Economic Benefits of BIS-Aided Assessment of Post-BC Lymphedema in the United States

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Objectives: To estimate the economic outcomes associated with routine use of bioimpedance spectroscopy (BIS) to aid in the assessment of lymphedema following breast cancer (BC) treatment.

Study Design: Budget impact analysis for a hypothetical payer, comparing a "current standard assessment methods" scenario with a hypothetical scenario in which BIS is used routinely.

Methods: A payer-perspective decision model was built to calculate the 1-year budget impact of using either current standard methods or BIS-aided assessments for lymphedema in post-BC patients among a hypothetical payer population. Parameter values were obtained from the medical literature, including population characteristics, lymphedema incidence, resource utilization, and costs associated with assessments and treatment. Alternate scenario analysis incorporated incidence and associated costs of downstream infections and excess mental health care.

Results: With 627 BC patients in a payer of 1M covered lives, base-case analysis shows cost savings of $315,711, or $0.03 per enrolled member per month (from the payer perspective), from implementation of BIS-aided assessments for lymphedema. Savings improved with consideration of sequelae (eg, infection, hospitalization). However, savings are reduced if specificity of current standard assessments improves by 25% (fewer unnecessary expensive treatments), or if cost of complex decongestive therapy falls by 25%. Sensitivity analysis showed that cost savings results were robust to changes in other model parameters.

Conclusions: Over 1 year, BIS-aided assessment of lymphedema for patients following treatment for BC results in cost savings, even without considering potential cost savings associated with averted downstream sequelae.

(Am J Manag Care. 2012;18(5):234-241)

For author information and disclosures, see end of text.

The American Cancer Society (ACS) estimates that more than 207,000 women are diagnosed with breast cancer (BC) annually.[1] Among the 2 million US BC survivors, as many as 20% to 47% will experience lymphedema following axillary lymph node dissection (ALND).[2-4] Intervention in axillary nodes is required in more advanced BC stages, although less invasive node dissection has become standard for less advanced BC stages and carries a much lower risk of lymphedema. Lymphedema is a chronic condition caused by accumulation of protein-rich fluid in interstitial space due to inadequate lymphatic drainage.[5] The associated swelling causes discomfort, disability, and can lead to cellulitis and lymphangitis, possibly predisposing the patient to systemic and sometimes life-threatening infection.[6]

Identifying lymphedema following axillary staging surgery for BC remains variable due to lack of standard definitions. The most widely used method to diagnose upper-extremity lymphedema is circumferential upper-extremity tape measurement using specific anatomical landmarks,[7] following patient self-report.[8] Arm circumference measures are used to estimate volume differences between the affected/unaffected arms. The water displacement method is another way to evaluate arm edema. A volume difference of 200 mL or more between the affected/opposite arms is typically considered to be a cutoff point to define lymphedema.[9] One common approach to defining and classifying lymphedema has been put forth by the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events v3.0 (CTCAE).[10] The inter-limb discrepancy in volume or circumference is a key feature of the criteria (Level I: 5-10%; Level II: 10-30%; Level II: >30%). Level III severity takes into account the gross deviation from normal anatomic contour as well as any interference with activities of daily living, while Level IV incorporates progression to malignancy or amputation. Finally, Level V severity is signified by death.

Once diagnosed at clinically evident stages, as is currently typical, lymphedema requires lifelong treatment, which could be costly from the payer perspective. A recent medical claims study shows that patients diagnosed with post-BC lymphedema incur significantly higher total healthcare costs (nearly $15,000 more, odds ratio [OR] 2.02, P = 0.009) after removing cancer-specific costs.[11] Medical therapy such as complex decongestive therapy

