Urologic Update:

PSA Guidelines & Pelvic Pain / Interstitial Cystitis

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Prostate Cancer

- Prostate cancer is the most commonly diagnosed non-skin cancer in men in the United States, with a lifetime risk for diagnosis currently estimated at 15.9%.

- Most cases of prostate cancer have a good prognosis, even without treatment, but some are aggressive; the lifetime risk of dying of prostate cancer is 2.8%.

- Prostate cancer is rare before age 50 years and very few men die of prostate cancer before age 60 years. Seventy percent of deaths due to prostate cancer occur after age 75 years

Controversy

- **U.S. Preventive Services Task Force Recommendation Statement 2012**

- Whereas the USPSTF previously recommended against PSA-based screening for prostate cancer in men aged 75 years and older and concluded that the evidence was insufficient to make a recommendation in younger men, the USPSTF now recommends against PSA-based screening for prostate cancer in all age groups.

American Urologic Association

- Prostate-Specific Antigen
- Best Practice Statement:
- 2009 Update

Many patients with low grade and volume cancers may be candidates for active surveillance.

In other patients, however, tumor growth may be more rapid, resulting in cancer spreading beyond the confines of the prostate.

Strategies for managing prostate cancer have therefore been aimed at early detection, with selective, tailored treatment.

- Prostate-specific antigen (PSA), a glycoprotein is a tumor marker currently used for early detection of prostate cancer. It is currently the only validated tumor marker available and approved

- Measurement of serum PSA levels has significant clinical application in other areas of prostate disease management.

Current information on the use of PSA testing

- The evaluation of men at risk for prostate cancer
- the risks and benefits of early detection
- assistance in pretreatment staging or risk assessment
- posttreatment monitoring
- use as a guide in management of men who recur after primary or secondary therapy

PSA is concentrated in prostatic tissue, and serum PSA levels are normally very low.

Disruption of the normal prostatic architecture, such as by prostatic disease, inflammation, or trauma, allows greater amounts of PSA to enter the general circulation.

Elevated serum PSA level has become an important marker of many prostate diseases – including benign prostatic hyperplasia, prostatitis, and prostate cancer…

An analysis of autopsy studies has shown that approximately one in three men over the age of 50 years had histologic evidence of prostate cancer, with up to 80% of these tumors being limited in size and grade and, therefore, clinically insignificant.

A recent study of incidental prostate cancer diagnosed in organ donors found prostate cancer in 1 in 3 men age 60-69, and this increased to 46% in men over age 70.

Fortunately, the lifetime risk of prostate cancer death is only about 3%.

- There has been a gradual but steady decline in prostate cancer mortality in the U.S. of approximately 30%.
- This trend began fairly soon after the introduction of PSA testing, there is evidence from statistical modeling studies that PSA testing has played a role.
- Screening with PSA is responsible for a substantial shift towards detection of prostate cancer at earlier stages
    - Etzioni, R., Gulati, R., Falcon, S. et al: Impact of PSA screening on the incidence of advanced stage prostate cancer in the United States: a surveillance modeling approach. Med Decis Making, 28: 323, 2008

AUA response to **U.S. Preventive Services Task Force Recommendation Statement 2012**

- “It is inappropriate and irresponsible to issue a blanket statement against PSA testing, particularly for at-risk populations, such as African American men. Men who are in good health and have more than a 10-15 year life expectancy should have the choice to be tested and not discouraged from doing so.”

There is strong evidence that PSA testing saves lives.

“There is strong evidence that PSA testing saves lives. The randomized trials used by the USPSTF do, in fact, show a benefit to patients.

PLCO trial, although imperfect, in a group of young men with no comorbidities, there was a significant reduction of prostate cancer death rates after a median follow-up of seven years” (JCO 2011;29:355-361)

- Göteborg Trial also showed a substantial 44 percent relative risk reduction in prostate cancer mortality occurring in men 50-64 years of age after a median of 14 years.

Importantly, the risk reduction occurred in a setting where many of the patients were not aggressively treated for prostate cancer, indicating that the harms of PSA-based screening can, in fact, be minimized by good clinical practice

(Lancet Oncol 2010;11:725-732).

40 percent reduction in prostate cancer-specific mortality in the United States over the most recent 20 years of PSA-based screening. This has occurred without substantial change in how men with prostate cancer were treated (primarily with surgery and radiation therapy). Models have suggested that more than 50 percent of this reduction is due to early detection

(Cancer Cases Control 2008;19:175-181).

"Rather than instruct primary care physicians to discourage men from having a PSA test, the Task Force should instead focus on how best to educate primary care physicians regarding targeted screening and how to counsel patients about their prostate cancer risk. The PSA test has allowed us to move beyond a time when men presented with high-grade, metastatic disease for which there were little or no treatment options other than palliative care.

Disparaging the PSA test when newer tests and diagnostics are not yet widely available does a great disservice to American men."

ATLANTA, GA, May 21, 2012–The American Urological Association (AUA)

- “26.9% of the men with PSA levels between 3.1 and 4.0 ng/mL had prostate cancer. Thus, of these men, whose PSA was previously thought to be ‘normal’, 15% were found to have cancer”.

