Three-Year Cost-effectiveness Model for Non–Animal Stabilized Hyaluronic Acid and Dextranomer Copolymer Compared With Sacral Nerve Stimulation After Conservative Therapy for the Management of Fecal Incontinence

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ABSTRACT

Background: Two new therapies for fecal incontinence (FI) are now available: non–animal stabilized hyaluronic acid and dextranomer copolymer (NA-SHA/Dx) and sacral nerve stimulation (SNS).

Purpose: This study aimed to determine the cost-effectiveness of NASHA/Dx compared with SNS and conservative therapy (CT) for the treatment of FI after CT failure.

Methods: Decision tree models with Markov sub-branches were developed to compare all direct costs and outcomes during a 3-year period from the viewpoint of the US third-party payer. Costs (in 2013 US dollars) of devices, medical and surgical care, and hospitalization were included. Outcomes included quality-adjusted life-years (QALYs) and incontinence-free days (IFDs). Both costs and outcomes were discounted at an annual rate of 3%. The incremental cost-effectiveness ratio was calculated for each outcome. One-way and probabilistic sensitivity analyses were performed to examine robustness of results and model stability. A budget impact analysis was also undertaken to estimate the potential cost and savings of NASHA/Dx for a payer with 1,000,000 covered lives.

Results: For the 3-year cost-effectiveness models, the expected cost was $9053 for CT, $14,962 for NASHA/Dx, and $33,201 for SNS. The numbers of QALYs were 1.769, 1.929, and 2.004, respectively. The numbers of IFDs were 128.8, 267.6, and 514.8, respectively. The incremental cost-effectiveness ratios per additional IFD gained were $42.60 for NASHA/Dx vs CT, $73.76 for SNS vs NASHA/Dx, and $62.55 for SNS vs CT. The incremental costs per QALY gained were $37,036 for NASHA/Dx vs CT, $244,509 for SNS vs NASHA/Dx, and $103,066 for SNS vs CT. The budget impact analysis evaluated the financial effect on the health care system of the use of NASHA/Dx and SNS. For the scenarios evaluated, when all of the patients receive NASHA/Dx, the net annual effect to the health care payer budget ranged from $571,455 to $2,857,275. When all of the patients receive SNS, the net annual effect to the health care payer budget ranged from $1,959,323 to $9,796,613.

Conclusion: Both NASHA/Dx and SNS have produced significant improvements in FI symptoms for affected patients. NASHA/Dx is a cost-effective and more efficient use of resources for the treatment of FI when compared with SNS. The budget impact analysis suggests that although reimbursement for NASHA/Dx treatment initially adds costs to the health care system, it is significantly less expensive than SNS for patients who are candidates for either treatment. (Clin Ther. 2014;36:890–905) © 2014 The Authors. Published by Elsevier HS Journals, Inc.

Key words: budget impact analysis, cost-effectiveness, fecal incontinence, incontinence-free days, incremental cost-effectiveness ratio, InterStim, NASHA/Dx, sacral nerve stimulation, Solesta, quality-adjusted life-years.

INTRODUCTION

Fecal incontinence (FI) is a socially devastating condition of varied origin. Conservative therapy (CT)
includes dietary changes, bulking agents, antidiarrheal medications, enemas, and biofeedback. Contingent on the severity of the incontinence, these noninvasive measures are often initial options. Conservative therapy can successfully improve FI in >30% to 50% of affected individuals.\(^1\)\(^-\)\(^4\) When CT is unsuccessful, other therapies may be considered. Anal sphincter repair, artificial bowel sphincter, muscle transfers, radiofrequency, and stomas are other treatment options for FI available in the United States. Historically, repair of anterior defects was favored; however, more recent research has revealed poor long-term results.\(^5\)\(^-\)\(^6\) Although an attractive alternative with often impressive long-term functional results, artificial bowel sphincter was found to have a 40% major infection rate, limiting its appeal.\(^7\)\(^-\)\(^8\) Muscle transfers are complex and associated with a high morbidity; thus, they have not been widely popularized. Radiofrequency collagen reformation is a promising modality but requires an anesthetic and an operating room or endoscopy suite for its application. A diverting stoma allows affected patients to function away from the toilet but interferes with their overall quality of life.

More recently, 2 therapies for FI have been approved by the US Food and Drug Administration (FDA), including non–animal stabilized hyaluronic acid and dextranomer copolymer (NASHA/Dx\(^*\)), approved in May 2011, and sacral nerve stimulation (SNS\(^\text{†}\)), approved in March 2011. NASHA/Dx is a bulking agent that consists of dextranomer microspheres in stabilized hyaluronic acid, which are injected into the submucosa. In the prospective randomized study conducted for FDA approval of NASHA/Dx, 52% of patients had a >50% reduction of FI versus 31% of sham-treated patients after 6 months ($P = 0.009$).\(^4\) These results were sustained in the NASHA/Dx treatment group at 36 months.\(^9\) A separate 24-month follow-up study evaluated the effectiveness of NASHA/Dx for FI under open-label conditions; 62.7% of the patients were treatment responders and experienced at least a 50% reduction in the total number of FI episodes.\(^10\)

