

Breast Implant Illnesses:
What's the Evidence?

National Center for Health Research
Diana Zuckerman, PhD, & Varuna Srinivasan, MBBS, MPH

Table of Contents

Women Requesting Financial Help to Remove Implants 1
The Role of the Food and Drug Administration (FDA) 2
Breast Implant Design Innovations 6
Frequency of Local Complications 7
Cancers, Lymphoma, and Lung Disease 9
The Main Controversy: Autoimmune, Connective Tissue Disease, and Breast Implant Illness 10
Does Research Prove that Breast Implants Don't Cause These Diseases? 13
Cohort Studies in the Meta-Analysis 17
Case-Control or Cross-Sectional Studies in the Meta-Analysis 20
Additional Studies in the IOM Report 24
Additional Studies from the 2016 Tufts Report Prepared with FDA Guidance 25
Conclusions 30

Breast Implant Illnesses: What's the Evidence?

More than 400,000 women and teenagers undergo breast implant augmentation surgeries every year, with 75% for augmentation of healthy breasts and 25% for reconstruction after mastectomy.[1] The popularity of breast implants has risen dramatically in the last 20 years and has more than tripled since 1997.[2] The increase in breast implant surgery, however, does not necessarily reflect a similarly dramatic increase in the number of women with breast implants. Many women who undergo surgery are replacing old implants that have broken or caused problems, and those replacements can occur every 10-15 years or more.

Debate swirls over the risks of breast implants, and physicians and patients are justifiably confused by the conflicting information available. As concerns about breast implant safety die down, new controversies arise. For example, in 2011, the FDA announced that breast implants might cause a rare type of lymphoma called ALCL, an international scandal revealed that tens of thousands of breast implants had been made with industrial silicone instead of medical grade silicone,[3,4] and the FDA issued a report reassuring women that the high complication rate for breast implants was no higher than expected. FDA discussion of complications then and now focuses on breast pain or hardness (called capsular contracture), implant rupture, and cosmetic problems in the breast area. The FDA has repeatedly reassured the public that studies "do not show evidence that silicone gel-filled breast implants cause connective tissue disease or reproductive problems"[5] and that "the FDA does not have evidence suggesting breast implants are associated with health conditions such as "chronic fatigue, cognitive issues and muscle pain."[6]

By 2018, there were more than 50,000 women reporting a range of symptoms they refer to as "breast implant illness" on two Facebook pages: *Breast Implant Illness and Healing* and *Breast Implant Victim Advocacy*. More than a dozen Administrators and patient advocates from these two Facebook pages met with FDA officials in September 2018 to discuss their health issues and to urge the FDA to do more to require the completion of large, long-term scientific studies and to better inform women of the health problems experienced by many women as a result of their breast implants.

Women Requesting Financial Help to Remove Implants

Since 2015, the National Center for Health Research has been contacted by more than 4,500 women who had breast implants that they wanted to remove because of rupture, breast pain, or medical symptoms that they believed to be related to their implants. Most of the women could not afford explant surgery, and asked for NCHR's assistance in persuading their health insurance, Medicare, or Medicaid to cover the cost of implant removal without replacement. NCHR has a project to assist these women if they have insurance but have had difficulty getting coverage for explant surgery. Most health insurance policies will cover the cost of breast

implant removal when it meets the policy's criteria for medical necessity. In almost all cases, medical necessity is defined as a leaking silicone gel breast implant or severe capsular contracture that causes breast hardness and pain. We are not aware of any policies that will cover removal due to systemic illnesses caused by implants, such as those described by thousands of women with breast implants. However, in many cases women have systemic illness in addition to having capsular contracture and a leaking silicone gel implant.

In November 2018, the Center began a ground-breaking study of more than 300 of the women who were able to get their implants removed. The women were asked to list the most important reasons why they wanted to have their implants removed and not replaced. Our preliminary analysis indicates that fewer than one-third had ruptured implants, approximately one half had breast pain, and 84% cited an array of other health issues that can be categorized as autoimmune or connective tissue symptoms, rather than diagnosed diseases.

At the time that their implants were removed, approximately three out of five of the women had implants in their body for 10 years or more, and many had these symptoms for years. After having their implants removed, 89% of the women reported that their symptoms improved.

It is important to note that when implant manufacturers submitted studies to the FDA that were used as the basis of FDA approval, the companies stated that they intentionally excluded women with a history of autoimmune diseases. FDA required that patient booklets provided by implant manufacturers must warn about that; For example, Allergan's booklet states: "Caution: Notify your doctor if you have any of the following conditions, as the risks of breast implant surgery may be higher: "Autoimmune Diseases (for example, lupus and scleroderma)."[7] Unfortunately, patients report they are not given the booklets or the warning prior to surgery, the FDA does not include that warning on its website, and in our preliminary analysis, 6% of the women in our study reported that they had been diagnosed with an autoimmune disease prior to getting implants.