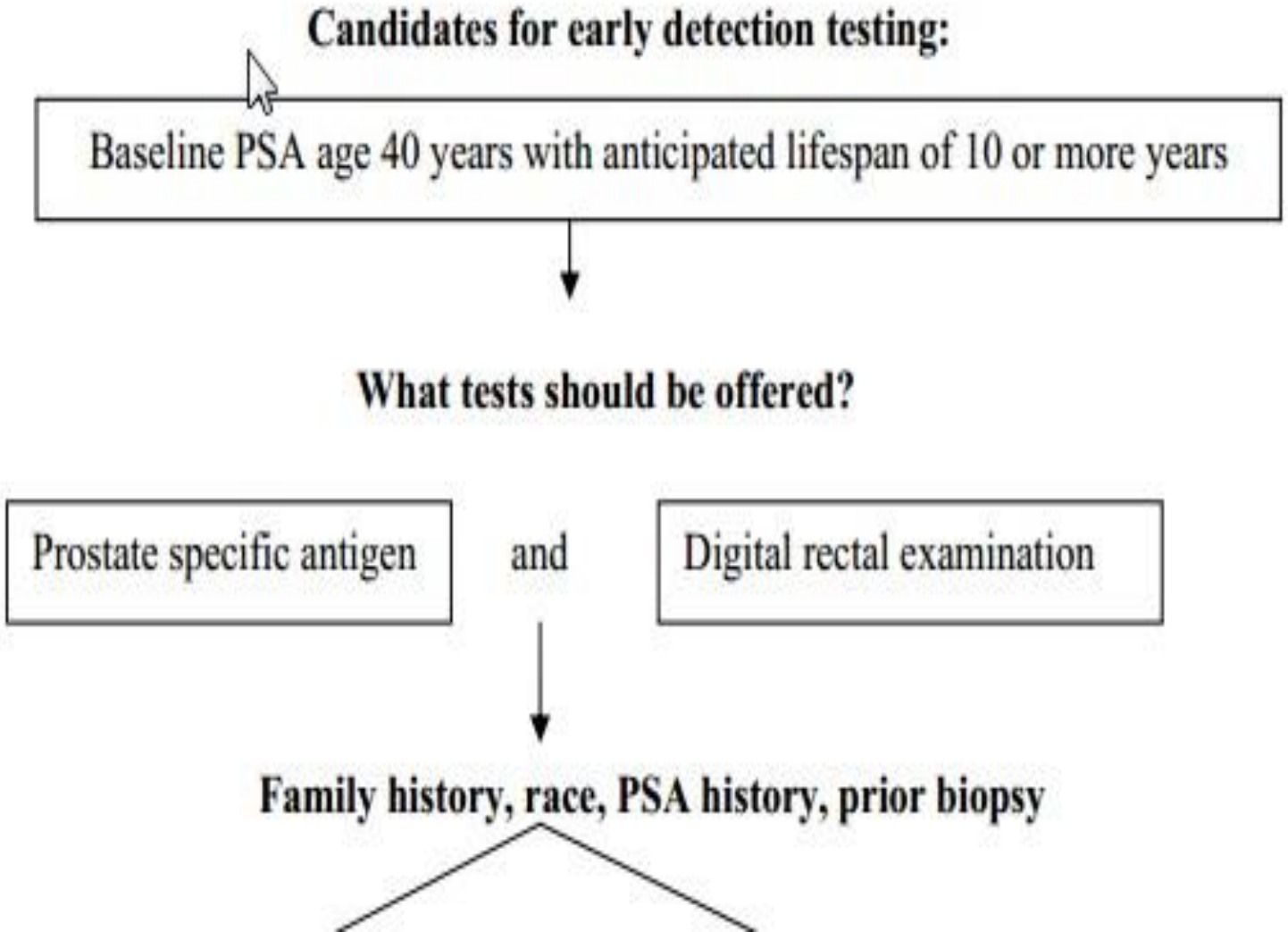
- “However, it remains unknown what proportion of these cancers includes clinically significant disease.”

- Prostate-Specific Antigen Best Practice Statement: 2009 Update, American Urological Association

Age Based PSA levels

Table 1. Age-Specific Reference Ranges for Serum PSA[111]			
	Reference Range		
Age Range	Asian-Americans	African-Americans	Whites
40-49 yr	0-2.0 ng/mL	0-2.0 ng/mL	0-2.5 ng/mL
50-59 yr	0-3.0 ng/mL	0-4.0 ng/mL	0-3.5 ng/mL
60-69 yr	0-4.0 ng/mL	0-4.5 ng/mL	0-4.5 ng/mL
70-79 yr	0-5.0 ng/mL	0-5.5 ng/mL	0-6.5 ng/mL

