. Biondi B, Fazio S, Carella C, et al. Cardiac effects of long term thyrotropin-suppressive therapy with levothyroxine. *J Clin Endocrinol Metab.* 1993;77(2):334-338.

35. Canaris GJ, Manowitz NR, Mayor G, Ridgway EC. The Colorado thyroid disease prevalence study. *Arch Intern Med*. 2000;160(4): 526-534.

36. Lytton SD, Ponto KA, Kanitz M, Matheis N, Kohn LD, Kahaly GJ. A novel thyroid-stimulating immunoglobulin bioassay is a functional indicator of activity and severity of Graves' orbitopathy. *J Clin Endocrinol Metab.* 2010;95(5):2123-2131. ■

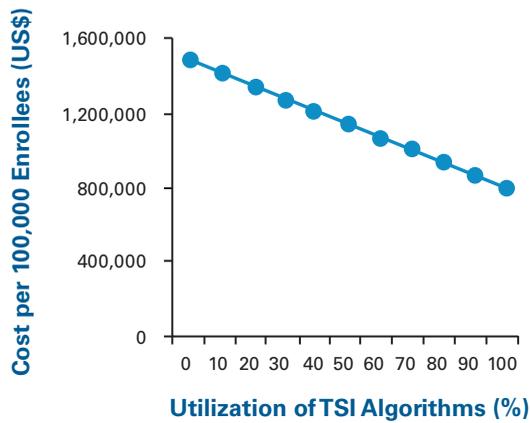■ **Appendix A.** Impact of TSI Algorithm Utilization on Costs of GD Diagnosis
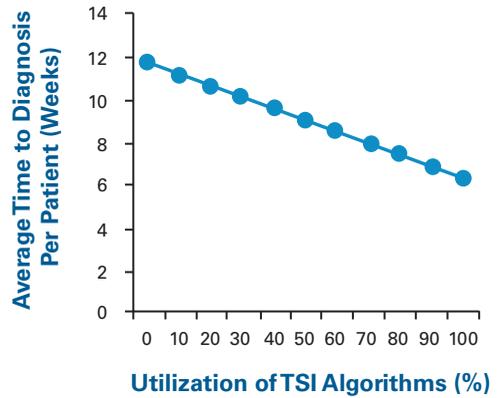
A   Total direct costs of GD diagnosis
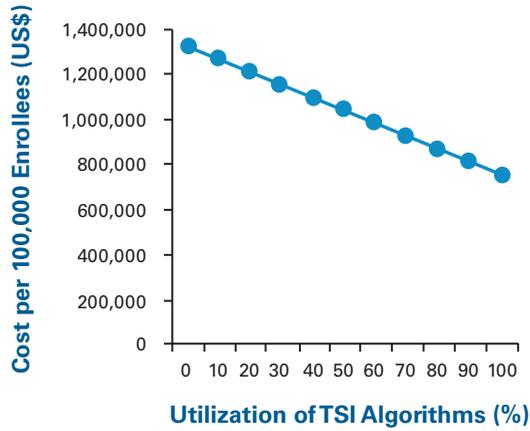
B   Total costs of misdiagnosis
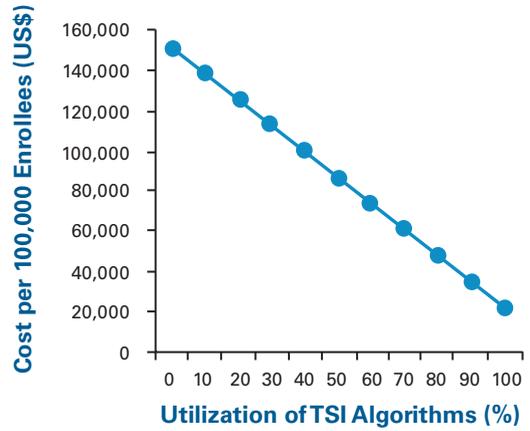
C   Total payer costs of GD diagnosis
(Direct costs + misdiagnosis costs)