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(CDT) and intermittent pneumatic compression and use of compressive garments have demonstrated various levels of efficacy for reduction of edema volume and prevention of fluid accumulation.[12] To potentially offset some of these medical costs, earlier identification of the condition might allow for the initiation of less expensive treatment with a potentially better therapeutic outcome[13]; recent research has found that lymphedema is reversible with minimal treatment following early detection (this study used subsequent measurements to confirm an early detection point of 3% excess fluid volume, the point of statistically significant difference over the contralateral arm adjusted for the difference between arms in a non-lymphedema control group,[4] as compared with a study which found an average of 11% volume difference between affected and non-affected arms following standard detection).[14] One measurement method that might prove useful in clinical assessments in order to detect lymphedema at preclinical stages is bioimpedance spectroscopy (BIS), given its ease of use and improved specificity/sensitivity as compared with other common diagnostic modalities (eg, 35%/89% for sum of arm circumferences >5 cm, or 65%/77% for self-report with BIS as a gold standard).[15-17] Because BIS measures total body water as well as differentiating between extracellular and intracellular water, it can estimate non-visible swelling,[18] thus facilitating detection of pre-clinical lymphedema.

Take-Away Points

Compared with standard assessment, routine use of bioimpedance spectroscopy (BIS) to aid in lymphedema assessment during post–breast cancer follow-up appointments may be associated with significant cost savings from a US payer perspective.

- Lymphedema treatments are less expensive following early detection with BIS, more than offsetting the cost of BIS.
- BIS remains an attractive economic option even under varied lymphedema incidence or resource use inputs.
- The cost savings may be greater still if downstream sequelae can be causally linked in the future.

An economic model was developed, synthesizing available data, to explore the potential economic impact of using routine BIS tests as an aid in the clinical assessment of lymphedema in post-BC patients.

METHODS

Model Structure and Perspective

A payer-perspective decision analytic budget impact model was developed in Microsoft Excel (Microsoft Corporation, Redmond, Washington) to compare the economic effects of 2 different methods of assessing lymphedema in a post-surgery BC population, including only direct medical costs over a 1-year horizon (most relevant to payers). The model used cohort simulation to track the hypothetical cohort of patients simultaneously through the model. Using this method, we assumed a common set of attributes based on population averages that may represent a population or an individual. Our cohort model considered 2 scenarios: 1) BIS testing performed routinely during post-BC follow-up visits; 2) current standard (CS) assessments are employed. In the CS scenario, at each follow-up visit, patients may self-report symptoms associated with lymphedema, leading to further clinical assessment. As our model compares the total costs of treating an average cohort in these 2 scenarios, this provides an assessment of the economic impact of employing BIS to aid lymphedema detection.

Population

The cohort model begins with a hypothetical population of 1 million covered lives. The cohort is then stratified by disease risk characteristics—US prevalence of adults (75.7%), female (50.7%),[19] and ACS BC incidence data (0.16%)[20]—in order to identify the cohort susceptible to an elevated risk of lymphedema (Table 1). Costs accrue for this at-risk population.

Lymphedema Characteristics

Peer-reviewed literature links lymphedema risk to type of lymph node intervention during BC treatment (eg, sentinel lymph node biopsy [SNB] vs ALND).[21] Because lymph node intervention is associated with BC severity,[22] most recent published Surveillance, Epidemiology and End Results (SEER) data on the breakdown of local versus regional BC diagnoses were used to approximate the population receiving SNB and ALND.[23] Lymphedema incidence is then defined differently for patients undergoing SNB versus ALND.

As a result of varying lymphedema clinical definitions, the model accommodates 2 sets of lymphedema incidence numbers to reflect current definitions as well as more conservative numbers. Because many studies presented incidence over varying time frames, 1-year incidence rates were calculated to reflect the proportion of cases that would be found by year 1 according to Herd-Smith's report of incidence at multiple time points over 5 years.[24] This data was insufficiently stratified for use itself, but shows the number of cases found at each time point over a 5-year horizon; the proportional relationship is then applied to other stratified data to derive 1-year values for the model. One set of stratified incidence numbers reflects a recent trend toward acknowledging the clinical importance of lower excess fluid volume. These numbers, which are based on NCI published CTCAE v3.0 (16.9% in the year