AUA: PSA Algorithim



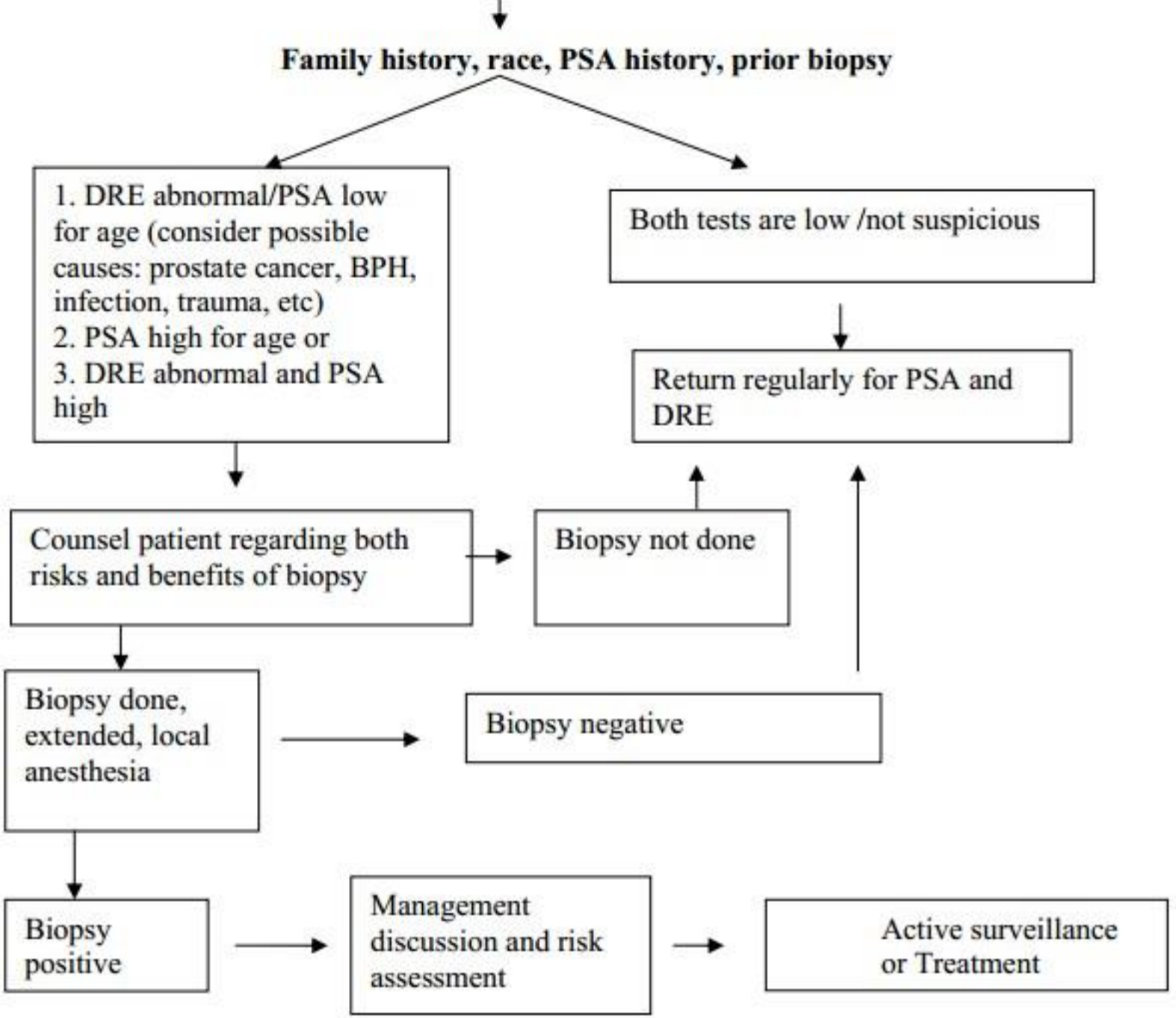


Figure 1: Early Detection

PELVIC PAIN

- Interstitial Cystitis ?
- Bladder Pain Syndrome ?
- Chronic Prostatitis ?
- Pelvic Pain Sydrome ?
- Pain associated with Endometriosis ?
- Levator dysfunction ?

Chronic Pelvic Pain – Interstitial Cystitis

- Interstitial cystitis (I.C.) is a condition that results in recurring discomfort or pain in the bladder and the surrounding pelvic region. It is also known as Painful Bladder Syndrome (PBS).

- Average age of onset for IC is 40 years, with 25% of patients under the age of 30.

Interstitial cystitis (I.C.)=Painful Bladder Syndrome

- Estimates vary suggesting 700k to 9 million people suffer from I.C.
- Inflammation of the tissues of the bladder wall
- Not believed to be caused by bacteria
- Does not respond to conventional antibiotic therapy.
- Not a psychosomatic disorder nor is it caused by stress.

- The average age of onset for IC is 40 years, with 25% under the age of 30.
- A late deterioration of symptoms is unusual.
- Up to 50% of patients experience spontaneous remissions probably unrelated to treatment, with a duration ranging from 1 to 80 months.
- Patients with IC are 10 to 12 times more likely than controls to report childhood bladder problems.
- Patients with IC are twice as likely as controls to report a history of urinary tract infection; however, over half of all IC patients report fewer than one such infection per year before the onset of IC.
- 50% of IC patients have pain while riding in car.