SNS has also produced major clinical benefits for patients with FI.\(^11\)\(^-\)\(^15\) This therapy involves the administration of long-term low-level electrical impulses to stimulate the sacral sensory and motor fibers. The SNS procedure is a staged process in which the patient first undergoes insertion of an electrode attached to an external pulse generator to assess benefit. If there is a >50% reduction in FI, a permanent electrode is inserted and connected to an implanted pulse generator. The mechanism of action of SNS includes local sensory improvement, probably secondary to cortical stimulation.\(^16\) In the 12-month study conducted for FDA approval of SNS, 90% of patients passed test stimulation and proceeded to long-term implantation; for those patients who received permanent implantation, 83% had therapeutic success, with 41% achieving complete continence.\(^15\) In a long-term study of SNS, Hull et al\(^17\) found sustained success, with 89% having a >50% reduction in FI at ≥5 years and 36% having complete resolution of FI.

Considering the various treatment interventions for individuals in whom CT fails and the associated cost burden, a number of studies of the cost-effectiveness of interventions with SNS for FI have been performed.\(^18\)\(^-\)\(^24\) In most cases, SNS was cost-effective, dominating in one Markov analysis from the Netherlands.\(^24\) A simulation model evaluating the cost-effectiveness of SNS treatment for FI in patients with an intact anal sphincter estimated an incremental cost-effectiveness ratio (ICER) of €38,662 per quality-adjusted life-year (QALY) gained in the Italian health care system.\(^18\) A similar simulation model developed to assess the cost-effectiveness of SNS treatment for a comparable patient population in the Spanish health care system yielded an ICER of €16,181 per QALY gained with minimal budget impact.\(^21\) This latter model was validated using a prospective comparison of 2 patient cohorts.\(^23\) The exception was a study from France comparing 2 patient cohorts; that study found significantly higher ICERs.\(^22\) Patients with FI who underwent implantation with sacral nerve modulation experienced improved disease-related quality of life when compared with patients without implants, but at an increased cost. For the FI patients, the 12- and 24-month ICERs were €90,082 and €185,160, respectively.

Although studies have investigated the cost-effectiveness of SNS, there is no published literature evaluating the cost-effectiveness of NASHA/Dx. In addition, no comparison has been made between these 2

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\(^*\)Trademark: Solesta\(^\text{®}\) (Salix Pharmaceuticals, Raleigh, North Carolina)

\(^\text{†}\)Trademark: InterStim\(^\text{®}\) (Medtronic Inc, Minnetonka, Minnesota).
treatment options to guide health care professionals in choosing one treatment option over the other for affected patients. The objective of the present study was to determine the cost-effectiveness of NASHA/Dx compared with SNS after failure of CT in the United States.

**METHODS**

A modified decision tree was used to analyze costs and QALYs for adult patients who have had FI symptoms for at least 12 months and did not respond adequately to CT. Figure 1 depicts the primary model structure. The analytic viewpoint was that of the US health care payer during a 3-year period.

**Model Structure**

A hybrid model was developed to compare costs and outcomes between NASHA/Dx with other options after CT failure. The modeling procedure was guided by the published literature and a panel of clinical experts in this field. To determine suitable treatment options, a literature review was performed, followed by a survey of practicing clinicians (see the Supplemental Survey 1 in the online version at http://dx.doi.org/10.1016/j.clinthera.2014.04.010). That survey was undertaken at the 23rd Annual International Colorectal Disease Symposium (Fort Lauderdale, Florida, February 2012). The questionnaires captured physician experiences and preferences regarding the testing, diagnosis, and treatment of FI. The survey was fielded to 50 clinicians, and 35 surveys were returned and analyzed (ie, 70% response rate). The survey responses indicated that SNS and NASHA/Dx were suitable treatment options. This information was used to construct the model, which reflected US practice.

The options for this analysis included continuing to receive CT (ie, the “do nothing” option), using NASHA/Dx, and undergoing SNS. Typically, CT involves dietary changes, bulking agents, antidiarrheal medications, glycerin suppositories, enemas, biofeedback, and other noninvasive measures. NASHA/Dx requires ≥1 injections of dextranomer microspheres in stabilized hyaluronic acid into the submucosa, whereas SNS involves the surgical implantation of a stimulation device under the skin to modulate neuronal impulses.

All treatment arms have an initial 6-month treatment phase (Figure 1) followed by Markov submodels that are 30 months in length, for a total period of 3 years (Figure 2). The cycle length is 1 month, which is based on having a reasonable period for a series of biofeedback treatments for FI. A half-cycle correction was not used for the Markov submodels because of the relatively short cycle length. Baseline medical management costs for patients with FI were estimated from the published literature. On the basis of physician guidance, biofeedback was included as a potential downstream treatment option for patients who did not achieve primary treatment success with NASHA/Dx or SNS. The model structures for CT and NASHA/Dx were identical; the SNS arm contains

![Figure 1](http://dx.doi.org/10.1016/j.clinthera.2014.04.010) Three Year Cost-effectiveness Model. FI = fecal incontinence; NASHA/Dx = non–animal stabilized hyaluronic acid and dextranomer copolymer; SNS = sacral nerve stimulation.
additional nodes to reflect the 2-stage process for the SNS procedure (ie, the initial stimulation phase and the implantation phase). The cost-effectiveness model that evaluated incontinence-free days (IFDs) as the outcome used the expected cost from the hybrid model and the 3-year discounted IFD values, which were calculated separately. The hybrid cost-effectiveness model was developed using TreeAge Pro 2014 (TreeAge Software Inc, Williamstown, Pennsylvania). The discounting and ICER calculations for the IFD outcome were evaluated in Microsoft Excel 2010 (Microsoft Corp, Redmond, Washington).

