Urogynecological mesh implants have been called both the “biggest medical scandal” since thalidomide and the “gold standard” for surgical treatment of stress urinary incontinence (SUI), which approximately half of all women experience at some point in their lives.

These divergent views of the devices, which have been implanted in millions of women worldwide to treat SUI and pelvic organ prolapse, illustrate the complexity of the ongoing debate over their safety and efficacy.

“It’s contentious because you have very polarizing views on this topic, both in the patient community and the physician community,” said urologist Gary Lemack, MD, who coauthored the American Urological Association’s guidelines on surgical treatment of SUI.

Women’s stories of complications from mesh implants are particularly compelling because they have to do with “incontinence, with sexual function, with a woman’s sense of self,” said Jan van der Meulen, PhD, a clinical epidemiologist at the London School of Hygiene & Tropical Medicine who has studied the rate at which SUI patients treated with mesh implants require reoperations.

In the United States, the attorneys general of Washington, California, Kentucky, and Mississippi have filed civil lawsuits against Johnson & Johnson and its subsidiary Ethicon for concealing the risks of their transvaginal mesh products. One manufacturer alone, Endo International, has already paid out or set aside more than $3.5 billion to settle tens of thousands of lawsuits brought by women who said they were injured by the company’s urogynecologic mesh products.

Authorities in several countries—spurred by horror stories told by women who said they developed complications such as antibiotic-resistant infections and vaginal erosion as a result of mesh implants—have limited the use of the devices for the treatment of pelvic organ prolapse and, in some cases, SUI. For example, officials in the United Kingdom—where the use of mesh devices to treat SUI fell by about half between 2008 and 2017—recently ordered public hospitals to suspend procedures using transvaginal mesh devices. In a draft guidance released in October, the UK National Institute for Health and Care Excellence said mesh implants should be used only as a last resort for prolapse or SUI.

Meanwhile, some urologists and gynecologists and their professional organizations have expressed concern that the lawsuits and restrictions on the use of mesh products will adversely affect women, not protect them.

In a recent letter to Attorney General Robert Ferguson, 63 Washington physicians—3 of whom acknowledged having been retained by Ethicon lawyers in connection with the attorney general’s lawsuit—argued that inexperienced surgeons, not the mesh products themselves, were to blame for the majority of significant complications. Instead of suing Johnson & Johnson, the physicians wrote Ferguson, the state should pass legislation that would prevent surgeons who lack the credentials recommended by the American Urogynecologic Society (AUGS) from implanting mesh in women.

Prolapse vs Incontinence

Surgical mesh has been used since the 1950s to repair abdominal hernias and since the 1970s for repair of pelvic organ prolapse through the abdomen. In the 1990s, gynecologists began using the mesh, which they cut themselves, to treat prolapse and incontinence through an incision in the vagina.
The FDA cleared the first mesh products designed specifically to treat SUI in 1996 and the first transvaginal mesh device for prolapse in 2002.

The newly cleared mesh midurethral "slings" were introduced as a less-invasive alternative to major abdominal surgery for treating SUI. The slings could be implanted in an outpatient procedure under local anesthesia, while colposuspension, an older surgical procedure for incontinence that involves lifting the neck of the bladder and stitching it in place, often requires a large incision and at least 1 night in the hospital.

"There are many benefits from using synthetic slings," said urologist Gamal Ghoniem, MD, a specialist in female pelvic medicine and reconstructive surgery at the University of California, Irvine. "Patients go home the same day. There are excellent results. Unfortunately, a lot of women...are afraid to have the surgery because of all this negativity surrounding the procedure."

In 2010, approximately 250 000 mesh sling procedures for SUI were performed in the United States, according to the FDA, which in 2016 issued a final order reclassifying mesh products for pelvic organ prolapse as high risk—thus mandating that they navigate the agency's most stringent device review pathway—but left those for SUI in the moderate-risk category. "Serious adverse events are NOT rare," FDA staff concluded in 2011 after reviewing the literature about the urogynecologic use of surgical mesh.

The FDA convened a panel of outside experts in February to discuss and make recommendations regarding the safety and efficacy of transvaginal mesh devices for pelvic organ prolapse, but mesh for SUI was not on the agenda.

"They're talking about something that doesn't matter anymore," said Mayo Clinic urologist Daniel Elliott, MD, noting that, in the face of mounting lawsuits and requests from the FDA to conduct postmarket surveillance studies, most manufacturers have already stopped selling transvaginal mesh devices for prolapse. "They need to be talking about the [midurethral] slings" for SUI.

**Incontinence Complications**

What gets lost amid the lawsuits and the headlines about women who've suffered complications is that the slings apparently help many women with SUI, at least anecdotally.

Although there are patients who have had significant problems with mesh and are outspoken about their complications, "you probably have many more patients who are saying little" said Lemack, because they're not having problems. "But they're out there, and they're the vast majority."

Take the mesh slings off the market, and "a lot of women have to suffer incontinence, and that's not right either," van der Meulen said. "The quality of life of women with urinary incontinence is really surprisingly poor."

What's more, the condition is underdiagnosed and undertreated, according to a 2017 *JAMA* review article. "Untreated incontinence is associated with falls and fractures, sleep disturbances, depression, and urinary tract infections," the authors wrote.

Because of the growing concerns about the safety of mesh slings and manufacturers abandoning the production of some, a nearly century-old procedure using a woman's own tissue to fashion a sling is making a comeback, Ghoniem wrote in a recent *JAMA* review and editorial.

The procedure, known as the pubovaginal sling (PVS), uses autologous rectus fascia to create a hammock on which the bladder neck and urethra can rest. Compared with synthetic mesh slings, the fascial sling has a lower rate of such adverse events as vaginal erosion, infection, and urethral damage, according to the review article.