- 63% of IC patients are unable to work full time.
- IC patients have suicidal thoughts 3-4 times above the national average.
- The quality of life of IC patients is worse than patients experiencing chronic renal failure and undergoing dialysis.
- IC related medical care cost in the US was $116.6 million in 1987 and IC related lost economic production was $311.7 million.
- Household size, marital status, sexual partners and education did not differ from the general population.
- *Ho N, Koziol J, Parsons CL. Epidemiology of Interstitial Cystitis, in G. Sant (Ed.), Interstitial Cystitis.Philadelphia: Lippincott-Raven Publishers, 1997; 9-15*

- The symptoms vary from case to case and even in the same individual. People may experience mild discomfort, pressure, tenderness, or intense pain in the bladder and pelvic area. Symptoms may include an urgent need to urinate (urgency), a frequent need to urinate (frequency), or a combination of these symptoms.

- People with severe cases of IC/PBS may urinate as many as 60 times a day, including frequent nighttime urination (nocturia).

- “Pain levels can range from mild tenderness to intense, agonizing pain. Pain typically worsens as the bladder fills and is then relieved after urination. Pain may also radiate to the lower back, upper legs, vulva and penis. Women's symptoms may fluctuate with their menstrual cycle, often flaring during ovulation and/or just before their periods. Men and women may experience discomfort during or after sexual relations. During flares, patients may also experience the “IC Belly,” a sudden and random swelling of the lower abdomen.”

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Painful Bladder Syndrome

- recurring discomfort or pain in the bladder and the surrounding pelvic region
- symptoms vary from case to case and even in the same individual
- patients may experience mild discomfort, pressure, tenderness, or intense pain in the bladder or pelvic areas

What do patients say?

- “I go to bathroom frequently because it hurts!”
- “I have pain with vaginal penetration”
- “Nobody believes me!”
- “I want to take my bladder out”
- “My quality of life is horrible”
- *And sometimes: “I need Dr. Schock!”*