Clinical Inputs
PubMed was reviewed for relevant studies pertaining to these interventions for the years 2004 to 2013. For the SNS group, PubMed was searched for the title keywords sacral nerve stimulation and fecal incontinence. For the NASHA/Dx group, PubMed was searched for the title keywords NASHA/Dx or hyaluronic acid and fecal incontinence or faecal incontinence. At the abstract level, it was required that studies reported the Responder50 end point for primary patient data. At the title level, the search resulted in 59 articles for SNS and 6 for NASHA/Dx. One study was not indexed on PubMed and was provided by an adviser. After the studies were reviewed at the abstract level, 9 remained for SNS and 5 for NASHA/Dx. After review at the manuscript level, 5 studies were used to provide data for the SNS group, and 5 studies were used to provide data for the NASHA/Dx group. The efficacy estimates were computed for 12, 24, and 36 months for SNS. The efficacy estimates were computed for 6, 12, 24, and 36 months for NASHA/Dx. The sample size weighted means were computed using the study sample sizes and the proportions of individuals who met the Responder50 end point at the respective time points. The efficacy estimate for the stimulation phase of SNS was derived from a multicenter prospective study. Table I summarizes the weighted mean success rates used as model inputs. The cost-effectiveness calculations for the IFD outcome use the number of IFDs for the CT group as the baseline value for the ICERs, which include CT.

Costs
Because the perspective is that of the health care payer, indirect costs were not included in the model. All direct costs were expressed in 2013 US dollars. The cost estimate for CT was drawn from a published study that reported the mean per person direct medical costs associated with FI. These costs include physician visits, laboratory tests, operations, hospitalizations, medications, and home health care. Since this cost was published using 2010 US dollars, it was adjusted to 2013 US dollars using the medical component of the Consumer Price Index values for mean yearly change. For NASHA/Dx, the cost was provided by the manufacturer (Salix Pharmaceuticals, Raleigh, North Carolina). Because a specific Current Procedural Terminology or Healthcare Common Procedure Coding System code for anoscopy with injection of NASHA/Dx does not currently exist, an estimated charge was developed using crosswalks to similar gastrointestinal endoscopic procedures.

Unit costs assigned to resources consumed were derived from Centers for Medicare and Medicaid Services sources, as available (Table II). Physician reimbursement (under a dedicated Current Procedural Terminology code) for the NASHA/Dx procedure was not currently available from Centers for Medicare and Medicaid Services; therefore, an estimated cost was assumed using similar procedures and guided by expert opinion. Biofeedback and the associated cost were included for treatment nonresponders for the last 30 months of the model. The cost of medical management was included in the last 30 months for all patients. This cost of medical management is the same value that is used for CT as previously noted. For the SNS and NASHA/Dx treatment arms, the medical management costs were decreased by 50% for
patients who achieved treatment success. All costs and outcomes were discounted at 3% per annum, as per current recommendations.\textsuperscript{37}

**Outcomes**

Outcome measures of effectiveness were QALYs and IFDs. Quality-of-life values (utility values) were assigned based on whether the patient was experiencing FI symptoms during the model period (Table I). QALYs were not derived directly from studies of NASHA/Dx or SNS because generic health preference outcomes were not available. Values were derived from published studies that evaluated European Quality of Life–5 Dimensions scores and estimated utility values for FI patients dependent on their symptomatic status.\textsuperscript{18,38} A utility value of 0.55 was assigned for periods associated with FI symptoms, whereas a utility value of 0.74 was assigned for periods associated with adequate relief of FI symptoms, which was defined as success with respect to the Responder\textsubscript{50} end point.

**Statistical Analysis**

The economic outcome of the analysis was the ICER for each of the outcomes of interest, which were
expressed as the incremental cost per QALY gained and per IFD gained during the 3-year period. To evaluate the robustness of model outcomes, 1-way sensitivity analyses were performed for cost inputs, probabilities, and utilities. For 1-way sensitivity analyses, plausible ranges were used to investigate the effect of deviations on a per variable basis. One-way sensitivity analyses were presented in ICER tornado diagrams (Figures 4–6). One-way sensitivity analyses were computed for the NASHA/Dx cost input, the decrease in medical management costs for treatment responders in the NASHA/Dx and SNS arms, and the NASHA/Dx subsequent treatment rate (Tables V–VII).

A probabilistic sensitivity analysis was performed to evaluate the overall variability of model outcomes using 10,000 iterations. The SEs for the probability values were estimated using the formula for binomial proportions and were used as the measure of variability in the probabilistic sensitivity analysis. Cost inputs were modeled as lognormal distributions, and probability and utility variables were modeled as β-distributions (see the Supplemental Table I in the online version at http://dx.doi.org/10.1016/j.clinthera.2014.04.010).