But, as Linda Brubaker, MD, noted, "incontinence surgery of any type, mesh or no mesh, has a specific type of complications." The problem is that younger surgeons aren't even learning how to perform incontinence procedures that don't use mesh, said Brubaker, a urogynecologist at the University of California, San Diego, and a *JAMA* associate editor. "Surgeons have to have all of these in their repertoire."

To get a better idea of the risk-benefit tradeoff for mesh slings, van der Meulen said, "we need surveys asking women how well they're doing"—not just women who've received mesh slings, but all women experiencing or being treated for SUI.

**"Very Poor" Evidence**

Within 9 years of mesh sling insertion, 3.3% of women had at least part of it removed, and 4.5% had a reoperation for SUI, according to a study by van der Meulen and coauthors that was recently published in *JAMA*. The retrospective cohort study included 95 057 women who received a mesh sling for the first time for SUI in National Health Service hospitals in England.

In a commentary on the study, Lemack, a specialist in female pelvic medicine and reconstructive surgery at the University of Texas Southwestern Medical Center, described the overall reoperation rates as "favorable" and noted that they were lower than that found earlier in a study involving more than 150 000 US women. However, he and his coauthor wrote, "this study is retrospective and unfortunately there is no information provided regarding overall complications."

However, the findings should not be used to support the argument that mesh slings are safe, van der Meulen cautioned. "That would concern us. We didn't write this paper to say everything is hunky dory. We think that what this debate needs are clear data, data based on analysis of relevant data sets."

When the FDA cleared mesh slings, evidence about their safety and efficacy was "very poor," mainly consisting of small *Scandinavian* studies, van der Meulen said. Low quality of evidence for medical devices isn't unique to the mesh sling products, as noted in this 2017 *JAMA* article. The FDA regulates many devices less stringently than it does drugs.

This is in part a result of a "giant loophole," wherein all manufacturers of devices classified as low or moderate risk have to do is claim, "We're just like this other device that you approved," and the FDA clears their products for marketing, Brubaker said. "There were no high-quality randomized controlled trials [for mesh slings] submitted to the FDA." Even when predicate devices were taken off the market, the devices that "piggybacked" on them remained, Brubaker noted.

Although the Washington physicians' letter to their attorney general, as well as a *Cochrane* Review on the subject, describe midurethral slings as the most extensively studied surgical treatments for SUI, Elliott said that's misleading. "There's a very important difference in words: The most studied vs the best-studied product," he said. "There have been tons and tons of papers on mesh slings. But there's no study where the sole focus was safety. That's not out there."
Quick Uptakes

Taking the Uncertainty Out of Interpreting BRCA Variants

Rebecca Voelker, MSJ

Interpreting genetic variants detected in BRCA1 and BRCA2 tests can be challenging. To help demystify the process, an international collaboration has developed a resource that may help guide clinical decision-making. Details of their work appeared recently in PLOS Genetics.

The Problem
Testing for BRCA1 and BRCA2 mutations identifies both benign and pathogenic genetic variants. But information about specific variants, particularly those of uncertain clinical significance (VUS), often isn't systematically curated, expertly reviewed, or easily searchable. In addition, different laboratories sometimes interpret test results differently.

Downstream Risk
Some patients whose variants don’t have a clear clinical meaning might seek or receive unnecessary care.

Statistically Speaking
About 3% of BRCA1 and BRCA2 findings on genetic tests are VUS. An estimated 15% to 20% of them are likely to be disease causing. As more people undergo genetic testing, clinicians will continue to see VUS.

Strategic Move
The Global Alliance for Genomics and Health in 2014 decided that “big data” could shine a spotlight on VUS in BRCA1 and BRCA2 genes. Plans emerged to launch an international effort aimed at creating a 1-stop shop to share information about BRCA1 and BRCA2 variants.

The Solution
Instead of wading through many databases with information that sometimes hasn’t been properly vetted, the BRCA Exchange was created as a central repository for expertly reviewed genetic variation data. It’s a web portal containing information from clinicians, clinical laboratories, and researchers around the world as well as existing clinical databases, including:

- ClinVar, a publicly available archive of genetic variants and their association with human phenotypes.
- Breast Cancer Information Core, an open access breast cancer mutation database.
- Leiden Open Variation Database—an open source database of gene variants.

Currently, the BRCA Exchange includes more than 20 000 unique BRCA1 and BRCA2 variants. The international Evidence-based Network for the Interpretation of Germline Mutant Alleles consortium provides expert classification of more than 6100 of those variants. So far, 3700 are classified as pathogenic.

Clinically Speaking
The BRCA Exchange is easy to use. “This is a website that you can go to, put in the variant, and it will give you the classification,” said Susan Domchek, MD, a coauthor of the PLOS Genetics paper and director of the Bass Center for BRCA at Penn Medicine’s Abramson Cancer Center in Philadelphia. “Anything that comes through as a variant of uncertain clinical significance in a commercial lab or things that are splice site or missense [mutations] are particularly valuable to have a second look at” in the BRCA Exchange.

Depending on the classification, clinicians and patients essentially have 3 options:

- A preventive approach such as breast or ovary removal for patients with a pathogenic variant.
- Targeted therapies for patients with a cancer diagnosis associated with a pathogenic variant.
- Periodically reappraising patients with variants of uncertain clinical significance.

“If the finding is a variant of unknown significance, we do not make management changes based on that classification,” Domchek said. “We recommend that people with variants of unknown significance check in with us yearly so we can check all the data sources to see if anything has changed.”

Note: Source references are available through embedded hyperlinks in the article text online.