Table 1. At-risk Population Estimation by National Characteristics[19,20] Based on a Population of 1 Million

Parameter	Cascading Percentage	Population Breakdown
Total population	100.00%	1,000,000
Female	50.70%	507,000
Adult (18+ years old)	38.37%	383,799
Incident breast cancer cases/year	0.16%	627
True cases by the end of 1 year	(Weighted by SNB/ALND risks)	156

ALND indicates axillary lymph node dissection; SNB, sentinel lymph node biopsy.

following SNB; 47.1% in the year after ALND),[25] are higher than more traditional definitions based upon 10% excess arm volume or 2 cm size increase,[9] with annual incidence rates of 7% following SNB and 15% in the year following ALND.[26,27] Clinically evident lymphedema incidence values are used for both BIS and CS detection despite differences in assumed volume upon detection, as no pre-clinical incidence data are available.

Comparators Inputs

Published literature and clinical expert opinions informed resource utilization inputs. In the base-case analysis, outpatient visits following BC treatment occur quarterly in year 1. In the BIS model arm, BIS is used at every appointment after establishment of a patient-specific baseline and the model accrues a cost/use in addition to the physician visit cost, while in the CS model arm, self-report and clinical examination incur no cost other than that of the physician visit (**Figure**).

BIS assessments have been shown to be 100% sensitive/98% specific when used according to currently validated reference impedance ratios, established according to a 3 standard deviation change in impedance ratios from pre-surgery reference values.[28] This early detection criterion is assumed to represent pre-clinical volume differences, shown to be treatable with compression sleeves[4] (the model employs sensitivity analysis to explore the impact of requiring further treatment in some patients with hypothetical higher volume at detection). Because payers may not reimburse for sleeves, sleeves are excluded from base-case costs; an alternate scenario is explored with costs accruing for a set of 2 sleeves replaced every 6 months. For a small fraction of the population (4.6%), obesity requires use of more expensive custom-fitted sleeves rather than off-the-shelf sleeves.[4]

For patients with lymphedema identified via CS methods (65% sensitive/77% specific in the same study population[28]), their clinically evident lymphedema has progressed enough, on average, that compression sleeves comprise only part of the treatment plan. These patients are assumed to undergo a 1-month course of CDT, defined as manual lymphatic drainage for 1 hour, compression wrapping of the limb, and daily decongestive exercises.[29,30] Finally, a proportion of patients found via the CS methods use pneumatic pumps in addition to CDT; in the absence of clear usage patterns, the model assumes that more severe cases (18.8%) would receive this adjunct therapy in the base case (further explored in sensitivity analysis).[31]

False positive cases in both the CS and BIS arms are assumed to be revealed after the 1-month CDT course or sleeve purchases, and thus accrue the same treatment costs as true positives in the 1-year time frame.