A cost-effectiveness acceptability curve was computed to evaluate the relationship between willingness-to-pay (WTP) thresholds and the likelihood of an intervention being cost-effective (Figure 3). For this curve, the sum of the respective probabilities is 1 for the range of WTP values. The WTP threshold ranges from 0 to $100,000. The net monetary benefit is used for the computations. The percentage of iterations favoring each intervention with respect to a range of WTP thresholds is presented (see the Supplemental Table II in the online version at http://dx.doi.org/10.1016/j.clinthera.2014.04.010).

### Budget Impact Analysis

A budget impact analysis (BIA) was performed to estimate the effect of FI treatment with NASHA/Dx and SNS on health care plan costs. The noninstitutionalized population of US adults was used as the base population, with estimates of the prevalence of FI (ie, 2.7%) derived from published sources.\(^\text{39,40}\) Effect estimates were based on a health care plan with 1,000,000 covered lives. NASHA/Dx is a relatively new intervention; hence, its use is not well known. The proportion of the population who seek care is 25%, and an estimated 80% of this population will initially be treated with CT.\(^\text{18}\) The estimated CT failure rate was 25%.\(^\text{18}\) The BIA was performed using a range of 5% to 25% for the likelihood that

<table>
<thead>
<tr>
<th>Variable</th>
<th>Time</th>
<th>Cost, $\text{a}^b$</th>
<th>Cost Range, $\text{a}^b$</th>
<th>Reference</th>
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<tbody>
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<td>Conservative therapy cost</td>
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<tr>
<td>NASHA/Dx costs</td>
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<td></td>
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</tr>
<tr>
<td>Physician(^c)</td>
<td>NA</td>
<td>281.03</td>
<td>224.82–337.23</td>
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<td>Device</td>
<td>NA</td>
<td>4900</td>
<td>2940–6860</td>
<td>(^g)</td>
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<tr>
<td>SNS (stimulation phase) cost(^d)</td>
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<tr>
<td>SNS (implantation) cost(^e)</td>
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<tr>
<td>Biofeedback session cost</td>
<td>Month(^f)</td>
<td>265.45</td>
<td>212.36–318.55</td>
<td>36</td>
</tr>
</tbody>
</table>

\(^a\)All costs are in 2013 US dollars.

\(^b\)Cost was published in 2010 US dollars, adjusted to 2013 US dollars using the medical component of the Consumer Price Index.


\(^d\)Test stimulation for SNS (Current Procedural Terminology code 64581).

\(^e\)2013 Medicare national mean for complete (permanent implantation) SNS procedure.

\(^f\)Biofeedback sessions (assumption is 3 treatments per week).

\(^g\)Salix Pharmaceuticals, Raleigh, North Carolina.
patients would choose or be assigned to NASHA/Dx. The BIA is computed for patients who are good candidates for both NASHA/Dx and SNS. The net effect to the health care payer is computed for the scenario when all patients receive NASHA/Dx, for a scenario when all patients receive SNS, and for a set of intermediate scenarios. The BIA was performed using Microsoft Excel 2010 (Microsoft Corp).

RESULTS
The cost-effectiveness models evaluated 2 end points: QALYs and IFDs. For the 3-year cost-effectiveness models (for both outcomes), the costs for CT, NASHA/Dx, and SNS were $9053, $14,968, and $33,201, respectively (Table III). Total IFDs during the 3-year periods associated with CT, NASHA/Dx, and SNS were 128.8, 267.6, and 514.8 days, respectively. The incremental costs per QALY gained were $37,036 for NASHA/Dx versus CT and $244,509 for SNS versus NASHA/Dx. The incremental cost per QALY gained for SNS versus CT was $103,066. The ICERs per additional IFD gained were $42.60 for NASHA/Dx versus CT, $73.76 for SNS versus NASHA/Dx, and $62.55 for SNS versus CT.

The cost-effectiveness acceptability curve presents the likelihood that the interventions are cost-effective over a range of WTP thresholds (Figure 3, Supplemental Table II in the online version at http://dx.doi.org/10.1016/j.clinthera.2014.04.010). For NASHA/Dx, 59% of simulations would be cost-effective at a WTP threshold of $50,000 and 63% at a WTP of $100,000. At a WTP of $40,000 per QALY, 53% of the simulations for NASHA/Dx would be cost-effective, which is slightly higher when compared with CT (46%). In comparison, SNS had only a 3% probability of cost-effectiveness at a WTP of $50,000 and 16% at $100,000.

The BIA was computed for a range of ratios for the use of NASHA/Dx and SNS. When all of the patients receive NASHA/Dx, the net annual effect to the health care payer budget ranged from $571,455 to $2,857,275 (Table IV). When all of the patients receive SNS, the
The net annual effect to the health care payer budget ranged from $1,959,323 to $9,796,613. Intermediate scenarios, where the use of both NASHA/Dx and SNS range from 25% to 75%, are also presented. Because the acquisition cost of NASHA/Dx is significantly less than SNS, the scenarios that favor more use of NASHA/Dx present less net effect to the health care payer.

