

**RADIOFREQUENCY MICRO-REMODELING FOR THE TREATMENT OF FEMALE STRESS
URINARY INCONTINENCE**
A Technology Assessment

INTRODUCTION

The California Technology Assessment Forum is requested by both Novasys Medical, Inc., the manufacturer of the Renessa® System and by Blue Shield of California to review the scientific evidence for the use of radiofrequency (RF) micro-remodeling for the treatment of female stress urinary incontinence.

BACKGROUND

Urinary leakage is common, affecting up to 25% of premenopausal and up to 40% of postmenopausal women.¹ Stress urinary incontinence (SUI) - defined as involuntary leakage of urine on exertion, effort, coughing or sneezing² – is the most common type of female urinary incontinence, with pure SUI accounting for half the cases, and mixed stress and urge urinary incontinence accounting for another third.³ Risk factors for SUI include obesity, pregnancy and vaginal childbirth. Women with persistent SUI at three months post-partum are very likely to have continued SUI five years post-partum.¹ Although there is a strong relationship between severity of SUI and quality of life, even women with severe SUI often do not seek medical help, in part because of low expectations of treatment benefit.^{3,4} There are, however, many treatment approaches available to women suffering from SUI, ranging from behavioral to minimally invasive to invasive (open surgical).

When women do seek medical help for SUI, first-line treatment is often behavioral – either pelvic floor exercises or weight loss. For some, performance of daily (30-50 daily) pelvic floor contractions is an effective approach to decreasing SUI frequency and severity; however, both ability to learn the exercises and improvement in SUI symptoms is quite variable.^{5,6} For obese women, weight loss (5-10% of baseline weight) can reduce incontinence frequency by about 50%.⁷ Pessaries - intravaginal devices designed to support the pelvic organs - are often fitted for women

with significant pelvic organ prolapse and appear to decrease SUI symptoms in 45% of patients; however, some women experience worsening or new SUI with pessary use.⁸ An anti-depressant, duloxetine hydrochloride, does appear to have moderate efficacy in the treatment of SUI, but is not currently approved for this indication in the United States.

For women who have either not had adequate relief from behavioral and other non-invasive approaches or who are unable to engage in these approaches, the mainstay of SUI treatment is surgical. The traditional gold standard treatment is the Burch colposuspension (Burch), an open retro-pubic procedure involving fixation of the bladder neck and proximal urethra retro-pubically in order to reduce urethral hyper-mobility. The Burch can also be performed laparoscopically. Increasingly, tension-free vaginal tape (TVT) is being used to treat SUI. TVT is a manufactured tape used as a pubo-urethral neo-ligament anchored suprapubically, which tightens around the urethra on increased abdominal pressure.⁴ Both the Burch and TVT have been extensively studied. The open Burch procedure results in high initial continence rates somewhere between 80-90%. Long-term continence rates are lower but still significant, ranging from 45-69% at 10-12 years.⁴ Comparisons of TVT to the Burch have found that TVT results in similar early rates of continence and has drop-off in efficacy equivalent to the Burch procedure at five years.⁹⁻¹⁴ TVT is considered a minimally invasive surgery and can be done with local anesthesia and under conscious sedation, resulting in decreased operative times, analgesia requirements and hospital stays compared to the Burch. However, there remains a risk of intra-operative complications, including bladder perforation, and post-operative complications including tissue erosion from the tape.⁴ Radiofrequency (RF) micro-remodeling with the Renessa® System is a minimally invasive office procedure which involves passing a 21 French probe transurethrally into the bladder and insufflating a balloon on the tip of the probe in the bladder outlet. RF energy is then delivered to four 23-gauge needle electrodes in submucosal tissue in the bladder neck and upper urethra. The probe and needles are repositioned nine times, delivering 60 seconds of RF energy to 36 tissue sites with the goal of denaturing collagen and resulting in firmer tissue and increased resistance to involuntary urinary leakage during times of increased intra-abdominal pressure.¹⁵ RF micro-remodeling can be done with local anesthesia and oral sedation. Potential advantages of this approach include that it is an office-based, non-surgical treatment requiring

minimal recovery and presumably associated with lower risk of serious complications (e.g. bladder perforation).¹⁵

TECHNOLOGY ASSESSMENT (TA)

TA Criterion 1: The technology must have final approval from the appropriate government regulatory bodies.