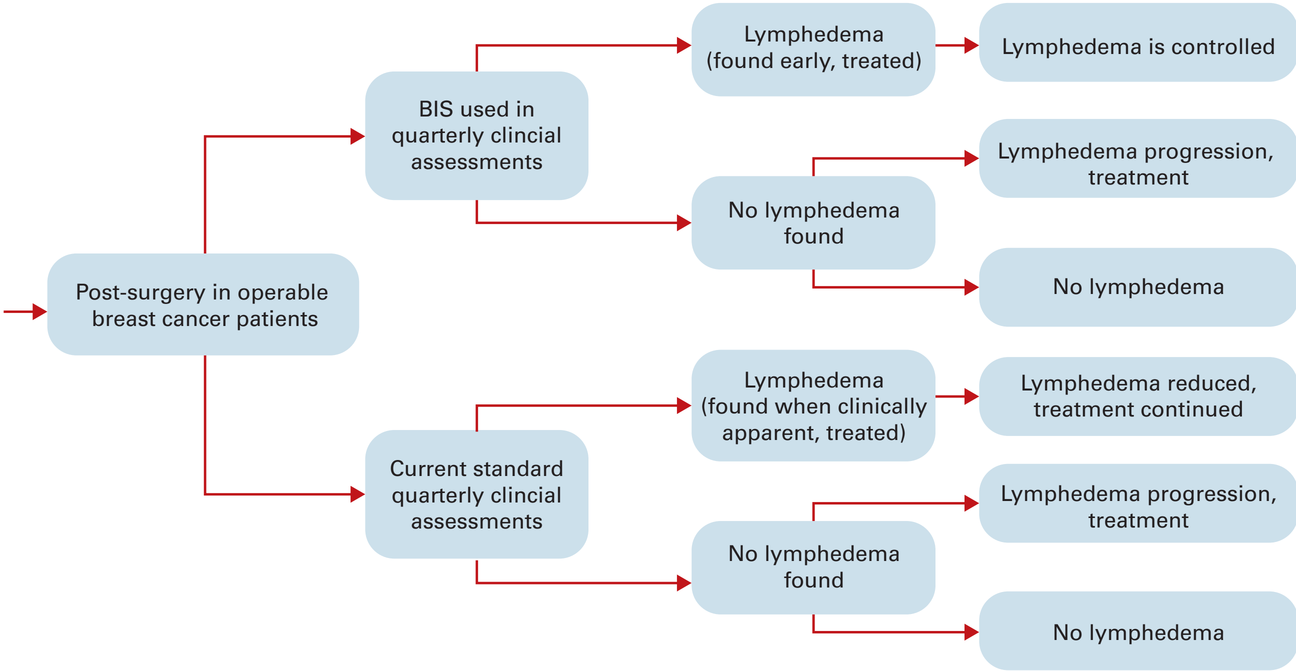
Sequelae

Clinical debate surrounds the direction of a causal link between lymphedema and sequelae (eg, infections, mental health concerns).[11] As such, the base-case scenario does not include these sequelae. However, because data suggest that more patients experience infections with greater lymphedema severity,[32] and because more mental health care resources are used by patients diagnosed with lymphedema,[11] we explore the economic impact of sequelae based on these data in sensitivity analysis.

Lymphedema-related infections (eg, cellulitis) have been estimated to occur at a rate of 1.1 infections per year with moderate disease,[33] or 0.3 per year in controlled lymphedema or "healthy" patients (excess volume below 5%) (value calculated by applying relative rate in Shih et al[11] to the value from Ko et al[33]). If CDT does not bring excess fluid volume below 5%, a rate of 0.65 per year is applied.[33] These rates, rather than proportions of the population experiencing an infection, are used in order to portray infections' recurring nature.

Based on these rates, associated treatment costs (eg, hospitalizations, antibiotics) are incorporated into the results via sensitivity analysis. Costs align with the following resource use: 90% of patients visit their physician, in an outpatient setting, prior to admission; antibiotic administration (3 days in hospital, 7 additional days of oral vancomycin). The remaining 10% of patients are assumed to visit an emergency department prior to admission for antibiotic administration, a

■ **Figure.** Lymphedema Management



conservative estimate informed by general skin infection ambulatory care data.[34]

Shih reports in her medical claims analysis that 6% of those diagnosed with lymphedema require mental health resources as compared with post-BC patients without lymphedema.[11] In sensitivity analysis incorporating sequelae, an average depression treatment cost is applied based on total national depression rates/expenditures.[35]

Healthcare Costs

Healthcare costs were derived from publicly available fee schedules, and where possible, reflect Medicare national average reimbursement rates.[36-38] No discount rate was applied to these costs due to the 1-year time horizon (Table 2).

RESULTS

Base-Case Analysis

For the 627 newly treated post-surgery BC patients, based upon the CTCAE v3.0 definition of lymphedema and other base-case model input values, the total 1-year budget impact, from the payer perspective, is $1,984,529 for CS assessment and $1,668,818 for BIS-aided early detection, for a savings of $315,711, or $0.03 per member per month (PMPM) (Table 3). Because of the default assumption that patients pay for sleeves, this result reflects no treatment costs for the BIS-aided assessment model arm. Treatments comprise the largest source of CS-assessment model arm costs, while the BIS-aided assessment costs can be attributed to assessments.