Results of the 1-way sensitivity analysis computed for the NASHA/Dx treatment cost appear in Table V. The base case cost for the NASHA/Dx treatment was $4900, and this value ranged from $2940 to $6860. Under this range of scenarios, the incremental cost per additional QALY gained for NASHA/Dx versus CT ranged from $16,986 to $57,086. The incremental cost per additional QALY gained for SNS versus NASHA/Dx ranged from $287,458 to $201,560. Under all scenarios, the incremental cost per QALY gained for NASHA/Dx was significantly less than the comparable value for SNS.

A 1-way sensitivity analysis was computed for the decrease in medical management costs for treatment responders (Table VI). The base case cost for the percentage of decrease in medical management costs for treatment responders was 50%; this value ranged from 0% to 50% in the sensitivity analysis. Under this range of scenarios, the incremental cost per additional QALY gained for NASHA/Dx versus CT ranged from $22,005 to $37,036. The incremental cost per additional QALY gained for SNS versus NASHA/Dx ranged from $244,036 to $244,509. Under all scenarios, the incremental cost per QALY gained for NASHA/Dx was significantly less than the comparable value for SNS.
A 1-way sensitivity analysis was computed for the NASHA/Dx subsequent treatment rate (Table VII). The base case for the retreatment rate is 63.4%, and this value ranged from 33% to 82% in the sensitivity analysis. Under this range of scenarios, the incremental cost per additional QALY gained for NASHA/Dx versus CT ranged from $27,175 to $43,069. The incremental cost per additional QALY gained for SNS versus NASHA/Dx ranged from $231,586 to $265,631. Under all scenarios, the incremental cost per QALY gained for NASHA/Dx was significantly less than the comparable value for SNS.

The tornado diagrams for the ICERs indicate the variables that have the most effect on the incremental costs per QALYs gained (Figures 4–6). In all cases, the variable that is most able to influence the ICERs is the utility value for treatment success. For the ICER for NASHA/Dx versus CT, the next 2 most influential variables are the cost for the NASHA/Dx treatment and the utility value for nonresponders (ie, treatment failure). The expected value for the ICER in this sensitivity analysis ranges from approximately $10,000 to $100,000 per incremental QALY gained (Figure 4). For the ICER for SNS versus NASHA/Dx, the next 2 most influential variables were the success rate for the SNS implantation procedure and the NASHA/Dx success rate. The expected value for the ICER in this sensitivity analysis ranges from approximately $150,000 to $600,000 per incremental QALY gained (Figure 5). For the ICER for SNS versus NASHA/Dx, the next 2 most influential variables were the utility value for nonresponders (ie treatment failure) and the SNS permanent implantation cost. The expected value for the ICER in this sensitivity analysis ranged from approximately

Figure 5. Tornado Diagram (ICER for NASHA/Dx vs CT). NASHA/Dx = non–animal stabilized hyaluronic acid and dextranomer copolymer; SNS = sacral nerve stimulation; CT = conservative therapy; ICER = incremental cost-effectiveness ratio; Trt = treatment; Phys = physician; Imp = implantation; EV = expected value; Stim = stimulation.
$60,000 to $260,000 per incremental QALY gained (Figure 6).

**DISCUSSION**

Fecal incontinence imposes a substantial health and economic burden on the US population; the estimates of the prevalence of this condition in some form have been as high as 24% in the general population but generally range from 2% to 8%.

For physicians and patients, there will undoubtedly be a variety of factors that affect decisions related to treatment options when CT has been proven unsatisfactory. From the patient’s point of view, the less invasive nature of the NASHA/Dx injectable and the favorable adverse event profile may make it an attractive intermediate option between CT and surgical options (eg, anal sphincteroplasty and sacral nerve stimulation).

From the payers’ point of view, FI exerts a substantial economic effect on the health care system. The costs associated with CT for FI (eg, dietary changes and biofeedback) are relatively low when compared with the costs associated with the treatment options when CT is not sufficiently effective. In the United States, the currently available treatment options after CT failure are NASHA/Dx, SNS, and anal sphincteroplasty. Although the costs associated with NASHA/Dx are not insignificant, they are
much less than for surgical treatment. When compared with SNS, the acquisition cost for the first treatment of NASHA/Dx represents only 18% of the cost for full SNS implantation. If subsequent treatment for all patients is assumed, the costs for NASHA/Dx still only represent approximately 36% of the SNS cost.

Considering the high prevalence and economic burden, as well as the associated negative effect on

### Table III. Results of the cost-effectiveness base case analysis. *

<table>
<thead>
<tr>
<th>Group and Outcome</th>
<th>Expected Cost, $</th>
<th>Incremental Cost, $</th>
<th>Effectiveness†</th>
<th>Incremental Effectiveness</th>
<th>ICER‡ (ΔCost/ΔEffect)</th>
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<td>Conservative therapy</td>
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<tr>
<td>Utility</td>
<td>9053</td>
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<td>1.769</td>
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<td></td>
</tr>
<tr>
<td>IFD</td>
<td>9053</td>
<td></td>
<td>128.78</td>
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<td></td>
</tr>
<tr>
<td>NASHA/Dx§</td>
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<tr>
<td>Utility</td>
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<td>Sacral nerve stimulation</td>
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<tr>
<td>Utility</td>
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<td>24,148</td>
<td>514.81</td>
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</table>

ICER = incremental cost-effectiveness ratio; IFD = incontinence-free day; NASHA/Dx = non-animal stabilized hyaluronic acid and dextranomer copolymer.