The Novasys Medical Transurethral RF System - Renessa® System (Novasys Medical, Inc., Newark, CA) received FDA 510(k) clearance on July 22, 2005. It is indicated for the transurethral treatment of female stress urinary incontinence due to hypermobility in women who have failed conservative treatment and who are not candidates for surgical therapy.

The SURx LP System (SURx, Livermore, CA) received FDA 510(k) clearance on January 8, 2002. It is indicated for shrinkage and stabilization of female pelvic tissue for treatment of Type II stress urinary incontinence due to hypermobility in women not eligible for major corrective surgery.

TA Criterion 1 is met.

TA Criterion 2: The scientific evidence must permit conclusions concerning the effectiveness of the technology regarding health outcomes.

The Medline, Embase, Biosis Previews, and Web of Science Citation Index databases, Cochrane clinical trials database, Cochrane reviews database and the Database of Abstracts of Reviews of Effects (DARE) were searched for relevant references. (See appendix for search terms) Of 68 potentially relevant citations, we found 11 papers from seven unique studies to include in this assessment. (See Figure below for study selection details) Of these seven studies, one was a randomized controlled trial of RF micro-remodeling (Renessa®) versus a sham procedure,¹⁶⁻¹⁸ and six were observational studies, including four of the SURx® surgical vaginal approach,¹⁹⁻²³ and two of the Renessa® non-surgical transurethral approach,^{18, 24, 25}

19 additional references were reviewed, but did not meet criteria for inclusion in this assessment. (References 30-48).