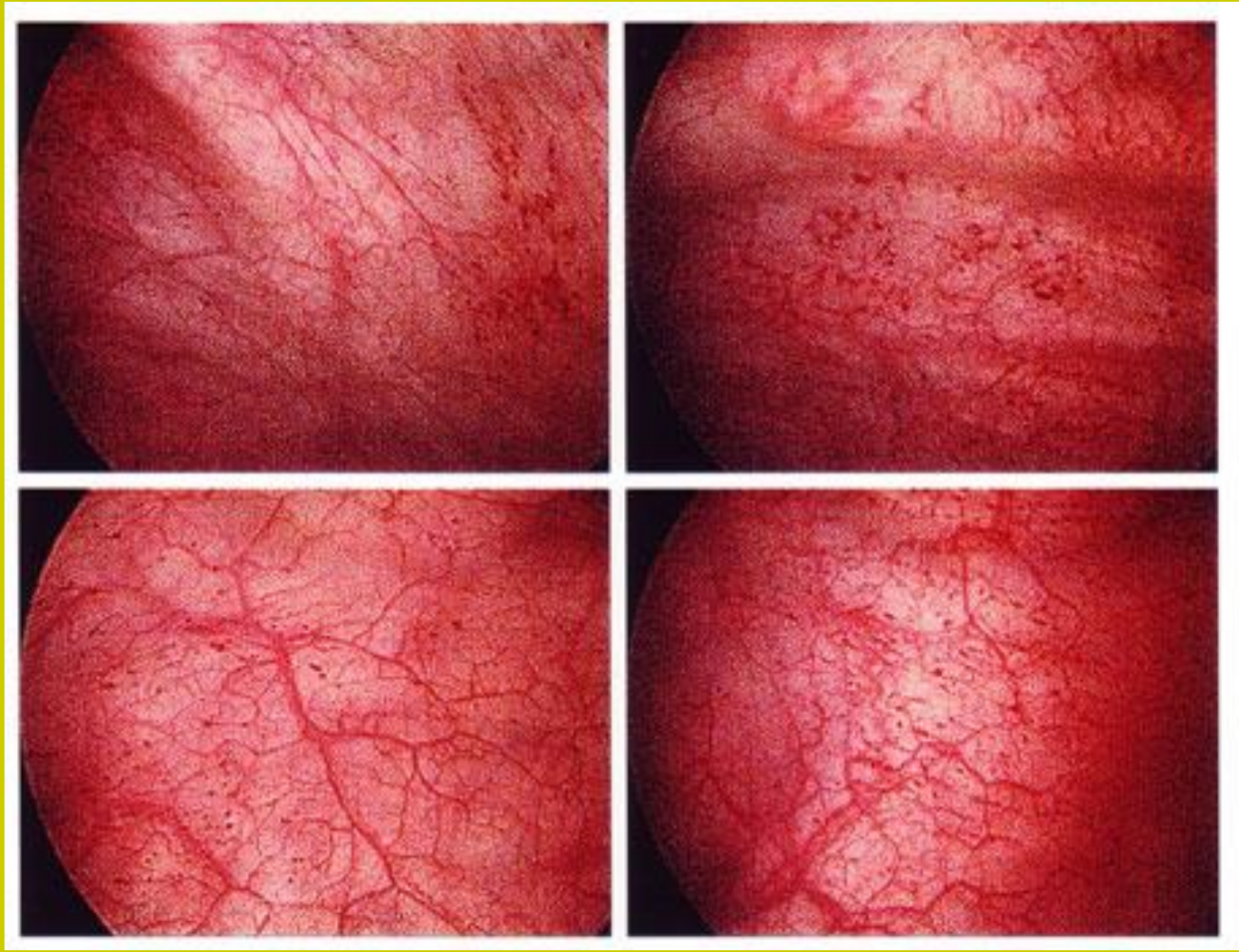
Painful Bladder Syndrome

- Pain with vaginal intercourse (dyspareunia)
- Sometimes worse during menstruation
- Symptoms may disappear without explanation or may coincide with an event such as a change in diet or treatment
- Even when symptoms disappear, they may return after days, weeks, months or even years.

Painful Bladder Syndrome

- Current therapy is aimed at relieving the symptoms
- Many people are helped for variable periods by one or a combination of different treatments.
- Symptoms may be coupled with urgency and/or frequency.
- Pain may change in intensity as the bladder fills with urine or as it empties.

Hunner's Ulcer in the Bladder (Glomerulations)



Treatment Options

- Highlights from 4th International Consultation on Incontinence, July 2008, Paris France

- Recommendations for IC/PBS were graded and applied evidence level assessments

1st Line Treatments

- Conservative Therapy
  - Physical therapy, behavioral modification
  - Patient education
  - Dietary manipulation
  - Non-prescription analgesics
  - Pelvic floor relaxation
  - Treatment of pain

2nd Line Treatments

- Oral therapies
- Intravesical therapies
- Physical therapies
- Treatment of pain

3rd Line Treatments

- Cystoscopy under anesthesia with bladder distension
- Fulgeration of Hunner's lesions
- Treatment of Pain

4th Line Treatments

- Neuromodulation
- Intramural botulinum toxin
- Pharmacological management
- Treatment of pain
- Urinary Diversion with or without cystectomy and substitution cystoplasty

“IC” diet

- Eliminate bladder irritants such as:
  - caffeine
  - alcohol
  - nicotine
  - spicy or acidic foods
  - Carbonated beverages
  - Teas with tannic acid (green tea)
  - Tomatoes
  - juices

- Self-help techniques can improve the quality of life
- Stress reduction
- Biofeedback
- Bladder retraining (timed voiding)
- Exercise
- Physical therapy

Treatment Options

- ELMIRON® *(pentosan polysulfate sodium):* Elmiron received FDA approval in 1996. It is the only oral medication approved specifically for use in IC. It is believed to work by repairing a thin or damaged bladder lining.

- Tricyclic antidepressants such as Elavil® (*amitriptyline*) have been shown to help with both the pain and frequency of IC. In IC, these medications are used for their anti-pain properties, not as a treatment for depression.

Multi-modal Approach

- Elmiron™ 100mg po tid
- Amytriptiline 25mg po qhs
- Hydroxizine 25mg po qhs
- Anti-Spasmotics
  - (oxybutnin,tolteradine,solfenicin,darafenacin,trospium chloride,etc)
- Physical therapy is often helpful for patients with pelvic floor dysfunction.

Off Label Treatment Options

- Gabapentin (Neurontin™)
- Lyrica ™
- Diazepam vaginal suppositories
- Uribel®, Prosed-DS ™
- Omeprazole
- Quercetin based supplements
- Pyridium ™
- Cystoprotek ™ (otc)

Bladder Distenstion / Instillations

- The bladder is *stretched* by filling it with water under general anesthesia. This is part of the diagnostic procedure for IC, and may be therapeutic as well
  - Performed with cystoscopy and / or biopsy (rule out other causes / or “hunners ulcers”
- DMSO *(dimethyl sulfoxide):*
  - instilled directly into the bladder. It is believed to work as an anti-inflammatory agent and therefore reduces pain. DMSO can be mixed with steroids, bicarb, heparin, and/or local anesthetics to form a bladder "cocktail.“

Treatment Options

- Transcutaneous Electrical Nerve Stimulation (TENS): This device, which is worn externally, relieves bladder pain in some people.

- Sacral Nerve Stimulation Implants (**Interstim™**)
  - surgically implanted devices are approved for use in treating urinary incontinence, urgency and frequency.

- SURGERY ?
  - *Last resort when all else fails*
  - cystectomy and urinary diversion

Rescue Intravesical Instillations

- Xylocaine
- Bupivicaine Hydrochloride
- Elmiron
- Heparin
- Sodium Bicarbonate

Interstim™ Neuromodulation "Pacemaker for the Bladder"

Neuromodulation is considered only after all other therapies / self-help strategies have been tried and failed.