*All costs are in 2013 US dollars

†Effectiveness is measured in quality-adjusted life-years for the utility model and IFDs for the IFD model.

‡The ICER effect is measured in quality-adjusted life years for the utility model and IFDs for the IFD model.

§Base case has a 63.4% subsequent treatment rate for NASHA/Dx.

‖The ICER is computed based on common baseline (ie, conservative therapy).

### Table IV. Budget impact analysis (per 1 million covered lives annually)

<table>
<thead>
<tr>
<th>Proportion Given</th>
<th>Effect for 100% NASHA/Dx</th>
<th>Effect for 75% NASHA/Dx and 25% SNS</th>
<th>Effect for 50% NASHA/Dx and 50% SNS</th>
<th>Effect for 25% NASHA/Dx and 75% SNS</th>
<th>Effect for 100% SNS, $</th>
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<tbody>
<tr>
<td>NASHA/Dx, %</td>
<td>NASHA/Dx Cost, $</td>
<td>SNS Cost, $</td>
<td>NASHA/Dx Cost, $</td>
<td>SNS Cost, $</td>
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<td>29,027</td>
<td>2,857,275</td>
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<td>6,326,944</td>
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</tbody>
</table>

NASHA/Dx = non-animal stabilized hyaluronic acid and dextranomer copolymer; SNS = sacral nerve stimulation.
quality of life, appropriate intervention for management of FI is important. NASHA/Dx and SNS are relatively new interventions in the United States, and both have produced significant clinical benefits. NASHA/Dx has some significant advantages, such as being less invasive and less costly, when compared with SNS. NASHA/Dx also has a good safety profile. One option for physicians and patients to consider would be to use NASHA/Dx before surgical options; if this procedure does not yield adequate results, then surgery would remain as a possible next step.

Our results are similar to those from other analyses, especially the studies from France and the United Kingdom, in that patients experienced improvements in FI episodes and quality of life but at an increased cost. However, the ICERs appear to be fairly reasonable, making NASHA/Dx a cost-effective choice. According to Laupacis et al., this analysis provides “moderate evidence for adoption and appropriate utilization” of this new technology. They also indicated that its cost-effectiveness would be comparable to that of hospital hemodialysis compared with ambulatory peritoneal dialysis. In contrast, SNS had only a 3% probability of cost-effectiveness at a WTP of $50,000 and 16% at $100,000.

The BIA presents the additional costs to the health care system for patients who are good candidates for both NASHA/Dx and SNS. The BIA models the input variables over relatively wide ranges because the real-world use of NASHA/Dx is not yet well understood. Initially, NASHA/Dx accrues additional costs for the health care system; however, this intervention may be able to provide satisfactory results for at least 50% of

<table>
<thead>
<tr>
<th>Medical Management Decrease, %</th>
<th>CT Arm Cost, $</th>
<th>NASHA/Dx Arm Cost, $</th>
<th>SNS Arm Cost, $</th>
<th>ICER (NASHA/Dx vs CT), $</th>
<th>ICER (SNS vs NASHA/Dx), $</th>
</tr>
</thead>
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<tr>
<td>0</td>
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<td>25,012</td>
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<td>13,528</td>
<td>31,740</td>
<td>28,018</td>
<td>244,225</td>
</tr>
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<td>14,008</td>
<td>32,227</td>
<td>31,024</td>
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<td>9053</td>
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<td>32,714</td>
<td>34,030</td>
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<td>9053</td>
<td>14,968</td>
<td>33,201</td>
<td>37,036</td>
<td>244,509</td>
</tr>
</tbody>
</table>

CT = conservative therapy; ICER = incremental cost-effectiveness ratio; NASHA/Dx = non-animal stabilized hyaluronic acid and dextranomer copolymer; SNS = sacral nerve stimulation.
patients in whom conservative medical management fails. NASHA/Dx may provide an opportunity for the health care payer to positively affect the health status of their patients and also potentially lessen net expenditures. Because some patients may be unwilling to undergo the risks associated with surgical treatment, this technology may represent an opportunity for health benefits for these patients.

Sensitivity analyses indicate that the cost-effectiveness results (for the incremental costs per QALY gained) are robust with respect to moderate deviations in input values that underlie the value of the NASHA/Dx to the health care payer. The ICERs for NASHA/Dx, for the range of sensitivity analyses investigated, all fall within the range acceptable for the adoption of a new technology. The favorable cost-effectiveness of NASHA/Dx for both outcomes reflects the increased benefits to the patient, which can be acquired for a lower cost. Some patients may not be able to achieve adequate outcomes using NASHA/Dx; consequently, they may elect to proceed to surgical options, such as SNS.