Search Results

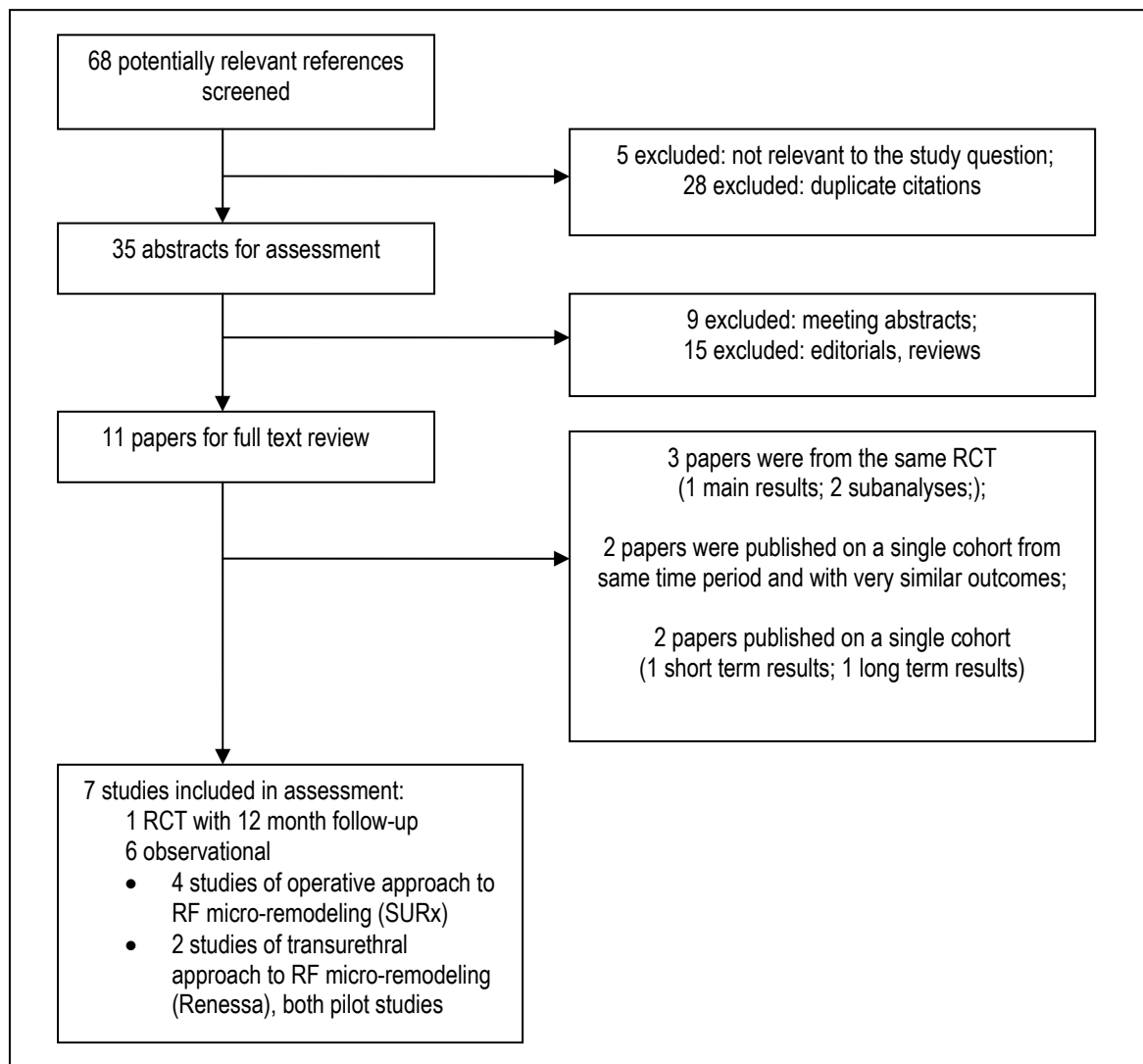


Figure 1. Study Selection for Radiofrequency Micro-remodeling for the Treatment of Female Stress Urinary Incontinence Assessment

Level of Evidence: 1, 4 for Renessa
 Level of Evidence: 1 for SURx

TA Criterion 2 is met for Renessa
TA Criterion 2 is not met for SURx.

TA Criterion 3: The technology must improve net health outcomes.

Of the six observational studies (Table 1), four were of a laparoscopic surgical approach using the SURx® system. Of these four, two were early (2002 and 2003) prospective cohorts,^{19, 20, 23} and two published more recently (2007 and 2008) were retrospective cohorts.^{21, 22} All of these studies showed mixed results of this more invasive approach to delivering RF energy endopelvic micro-remodeling, with some a considerable proportion of women demonstrating negative leak point pressure (LPP) after treatment (61-79%), and others with complete treatment failure and even increased incontinence episode frequency (4-19%). The remaining two observational studies address the less invasive transurethral approach to RF micro-remodeling. These studies were pilot studies demonstrating technique feasibility with short and longer-term outcomes,^{24, 25} and feasibility of using local anesthetic and oral sedation for pain control.¹⁸

Table 1. Observational Studies of Radiofrequency Micro-remodeling for Female Stress Urinary Incontinence.