D   Average time to diagnosis

GD indicates Graves' disease; TSI, thyroid-stimulating immunoglobulin.
A. Total costs of GD diagnosis are shown with increased utilization of TSI algorithms.
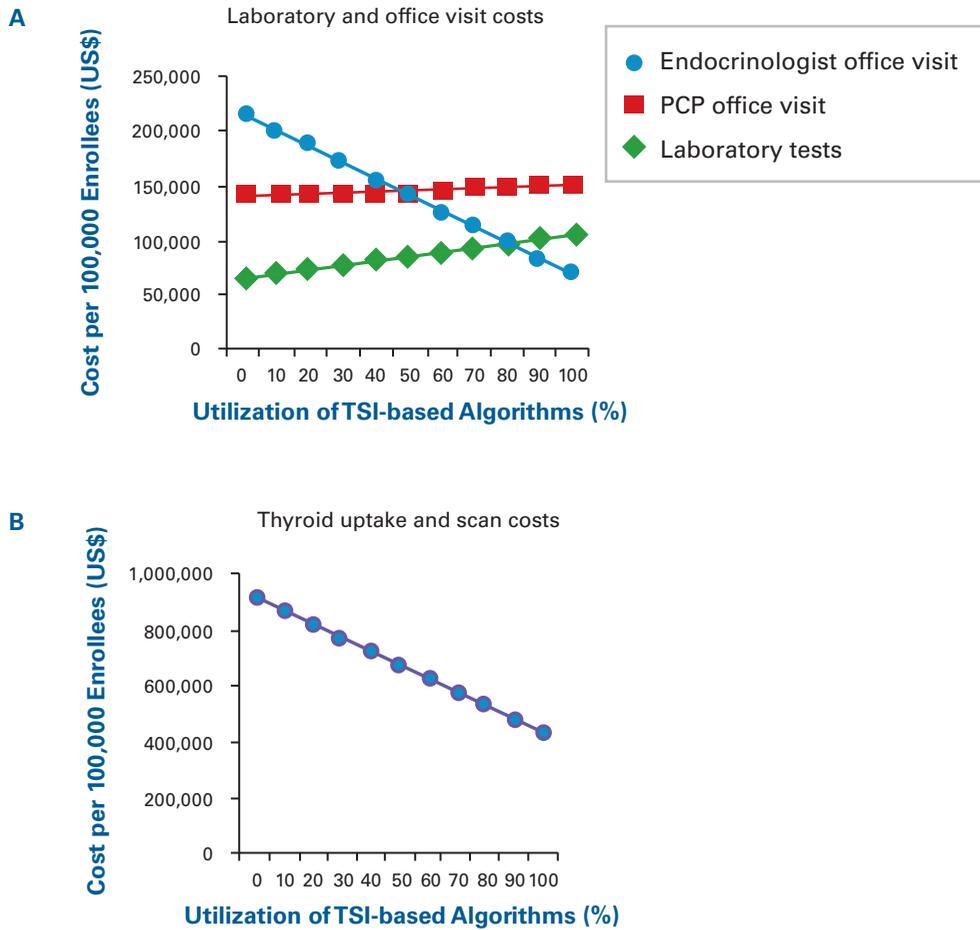B. Total costs of misdiagnosis are shown with increased utilization of TSI algorithms.
C. Annual cost to payers in a population of 100,000 enrollees is shown with increased utilization of TSI algorithms and includes direct costs of diagnosis and misdiagnosis.
D. The average number of weeks to GD diagnosis per patient is shown with increased utilization of TSI algorithms.

■ **Appendix B.** Impact of Increased TSI Algorithm Utilization on Laboratory Test Costs, Office Visit Costs, and RIUS Test Costs

A

Laboratory and office visit costs
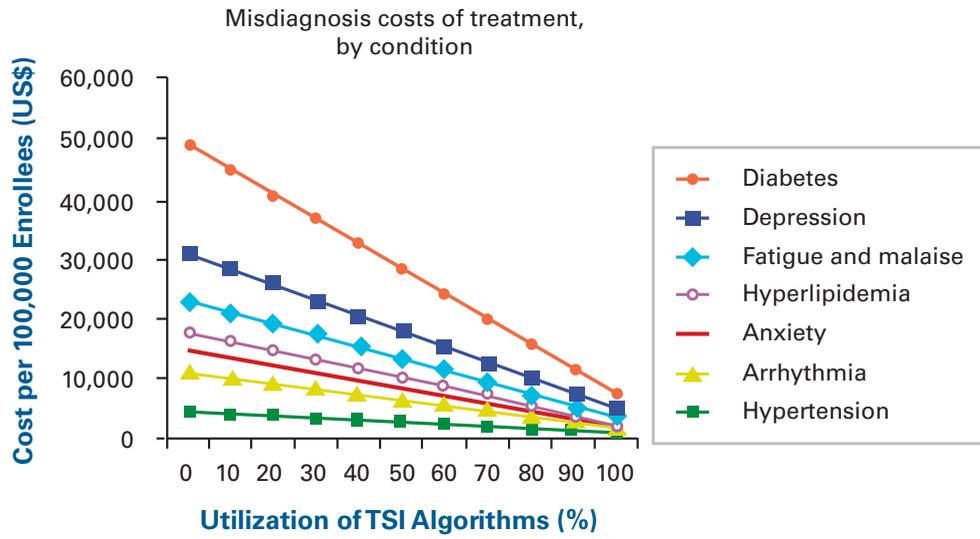

B

Thyroid uptake and scan costs

PCP indicates primary care physician; RIUS, radioactive iodine uptake and scan; TSI, thyroid-stimulating immunoglobulin.
A. Costs of laboratory tests (green diamonds), office visits to PCPs (red squares), and office visits to endocrinologists (blue circles) with increasing utilization of TSI algorithms are shown.
B. Costs of the thyroid RIUS test are shown. Costs of the actual RIUS test (blue circles) are shown as a function of increased TSI algorithm utilization.

■ **Appendix C.** Annual Costs of Treatment of Common Conditions That Are Misdiagnosed in GD Patients Are Shown With Increased Utilization of the TSI Test

Misdiagnosis costs of treatment, by condition

GD indicates Graves' disease; TSI, thyroid-stimulating immunoglobulin.