Because both of these technologies have been approved by the FDA as recently as 2011, the availability of long-term data is limited. What currently exist are largely follow-up data from the clinical trials. This analysis used results from clinical trials, which may limit the generalizability to real-world practice. For NASHA/Dx, the length of follow-up available in the literature was limited to 3 years, hence the period for this model. For SNS, most of the data available from the literature is ≤3 years. However, a few studies have reported data that report the efficacy during at least 5 years. The efficacy estimates for these studies range from 74% to 89%. An additional study reported the efficacy of SNS treatments for FI for a median follow-up duration of 114 months; in this study 48% of the patients maintained full continence. These studies represent some evidence of the durability of effect for SNS treatments. The durability of effect for NASHA/Dx treatments needs to be evaluated in future research.

One consideration that may be important is the need for battery replacement for the SNS procedure, which typically occurs 3 to 5 years after the procedure and adds to the overall costs and any potential complications associated with replacement. Although this example is stated for SNS, there may also be important long-term considerations related to NASHA/Dx that have not been included in this analysis. Only 2 of the referenced studies included a control group; therefore, the efficacy estimates for NASHA/Dx and SNS have been estimated directly from the literature and have not been standardized through a common comparator.

Another limitation lies in the limited number of clinical outcomes that are incorporated into this economic analysis. This analysis is built on the Responder end point and the number of IFDs. These end points likely capture a large portion of the improvement in FI; however, there are other end points that complement the understanding provided by these outcomes. For instance, the disease-specific quality-of-life instruments, including the Fecal Incontinence Quality of Life Scale, are sensitive to improvements in FI patients’ quality of life; however, methods for quantifying this improvement within the context of an economic analysis have not yet been established.

### Table VII. One-way sensitivity analysis for NASHA/Dx subsequent treatment rate.

<table>
<thead>
<tr>
<th>Medical Management Decrease, %</th>
<th>CT Arm Cost, $</th>
<th>NASHA/Dx Arm Cost, $</th>
<th>SNS Arm Cost, $</th>
<th>ICER (NASHA/Dx vs CT), $</th>
<th>ICER (SNS vs NASHA/Dx), $</th>
</tr>
</thead>
<tbody>
<tr>
<td>33.0</td>
<td>9053</td>
<td>13,393</td>
<td>33,201</td>
<td>27,175</td>
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<td>42.8</td>
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<td>13,901</td>
<td>33,201</td>
<td>30,354</td>
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<td>52.6</td>
<td>9053</td>
<td>14,409</td>
<td>33,201</td>
<td>33,533</td>
<td>252,013</td>
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<tr>
<td>62.4</td>
<td>9053</td>
<td>14,917</td>
<td>33,201</td>
<td>36,711</td>
<td>245,204</td>
</tr>
<tr>
<td>72.2</td>
<td>9053</td>
<td>15,424</td>
<td>33,201</td>
<td>39,890</td>
<td>238,395</td>
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<td>9053</td>
<td>15,932</td>
<td>33,201</td>
<td>43,069</td>
<td>231,586</td>
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</table>

CT = conservative therapy; ICER = incremental cost-effectiveness ratio; NASHA/Dx = non-animal stabilized hyaluronic acid and dextranomer copolymer; SNS = sacral nerve stimulation.
CONCLUSION
NASHA/Dx and SNS have both produced significant improvements in FI symptoms for affected patients. NASHA/Dx represents a more efficient use of resources for the treatment of FI when compared with SNS. The present analysis provides the patient, physician, and payer with a potential pathway for the management of FI for patients whose conditions are not well controlled with CT. When considering the 2 options when CT fails, NASHA/Dx should be considered as the first option because it provides a less invasive and lower cost intervention, which also has the benefit of reducing by > 50% the population who may proceed to SNS.

ACKNOWLEDGMENTS
Financial support for this study was provided by Salix Pharmaceuticals Inc, Raleigh, North Carolina.

Dr. Bernstein contributed to the study design and the writing of the manuscript. Mr. Magar contributed to the study design, literature search, data interpretation, analysis and the writing of the manuscript. Ms. Becker contributed to the writing of the manuscript. Mr. Purdy contributed to the literature search, figure creation, study design, data collection, analyses, data interpretation and writing of the manuscript.

CONFLICTS OF INTEREST
This study provided a paid contract to AHRM Inc for the development of the economic models and manuscript. Employees of AHRM Inc include Raf Magar and Chris Purdy. Alison Becker is a consultant to AHRM Inc. AHRM Inc. received consultancy fees for other studies prior to this study. Salix Pharmaceuticals Inc provided consulting compensation for Dr. Mitchell A. Bernstein during the development of the economic models. No compensation was provided for manuscript development to Dr. Mitchell A. Bernstein. Salix Pharmaceuticals Inc at no time provided any communication about approval of results before submission. Salix Pharmaceuticals did not contribute to the study design, data collection, analysis or the interpretation of the data. Salix Pharmaceuticals contributed to the decision to submit the manuscript for publication.

SUPPLEMENTARY MATERIALS
Supplemental tables accompanying this article can be found in the online version at http://dx.doi.org/10.1016/j.clinthera.2014.04.010.

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41. Varma MG, Brown JS, Creasman JM, et al. Fecal incontinence in females older than aged 40 years: who is at


44. Laupacis A, Feeny D, Detsky AS, Tugwell PX. How attractive does a new technology have to be to warrant adoption and utilization? tentative guidelines for using clinical and economic evaluations. CMAJ. 1992;146:473–481.