Study	Design SUI population and Baseline characteristics	Intervention	Results	Comments
Studies of transurethral approach (Renessa)				
Sotomayor 2003 ²⁵ Sotomayor 2005 ²⁴	Prospective cohort; 41 women with history of SUI and physician witnessed SUI and urethral hypermobility; 36 women at follow-up Baseline: IEF: mean 3.7 (range .4-12); I-QOL: mean 52 (range 18-84);	Transurethral radiofrequency micro-remodeling probe: <u>4 groups</u> I: 24 sites, 7.5 minutes RF (urethra only) II: 36 sites, 10.5 min RF (urethra & bladder neck) III 48 sites, 12 min RF (urethra only) IV: 60 sites, 15 min RF (urethra & bladder neck)	<i>At 12 months:</i> IEF ≥50% reduction I: 63% II: 67% III: 70% IV: 89% 'Cure' I: 40% II: 22% III: 40% IV: 67% I-QOL ≥10 point improvement I: 63% II: 44% III: 70% IV: 7%	This study used as basis for intervention technique in the RCT Single site No comparison group No adjustment for potential confounding Small numbers in each group
Lenihan 2005 ¹⁸	Prospective case series 16 women SUI by history Urethral hypermobility	Transurethral radiofrequency micro-remodeling probe: local anesthesia and oral sedation (midazolam and/or tramadol)	No conversions to IV sedation (0% anesthesia failure rate) Immediate post-treatment visual analog pain scale (range 0-10): 1.8 ± 2.0	Small feasibility pilot to of local anesthetic and oral sedation use for future trials
Studies of operative approach SURx				
Ross 2002 ¹⁹ and Fulmer 2002 ²³	Prospective cohort; 94 women (84 at follow-up); Baseline: Leak point pressure >60 Impact on QOL None-mild: 39% Moderate: 54% Severe: 5%	Laparoscopic RF energy delivered to paraurethral endopelvic fascia	<i>At 12 months:</i> Compared to baseline Reduced episodes 73% Unchanged 24% Increased episodes 4% Impact on QOL None-mild group 88% Moderate group 11% Severe: 1% 79% (66/84) with negative LPP	Early study using operative approach No comparison group No adjustment for potential confounding

<p>Dmochowski 2003²⁰</p>	<p>Prospective cohort 120 women (109 at follow-up) Baseline Urethral hypermobility Valsalva LPP >90</p>	<p>Transvaginal surgical approach for RF energy delivery to endopelvic fascia</p>	<p><i>At 12 months:</i> Compared to baseline Reduced episodes 64% Unchanged 17% Increased episodes 19%</p> <p>73% 'cured' or improved (30 complete treatment failures)</p> <p>61% (66/109) with negative LPP</p> <p>Satisfaction 39% extremely satisfied 16% moderately satisfied 14% mildly satisfied 19% dissatisfied 13% very dissatisfied</p>	<p>Early study using operative approach</p> <p>No comparison group</p> <p>No adjustment for potential confounding</p>
<p>Buchsbaum 2007²¹</p>	<p>Retrospective cohort 18 women: 11 SUI only; 7 mixed urinary incontinence, stress predominant (16 at follow-up)</p>	<p>Transvaginal surgical approach for RF energy delivery to endopelvic fascia</p>	<p><i>At 3 months:</i> 6 women without SUI symptoms post-treatment</p> <p>10 women with continued SUI symptoms, but decreased incontinence episodes</p> <p>7 women sought additional treatment within one year</p>	<p>Retrospective study of operative approach</p>
<p>Ismail 2008²²</p>	<p>Retrospective cohort 24 women</p>	<p>Transvaginal surgical approach for RF energy delivery to endopelvic fascia</p>	<p><i>At 12 months</i> "Success" rate 46% (95% CI 26%-67%)</p>	<p>Retrospective study of operative approach</p>

The single randomized controlled trial of RF micro-remodeling¹⁶ was done comparing the transurethral approach (Renessa®) to a sham procedure in which all but the actual delivery of the RF energy was the same. (Table 2) Patients were blinded to treatment group and the procedure was done under conscious sedation, so presumably they would not be aware of the delivery of the RF energy. However, it does not appear that investigators were blinded to treatment group, potentially introducing bias in particular to the investigator dependent measure of LPP. All of the women in this study had a LPP ≥ 60 at baseline as well as visualized bladder outlet hypermobility on physical exam. Women who had findings consistent with a primary urge incontinence, urinary retention, or significant pelvic organ prolapse were excluded. Women with previous surgical or bulking agent treatment for SUI, who were pregnant or were found to have an active urinary tract infection were also excluded. Thus, the population in this study consisted of non-pregnant women with likely primary SUI and no significant pelvic organ prolapsed which would otherwise require surgery, and no previous invasive SUI treatment.