Sensitivity Analyses—Univariate

Univariate sensitivity analyses were performed for each model parameter, as well as specific scenarios and multivariate combinations. Where data fail to indicate a range, ±25% is used to evaluate model sensitivity to parameters. Univariate results for the most sensitive parameters are presented in Table 4.

The budget impact varies importantly according to the proportion inappropriately diagnosed and treated post–CS assessments, characterized by the specificity of CS assessments. If CS assessment specificity is 25% over the default value, then BIS-aided assessment is no longer cost saving, and total budget impact becomes $649,475, or $0.08 PMPM; cost savings is lost at specificity ≥85%. If CDT is likewise 25% less expensive than the default, cost savings of BIS-aided assessment is lost, for a budget impact of $26,270 (negligible PMPM); the cost-savings threshold is just over $2260 per CDT course. Alternatively, if CS assessment is less specific than the default value, or CDT costs significantly more, as has been suggested by clinical experts, then cost savings of BIS-aided detection more than doubles (to $754,975 and $657,692, respectively, for upper-range values in Table 2). Cost savings due to BIS-aided detection is robust to ±25% changes even in other sensitive variables, including proportion/cost of pneumatic pump

Table 2. Model Parameters

Parameter	Default Value	Sensitivity Range (+/-25% of Default Where Otherwise Unspecified)	Sources
Lymphedema Characteristics			
Annual lymphedema incidence			
SNB	16.9%	7%	24, 25, 26, 27
ALND	47.1%	15%	
Comparator Inputs			
BIS-aided assessment			
Sensitivity	100%	75%-100%	13
Specificity	98%	74%-100%	
CS assessment			
Sensitivity	65%	49%-81%	17
Specificity	77%	53%-96%	
Treatment when found early (3% excess fluid volume)			
Compression sleeves			
Off-the-shelf	95.4%	94.3%-100%	4
Custom	4.6%	0%-5.8%	
Treatment when found later (11% excess fluid volume)			
Compression sleeves			
Off-the-shelf	50%	37.5%-62.5%	Conservative estimate based on 39
Custom	50%	37.5%-62.5%	
CDT (1 month)	100%	75%-100%	29, 30
Pneumatic pump use	18.8%	14%-23.5%	31
Resource Costs			
BIS device (per use)	$600		Assumption n
Outpatient doctor appointment	$66	$50-$83	36
Set of 2 compression sleeves + gloves			
Off-the-shelf	$128	$96-$160	37
Custom	$800	$600-$1000	39, 40
CDT (1 month)	$2940	$2205-$5000	41
Pneumatic pump	$5149	$3862-$6436	37
Outpatient device therapy appointment, 1 hr	$32	$24-$40	36
Treatment for each cellulitis-related infection			
ED physician fee	$171	$128-$214	36
Inpatient physician fee, first visit	$103	$77-$129	36
Inpatient physician fee, follow-up visits	$31	$23-$39	36
Outpatient physician fee	$106	$80-$133	36
Hospitalization (IV administration, vancomycin 1g)	$4188	$3141-$5235	38
Subsequent oral antibiotic therapy	$679	$509-$849	42
Annual cost for depression treatment	$681	$511-$851	35

ALND indicates axillary lymph node dissection; BIS, bioimpedance spectroscopy; CDT, complex decongestive therapy; CS, current standard; ED, emergency department; SNB, sentinel lymph node biopsy.