FDA indication:

- Urgency
- Frequency
- Urge incontinence
- Urinary retention

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Interstim™ Neuromodulation "Pacemaker for the Bladder"

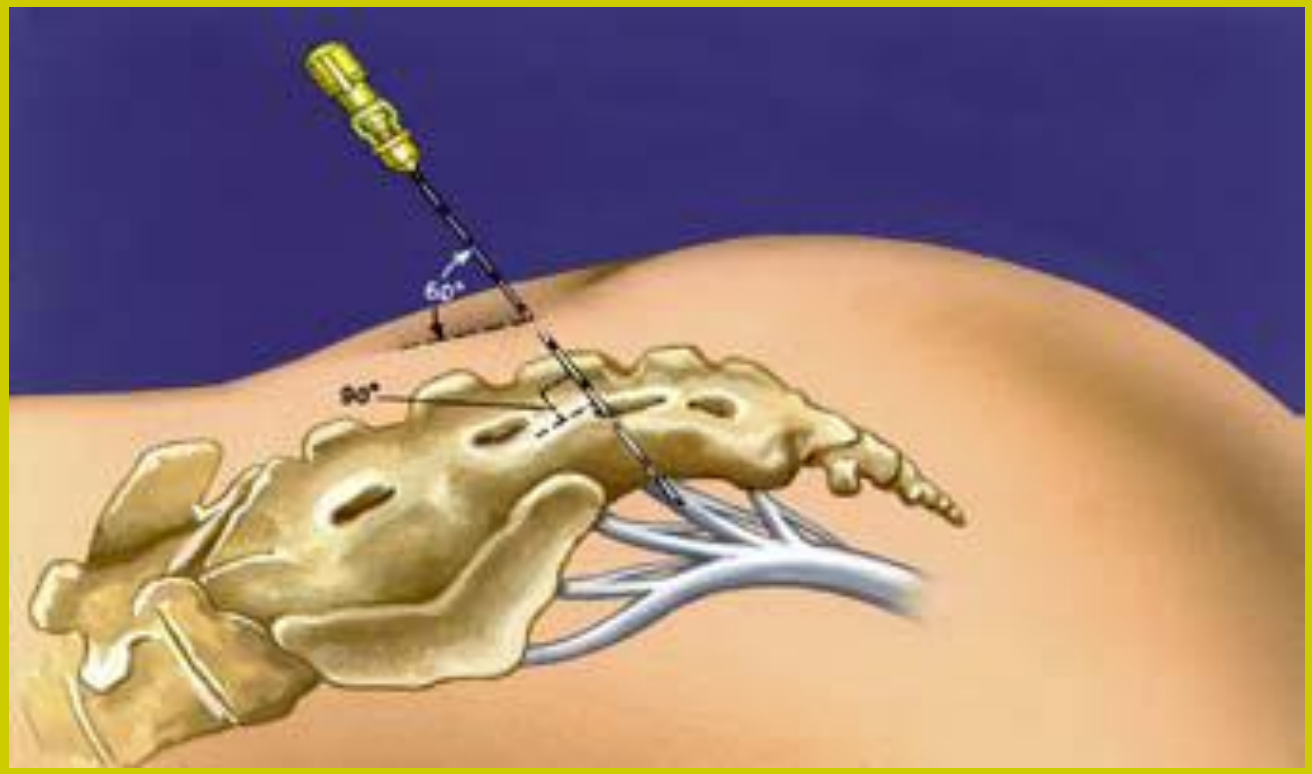
- Mild electrical stimulation of the sacral nerves that influence the behavior of the bladder, sphincter, and pelvic floor muscles.

- 30-50% implanted for pelvic pain / interstitial cystitis (*with urgency/frequency dx*)

Mobile Interstim Trailer

- Percutaneous Interstim test procedure
- Bilateral S3 foramen leads
- Minimally Invasive
- Eliminates “guess work” for stage 2 hopsital implant

Interstim™ Neuromodulation "Pacemaker for the Bladder"