Table 2. Description of Single RCT Conducted to Evaluate Efficacy and Harm of Radiofrequency Energy Micro-remodeling for the Treatment of Female Stress Urinary Incontinence (Appell 2006)¹⁶

<u>Patient Population</u>	<p>173 women with stress urinary incontinence (SUI) 110 treatment arm 63 sham treatment arm</p> <p><u>Characteristics – no statistically significant difference between groups</u> Mean age 50 (range 22-76) Mean SUI duration 8 years (range 1-49) Mean BMI 29 (range 18-44) 43% pre-menopausal</p>
<u>Study Design</u>	<p>Randomized Control Trial Patients blinded to treatment group No mention of investigator blinding</p>
<u>Definition of SUI</u>	<p>1) Bladder outlet hypermobility on exam, and 2) baseline leak point pressure ≥ 60cm</p>
<u>Exclusion criteria:</u>	<p>1) evidence of detrusor overactivity on cystometrogram 2) post-void residual >50cc 3) significant pelvic organ prolapse on exam 4) history of overactive bladder 5) previous surgical or bulking agent therapy for SUI 6) pregnancy 7) active urinary tract infection</p>
<u>Treatment</u>	<p><u>Intervention</u> Patients under conscious sedation;</p> <p>21 French transurethral radiofrequency micro-remodeling probe passed trans-urethrally into bladder, balloon on tip insufflated in bladder outlet & palpably anchored;</p> <p>Radiofrequency delivered to four 23-gauge needle electrodes in submucosal tissue targets for 60 sec at a time, via rotation of needles, total of 9 different positions per needle (36 sites)</p> <p><u>Sham</u> Patients under conscious sedation;</p> <p>21 French transurethral radiofrequency micro-remodeling probe passed trans-urethrally into bladder, balloon on tip insufflated in bladder outlet & palpably anchored;</p> <p>No needles on end of sham probes, no radiofrequency delivered, but sound of generator same as in intervention..</p>

There were two primary outcome measures in this randomized controlled trial (RCT) – one subjective, one objective. The subjective outcome was based on a validated incontinence quality of life (I-QOL) scale which has been used extensively in urinary incontinence studies.²⁶⁻²⁸ In this RCT, the investigators used a 10-point increase on the I-QOL as their primary subjective outcome; a 10-point improvement in the I-QOL has been previously associated with improvement in other measures of incontinence, including 25% decrease in pad weight, 25% decrease in incontinence episode frequency, and a woman's global perception that her incontinence was 'much better'.²⁷ The investigators found no difference at 12 months post-treatment in the percentage of women in the treatment and sham groups who had at least a 10-point improvement on the I-QOL (treatment 48% vs. sham 44%; $p=.7$). (Table 3) In a subanalysis which separated women with moderate/severe SUI (0-60 points on baseline I-QOL) from those with mild SUI (61-90 points on baseline I-QOL), they did find that for those women with moderate/severe SUI a significantly higher proportion of women in the treatment group than in the sham group had at least a 10-point improvement on the I-QOL (treatment 74% vs. sham 50%; $p=.03$). Improvement was minimal and without difference by group for those women with mild SUI at baseline. This stratified analysis may introduce unmeasured bias into these results since the women were not randomized by baseline disease severity; however, these results do make sense given that women with mild SUI as defined by the I-QOL have less opportunity for improvement on the I-QOL.

The objective outcome measure was LPP in which the clinician/investigator measures the minimal abdominal pressure required to drive urine across the urethral sphincter. An increase in LPP is considered an improvement (decrease) in SUI.²⁹ This RCT found an increase in LPP of 13.2 points for the treatment arm and a decrease of 2.0 points for the sham arm ($p=.02$). (Table 3) While clearly a statistically significant difference between the groups, it is unclear how an increase of this magnitude translates to clinical improvement.

In terms of harm (see Table 3), adverse events included dysuria and urinary tract infection, presumably related to the passage of the probe transurethrally. While not a statistically significant difference, there was more dysuria in the treatment than in the sham group. The authors state that

“all cases of dysuria, hematuria, and hesitancy were mild and transient”, however they do not provide quantification of severity or time. Also of note, were the number of cases of overactive bladder – these were equivalent in the two treatment groups and may represent an underlying proportion of the study sample with mixed stress-urge incontinence. Overall, the adverse events were relatively minor, and according to the authors, transient.