Table 3. Budget Impact Base-Case Results, 1 Year

	Assessments	Lymphedema Treatments	Total Costs
CS assessment	$ 164,633	$ 1,819,896	$ 1,984,529
BIS-aided assessment	$ 1,668,818	$ 0	$ 1,668,818
Overall cost/(savings) of BIS-aided assessment	$ 1,504,185	$ (1,819,896)	$ (315,711)

BIS indicates bioimpedance spectroscopy; CS, current standard.

use, assessment rate, and CS assessment sensitivity, as well as the more conservative set of annual lymphedema incidence rates.

Scenario Analyses

Compression Sleeve Coverage

Payers may incur additional costs if they reimburse for compression sleeves. With all other inputs set to base-case values, 1-year budget impact of BIS-aided assessment grows to a savings of $685,741 from the base case of $315,711, due to greater use of expensive custom sleeves among the more severe cases found by CS-assessment methods. Savings slightly decrease if custom sleeves are covered but patients pay for off-the-shelf sleeves (cost savings of $673,636). Savings decrease further if the proportion of patients requiring custom sleeves following BIS-aided assessment increases by 25%, or if the proportion of patients using custom sleeves following the CS-assessment method decreases by 25%. Even eliminating sleeve use entirely from treatment following CS assessment and requiring all patients following BIS-aided assessment to use custom sleeves results in cost savings, although minimal at only $4843 for the population. Other post-CS-assessment costs, such as CDT and pneumatic pumps, outweigh the costs of covering compression sleeves.

Pneumatic Pump Use

As pneumatic pumps are used by only a proportion of patients (modeled as adjunct to CDT for severe patients), the budget impact may differ based upon practice patterns. If pumps are eliminated entirely, budget impact becomes positive at $136,259, but still a minimal $0.01 PMPM. The cost savings return if more than 5% of patients found at clinically evident volumes use pumps as part of lymphedema therapy.

Higher Treatment Costs for BIS-Detected Cases

Although lymphedema detected at pre-clinical stages has been shown to be reversible, a scenario in which a portion of these cases progress and require CDT within the year is worth examining. If 25% of cases found with BIS ultimately receive treatment according to the treatment pattern modeled following CS detection, there is still a cost saving of $125,596 for the BIS arm. This cost saving is retained until ≥42% require the same treatment as CS-detected patients.

Low-/High-risk Populations Only

If BIS is used for only a subset of post-BC patients, according to risk group, the cost savings falls to represent only a portion of the base-case cost savings. Following SNB for localized BC, 382 at-risk patients result in savings of just under $150,000, and savings following post-regional BC (194 patients) are higher, at over $160,000.

Sequelae Inclusion

Infection prevention may be a significant benefit of early detection of lymphedema and may interest payers. With all other base-case values, the inclusion of sequelae-related

Table 4. Most Sensitive Parameters, Budget Impact Sensitivity Analysis Results

Varying Parameter	Low Range Budget Impact (Savings)	High Range Budget Impact (Savings)
Incidence (ACOSOG)	$(171,002)	N/A
Assessment characteristics:		
Specificity of CS method[a]	$(754,975)	$649,475
Sensitivity of CS method	$(266,929)	$(339,639)
CDT cost	$26,270	$(1,274,790)
Pneumatic pump use, %	$(202,719)	$(428,704)
Annual rate of assessment visits	$(445,474)	N/A
Cost of pneumatic pump	$(279,332)	$(352,837)

ACOSOG indicates American College of Surgeons Oncology Group; CDT, complex decongestive therapy; CS, current standard.
[a]Most sensitive parameter.

costs nearly doubles the cost savings from BIS-aided assessment ($630,319, or $0.05 PMPM). If infection rates are significantly lower than the base-case values (with 0 infections/year for healthy patients or those with excess fluid volume under 5% and only 0.1/year for those who have more than 5% volume), there is still cost savings of $408,100 due to early detection.

Extreme Value Multivariate Analyses

The model also explored the most/least favorable scenarios for the intervention under consideration while holding assessment sensitivity/specificity at default values, using the sensitivity ranges found in Table 2. When costs of treatments following diagnosis at the more severe stage are all less expensive, and a smaller proportion of CS-assessment patients require the pneumatic pump, cost savings from BIS-aided early detection disappears: CS assessment accrues total costs of $1,300,702, compared with BIS-aided assessment costs of $1,627,528. However, the budget impact of $326,827 is still relatively low, at only $0.03 PMPM.