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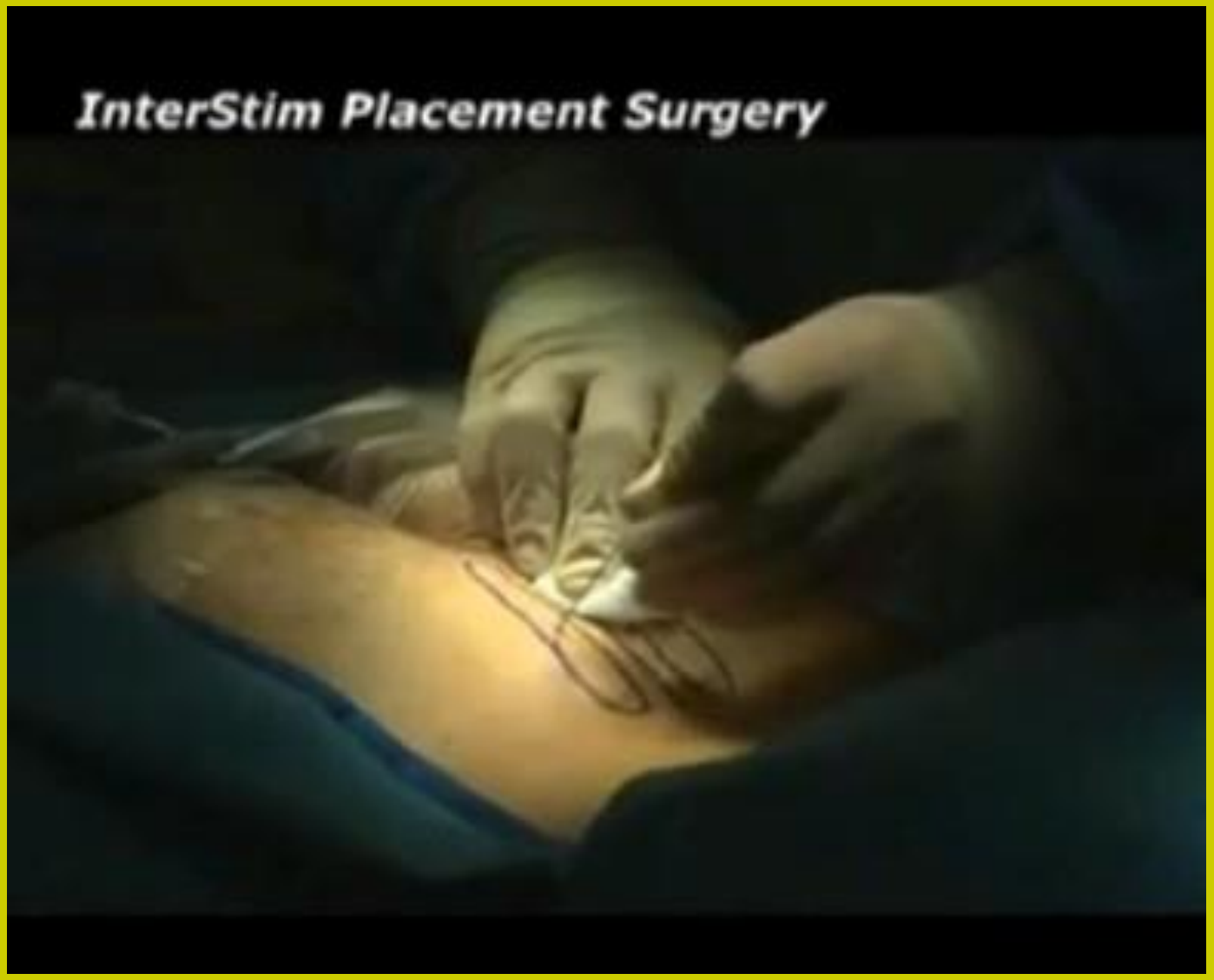

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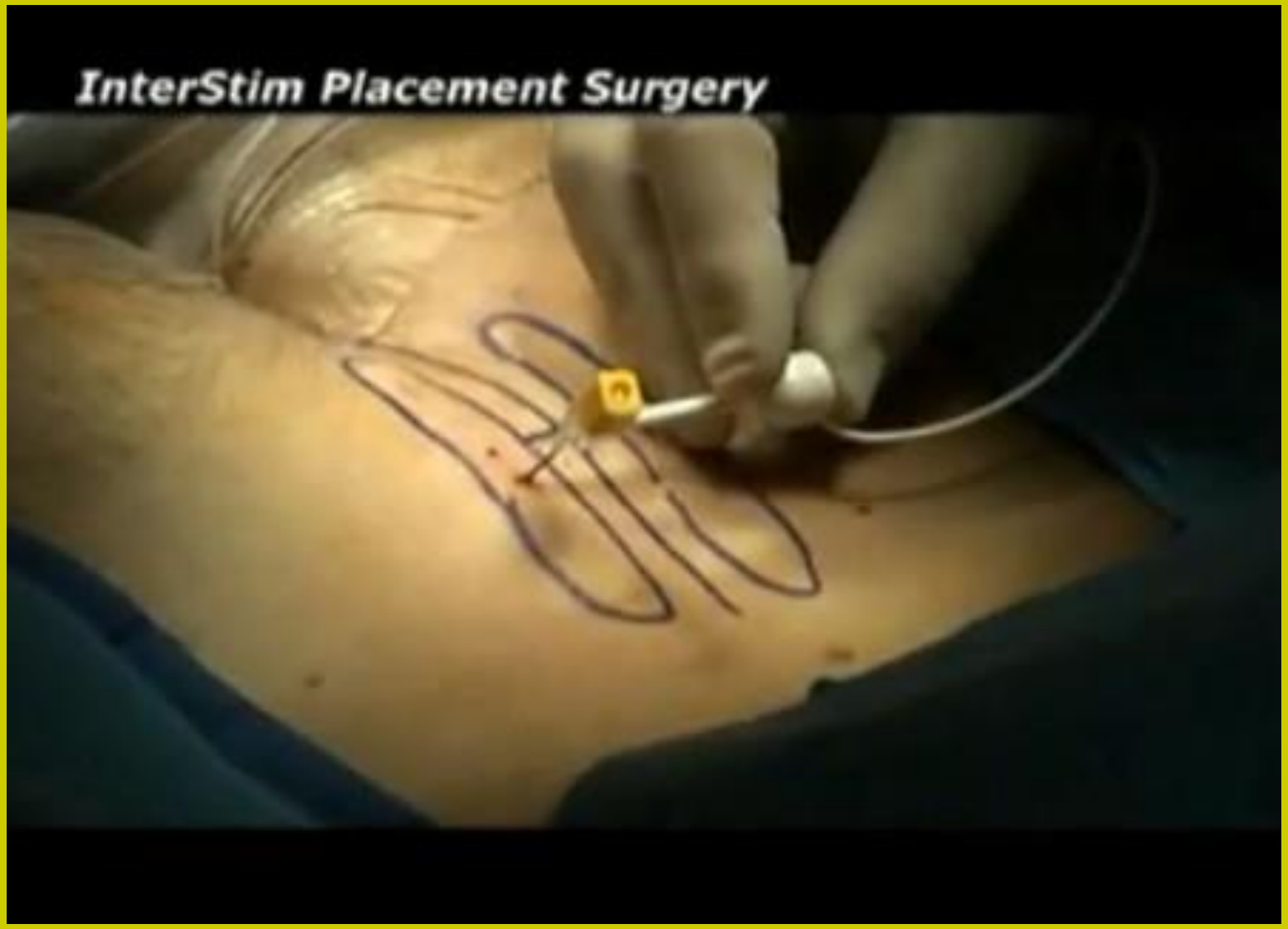