Table 3. Results of Single RCT Conducted to Evaluate Efficacy and Harm of Radiofrequency Energy Micro-remodeling for the Treatment of Female Stress Urinary Incontinence (Appell 2006)¹⁶

	Treatment	Sham	p-value
Quality of Life Scale ≥ 10 point improvement at 12 months N=142 (80% treatment; 84% sham) Overall	48%	44%	.7
Secondary analysis Moderate/severe SUI Mild SUI	74% 22%	50% 35%	.03 .2
Leak Point Pressure at 12 months N=136 (79% treatment; 78% sham)	+13.2 ± 39.2cm	-2.0 ± 33.8 cm	.02
Adverse Events recorded over 12 months			
Dysuria	10 (9%)	1 (2%)	.06
Hematuria	1 (1%)	0 (0%)	1.0
Urinary retention	1 (1%)	0 (0%)	1.0
Urinary tract infection	5 (5%)	3 (5%)	1.0
Hesitancy	0 (0%)	1 (2%)	.4
Asymptomatic detrusor overactivity	2 (2%)	4 (6%)	.2
Dry overactive bladder	8 (7%)	2 (3%)	.3
Wet overactive bladder	11 (10%)	6 (10%)	1.0

No randomized control trial has been done for RF micro-remodeling for the SURx® system.

TA Criterion 3 is met for Renessa®

TA Criterion 3 is not met for SURx®

TA Criterion 4: The technology must be as beneficial as any established alternatives.

The improvements described above at one year after treatment with RF micro-remodeling (Renessa®) are significant, but less so than the gold-standards of the Burch and TVT described in the background section above. Studies of the Burch and TVT describe higher rates of 'cure' based both on objective urodynamic studies and subjective measures (60-90% at 1-2 years and 40-50% at five years with only 10% bothersome symptoms at five years).^{9-11, 13, 14} These outcomes with established alternatives are considerably higher than with RF micro-remodeling in the one RCT available. However, both the Burch and TVT carry more risk than RF micro-remodeling with the transurethral approach seems to. This risk is associated with the surgical nature of the Burch (in particular) and TVT as well as with the potential for tape erosion with TVT. Thus, while the benefits are clearly not as great as with the available gold standards, the benefit to risk ratio is favorable for RF micro-remodeling (Renessa®) and does provide options for women with SUI, particularly for those who are not eligible for surgical intervention. Because TA Criterion 3 is not met for the SURx® system of RF micro-remodeling, it does not meet TA Criterion 4.

TA Criterion 4 is met for Renessa®
TA Criterion 4 is not met for SURx®

TA Criterion 5: The improvement must be attainable outside of the investigational setting.

As with other procedures, RF micro-remodeling (Renessa®), requires training and clinical experience for success. The insertion of the probe itself is similar to the insertion of a urinary catheter, and thus likely familiar to all or most clinicians. Training and initial proctorship should be required, however, for the positioning and repositioning of the needles, and the delivery of the RF energy itself. In addition, although there is a small pilot study (n=16) indicating that this procedure can be done safely and comfortably with local anesthesia and oral sedation,¹⁸ the RCT was done with local anesthesia and conscious sedation and thus, until larger studies show safety and efficacy with oral analgesia, RF micro-remodeling (Renessa®) will require appropriate training and certification for use of this medication and/or the presence of an anesthesiologist. There is, however, no reason to suspect that the results shown in the RCT cannot be attainable outside of

the investigational setting. . Because neither TA Criterion 3 nor 4 is not met for the SURx® system of RF micro-remodeling it does not meet TA Criterion 5.