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1. How many fecal incontinence (FI) patients would you see per month in your practice?
   i. Less than 5
   ii. Between 5 and 10
   iii. Between 10 and 15
   iv. Between 15 and 25
   v. More than 25

2. For your practice, what percentage of FI patients who are female? __ __ __ %

3. Do you use any of the following instruments to assess the severity of FI in normal clinical practice?
   Please circle any of the following which apply:
   i. Do not use any instrument
   ii. Fecal Incontinence Quality of Life Scale
   iii. Cleveland Clinic Florida/Wexner Incontinence Score
   iv. Other __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __

4. What is your first-line therapy for the management of minor fecal incontinence?
   Please circle any of the following which apply:
   i. Dietary Changes (ie, Supplementary Fibers)
   ii. Antidiarrheal Medications
   iii. Biofeedback Training
   iv. Other (please indicate) __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __

5. Which of the following do you use in the evaluation of fecal incontinence patients?
   Please circle any of the following which apply:
   i. Anoscopy/Proctoscopy/Sigmoidoscopy
   ii. Anorectal Manometry
   iii. Anal Endosonography
   iv. Defecography
   v. Pudendal Nerve Terminal Motor Latency
   vi. Other (please indicate) __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __

6. If first-line therapy for minor FI is not successful, please indicate your treatment preference. Please rank from 1-5 with 1 being the most often recommended:
   i. Injectable Bulking Agent __ __ __ __ __
   ii. Sacral Nerve Stimulation (SNS) __ __ __ __ __
   iii. Sphincteroplasty __ __ __ __ __
   iv. Radiofrequency treatment of the anal canal __ __ __ __ __
   v. Other __ __ __ __ __ If “Other” please indicate: __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __

7. If you were to use injectable bulking agents over SNS, please indicate why (check all that apply):
   i. Better outcome
   ii. Low risk of complication
   iii. Patient preference
   iv. Good reimbursement
   v. Better experience with injectable bulking agents
   vi. Durability for response
   vii. Other
Supplemental Survey 1. (continued).

8. If “Other” please explain: ____________________________

If you were to use SNS over injectable bulking agents, please indicate why (check all that apply):
   i. Better outcome   
   ii. Low risk of complication 
   iii. Patient preference 
   iv. Good reimbursement  
   v. Better experience with SNS   
   vi. Durability for response 
   vii. Other

If “Other” please explain: ____________________________

9. If you have used injectable bulking agents for the treatment of FI and treatment was not successful; what is
your next treatment option? Please explain. ____________________________

10. How does the condition of the anal sphincter (ie, intact or structurally deficient) affect the treatment
algorithm for the FI patient? Please explain. ____________________________
Supplemental Table I. Distributions for probabilistic sensitivity analysis.*

<table>
<thead>
<tr>
<th>Distribution</th>
<th>Distribution Type</th>
<th>Parameter 1†</th>
<th>Parameter 2‡</th>
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<tr>
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<td>β</td>
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<td>5.0024</td>
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<td>Utility (failure)</td>
<td>β</td>
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<td>Conservative treatment success</td>
<td>β</td>
<td>21.6831</td>
<td>48.2625</td>
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<td>NASHA/Dx treatment success</td>
<td>β</td>
<td>52.8175</td>
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<td>SNS stimulation treatment success</td>
<td>β</td>
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<td>SNS implantation treatment success</td>
<td>β</td>
<td>23.5030</td>
<td>5.2997</td>
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<td>No FI symptoms (conditional on no FI symptoms)</td>
<td>β</td>
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<td>Conservative treatment cost</td>
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<td>Biofeedback treatment cost (month)</td>
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<td>SNS stimulation cost</td>
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<tr>
<td>SNS implantation cost</td>
<td>LogNormal</td>
<td>9.9581</td>
<td>0.3203</td>
</tr>
</tbody>
</table>

FI = fecal incontinence; NASHA/Dx = non-animal stabilized hyaluronic acid and dextranomer copolymer; SNS = sacral nerve stimulation; TRT = treatment.

*Monte-Carlo simulation with 10,000 iterations.

†For LogNormal distributions, parameter 1 is μ; for β distributions, parameter 1 is α.

‡For LogNormal distributions, parameter 2 is σ; for β distributions, parameter 2 is β.

§The Prob(FI symptoms | FI Symptoms without treatment) = 1 − Prob(No FI Symptoms | FI Symptoms without TRT) = 0.85.

---

Supplemental Table II. Strategy selection by WTP thresholds.*

<table>
<thead>
<tr>
<th>WTP Threshold, US$</th>
<th>Iterations Favoring SNS, %</th>
<th>Iterations Favoring NASHA/Dx, %</th>
<th>Iterations Favoring CT, %</th>
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</thead>
<tbody>
<tr>
<td>0</td>
<td>0.0</td>
<td>2.7</td>
<td>97.3</td>
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<td>25,000</td>
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<td>100,000</td>
<td>16.1</td>
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WTP = willingness to pay.

*Probabilistic sensitivity analysis results used for this analysis and for the cost-effectiveness acceptability curve (Figure 3, Figure 2).