In contrast, when these variables are altered to their higher ranges, with high costs for treatment and more pneumatic pump users, routine BIS use saves significantly more money for the covered population than the default. The BIS-aided assessment total costs remain the same, but CS-assessment total costs rise to $3,049,779 per year. The difference of $1,422,250 translates into a savings of $0.12 PMPM.

DISCUSSION

The model demonstrates that, over a 1-year time horizon, using BIS-aided lymphedema assessment in post-surgery BC patients is cost saving by $0.03 PMPM for a payer with a nationally representative population when compared with CS assessment, due to earlier detection. The savings are primarily due to the more costly interventions required to treat this condition when it is found, on average (in our model cohort), at more severe stages associated with CS assessment methods. Additional savings result from the higher specificity of BIS, leading to fewer non-lymphedema patients being treated unnecessarily. Detecting lymphedema when average excess fluid volume is reversible allows compression sleeve use to control the condition, whereas at clinically evident volumes, the lymphedema is treated with CDT and compression sleeves, with some patients using pneumatic pumps as well.

These results are robust to varying parameter values, including lower incidence of lymphedema and different resource-use patterns. Although the base-case analysis excludes any cost offsets due to improved downstream health from early detection and treatment, the model results only become more favorable if serious and costly sequelae are prevented.

Limitations

Despite robust results, this study is limited by a number of elements. Foremost is the lack of a clear natural history of lymphedema (and associated incidence) and severity at the time of detection and associated resource use (eg, sequelae). Much of the peer-reviewed epidemiological literature is based upon circumference measurements or contralateral arm volume comparisons to define degree of swelling; this can poorly represent the presence of lymphedema given natural volume/circumference differences by arm dominance. In particular, risk-stratified incidence data are lacking. Although Herd-Smith present longitudinal data, it is not stratified by risk group, which impacts our assumptions and associated incidence rates; we applied the proportion of total cases found in the first year from Herd-Smith to both SNB and ALND when calculating 1-year values from alternate length studies. Similarly, our use of an equal incidence for BIS and CS detection is a simplification, as the literature-based incidence values reflect clinically evident disease and thus may underestimate BIS detections. Despite this assumption, base-case results remain unchanged. Using extensive sensitivity analyses, our study addresses the previously mentioned literature gaps around key parameter values to show changes to budget impact based upon this potential parameter variability.

Another limitation is noted around the lack of variability in population lymphedema characteristics, due to cohort modeling with population averages (standard modeling practice) and data limitations. In order to account for this, sensitivity analysis is applied to demonstrate the possible variation around average budget impact. A 1-year time horizon, of particular interest to payers, is utilized, though there may be additional costs or savings if BIS is continued beyond that.

Finally, there may be non-economic benefits to routine BIS testing as well,[43] if patients experience a quality of life improvement or if use of compression sleeves, rather than CDT, allows patients to miss fewer days of work. Improved data around these parameters, establishing firm lymphedema definitions to clarify natural history and associated clinical assumptions, and research to verify causal relationships with downstream sequelae will allow a more detailed and longer-term picture of budget impact in the future.

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Funding Source: ImpediMed, Inc.

Author Disclosures: Ms Bilir, Mr Dekoven, and Ms Munakata report employment with IMS Health, Inc, and report receiving payment for involvement in the preparation of this manuscript.

Authorship Information: Concept and design (SPB, MPD, JM); acquisition of data (SPB); analysis and interpretation of data (SPB, MPD, JM); drafting of the manuscript (SPB, MPD); critical revision of the manuscript for important intellectual content (SPB, JM); obtaining funding (MPD); administrative, technical, or logistic support (MPD, JM); and supervision (MPD, JM).

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