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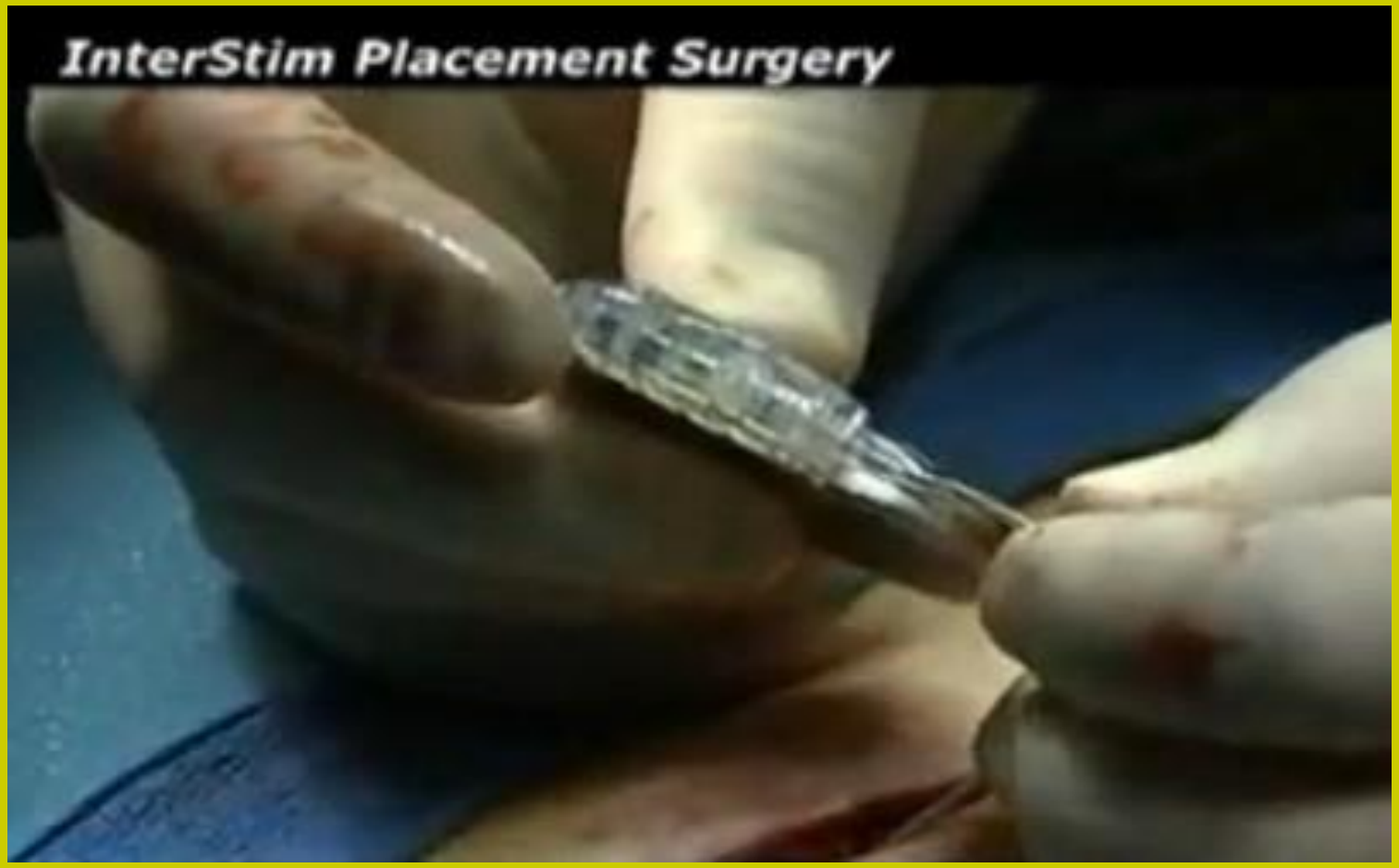

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Interstim™ Neuromodulation "Pacemaker for the Bladder"

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