TA Criterion 5 is met Renessa®
TA Criterion 5 is not met for SURx®

CONCLUSION

In summary, while RF micro-remodeling (Renessa®) for SUI does not show as high success rates as the gold standard approaches (Burch and TVT), it does demonstrate a good safety profile and moderate improvement in objective urinary leakage and quality of life, particularly for women with moderate to severe SUI. Some questions remain, including whether there is drop-off in improvement over time and how much, and whether women who undergo RF micro-remodeling (Renessa®) can subsequently undergo other SUI procedures such as the Burch and TVT without undo complication, and confirmation in larger studies that RF micro-remodeling (Renessa®) can be comfortably undergone as a simple office procedure with local anesthesia and oral analgesia/sedation.

RF micro-remodeling using the SURx® system has not been directly compared to either a sham procedure or a gold-standard surgical approach to SUI, nor has it been studied in an RCT. Unlike the transurethral approach, the surgical approach to micro-remodeling is not likely to have the advantage of very low risk/morbidity that allows a favorable risk/benefit profile.

DRAFT RECOMMENDATION

It is recommended that radiofrequency micro-remodeling with the Renessa® system *meets* CTAF criteria 1-5 for safety, effectiveness and improvement in health outcomes for the treatment of moderate to severe female stress urinary incontinence in non-pregnant women who are either not able or not willing to undergo surgery for their SUI treatment.

It is further recommended that radiofrequency micro-remodeling with the SURx[®] system *does not* meet CTAF criteria 2-5 for safety, effectiveness and improvement in health outcomes for the treatment of female stress urinary incontinence.

October 15, 2008

RECOMMENDATIONS OF OTHERS

Blue Cross Blue Shield Association (BCBSA)

The BCBSA Technology Evaluation Center has not conducted an assessment of this technology.

Centers for Medicare and Medicaid Services (CMS)

CMS does not specifically address the use of this technology for the treatment of SUI.

American College of Obstetrics and Gynecology, District IX (ACOG)

An ACOG District IX representative will be attending the meeting. A search of the ACOG website and www.guideline.gov did not reveal a formal opinion on the use of this technology.

California Urological Association (CUA)

The CUA has been invited to provide an opinion regarding this technology and to have a representative participate at the meeting.

ABBREVIATIONS USED IN THIS REVIEW

RF	Radiofrequency
SUI	Stress urinary incontinence
TVT	Tension-free vaginal tape
DARE	Database of Abstracts of Reviews of Effects
LPP	Leak point pressure
RCT	Randomized controlled trial
I-QOL	Incontinence quality of life

APPENDIX 1: Search Terms

Medline: RADIOFREQUENCY OR "RADIO FREQUENCY" OR RADIO WAVES OR RADIO WAVE OR RADIOWAVE* OR MICRO REMODEL* OR (BIPOLAR AND (ELECTROTHERM* OR ENERGY)) OR (COLLAGEN AND (ENERGY OR DENATUR*)) AND STRESS INCONTINENCE

Embase: ('radiofrequency'/exp OR 'radiofrequency') OR 'radio frequency' OR ('radio waves'/exp OR 'radio waves') OR ('radio wave'/exp OR 'radio wave') OR radiowave* OR (micro AND remodel*) OR (bipolar AND (electrotherm* OR ('energy'/exp OR 'energy')))) OR (('collagen'/exp OR 'collagen') AND (('energy'/exp OR 'energy') OR denatur*)) AND (('stress incontinence'/exp OR 'stress incontinence') OR ('stress urinary incontinence'/exp OR 'stress urinary incontinence'))

Cochrane: (radiofrequency or "radio frequency" or radio waves or radio wave or radiowave* or micro remodel* or (bipolar and (electrotherm* or energy)) or (collagen and (energy or denatur*))) and (stress incontinence or "stress urinary incontinence") In 'SEARCH ALL TEXT' field

Web of Science and Biosis Previews: Topic=(RADIOFREQUENCY OR RADIOWAVE* OR RADIOWAVES OR "RADIO WAVES" OR "RADIO WAVE" OR "MICRO REMODEL*" OR (BIPOLAR (ELECTROTHERM* OR ENERGY)) OR (COLLAGEN AND (ENERGY OR DENATUR*))) AND Topic=(STRESS INCONTINENCE OR STRESS URINARY INCONTINENCE)

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