The goal of this report is to consider all the research evidence to determine what is known and not known about the risks of breast implants, scrutinizing the research that has been conducted. We will start with a summary of the role of the FDA and the less controversial issues regarding local complications from breast implants, and then focus on the most controversial issues: The strengths and weaknesses of the key studies that have been repeatedly quoted as evidence that breast implants do not cause autoimmune or connective tissue health problems. We will also use the information gathered in NCHR's preliminary study of women with implant problems to help understand the conflicting evidence of published studies.

The Role of the Food and Drug Administration (FDA)

Breast implants were first sold in the 1960s, but the FDA did not have the authority to regulate medical devices until 1976. The 1976 law created three categories of medical devices based on risk, with Class III defined as high risk. Breast implants were "grandfathered" onto the market, but by the late 1970's, many doctors and scientists had expressed concerns about their safety.[8] In

1978, an FDA Advisory Panel proposed that breast implants be categorized as moderate-risk Class II devices, which would not require any clinical trials proving safety or effectiveness for new implants to go on the market. The FDA instead proposed a Class III designation in 1982, and in 1983 the FDA Advisory Panel unanimously agreed. In 1988, the FDA Advisory Panel met again and an FDA official, Dr. Nirmal Mishra, listed the possible risks of breast implants that needed to be studied, including:

➢ Capsular contracture (the painful tightening of the scar tissue around the implant)

➢ Breakage

➢ Micro-leakage (sweating or bleeding of silicone outside the shell)

➢ Silicone leakage to the lymphatic system

➢ Interference with the accuracy of mammography

➢ Immune disorders

➢ Cancer

Thirty years later, these are still the issues of greatest concern, and the incidence of these complications as implants age is still unknown.

By 1990, almost one million women had breast implants, even though there were no published clinical trials about their safety and the FDA had never approved them. The FDA oversight committee in the House of Representatives, under the Chairmanship of Rep. Ted Weiss, held a hearing in December of 1990, pointing out that the only studies implant makers had submitted to the FDA were silicone injections in rats and rabbits, and that the agency had ignored that law requiring them to promulgate a rule requiring that human clinical trial data be submitted by the breast implant companies to the FDA if the wanted to keep selling their implants.[8] Scientists testified about their research indicating substantial safety concerns, and patients testified for and against implants, depending on their personal experiences.

In response to Congressional pressure and negative media coverage, the FDA finally required the manufacturers of silicone gel breast implants to submit safety studies in 1991. Studies of saline breast implants were not required at that time. Unfortunately, the studies of silicone gel implants that were submitted to the FDA were poorly designed and conducted; for example, in the McGhan study, two out of three patients were followed for less than three months after their surgery, and there were only three breast cancer reconstruction patients.[8]

Early in 1992, internal memoranda dating from 1960-1987 from Dow Corning, the major breast implant manufacturer at that time, were publicly released.[8] The documents were widely reported in the media, with quotable quotes such as a marketing representative telling physicians "with fingers crossed" that safety studies were underway. Several memoranda complained that new

breast implants were "greasy," indicating the micro-leakage of intact implants that the FDA had been concerned about years earlier. Given the poor quality of the studies submitted to the FDA and the controversy about the internal documents, it is not surprising that silicone gel breast implants were not approved at that time.

Nevertheless, the FDA made sure that breast implants could still be sold in the U.S., by issuing a compassionate need exemption policy on October 23, 1992.[8] This policy restricted silicone gel implants in the U.S. to women willing to participate in studies, including a large "Adjunct Study" for reconstruction patients and for women who wanted to replace broken implants (called "revision" patients). Approximately 1,000 women, including first-time augmentation, reconstruction, and implant replacement patients participated in each company's "Core Study." It is important to note that the companies defined reconstruction patients to include many women who were not mastectomy patients. Women were also "reconstructed" to correct "deformities" such as droopy breasts (not uncommon after women have breastfed a child) and "severe" asymmetry; deformities were subjectively defined by the plastic surgeons.

Implant manufacturers could have collected and published extensive safety data from these studies. Instead, major shortcomings were reported; for example, many patients reported that their physicians encouraged them to enroll in the Adjunct study as a way to qualify for silicone gel implants, explaining that they could drop out immediately after surgery. That anecdotal claim is supported by the large proportion of participants who dropped out between enrollment and the first follow-up, and even more after that: only 27% of Inamed's reconstruction patients and 20% of their revision patients were followed for three years, as were 18% of Mentor's revision patients and 19% of their reconstruction patients.[9] The problem when so many patients drop out of studies is that it is impossible to know if the ones that dropped out have better or worse experiences than those in the study. As a result of losing data from approximately three-quarters of the women before the study was completed, these Adjunct "studies" did not provide meaningful safety information.

After that same 2003 Advisory Panel meeting, the FDA considered the scientific data that had been provided and decided not to approve Inamed silicone gel breast implants in January 2004.[10] At the same time, the FDA issued a new guidance specifying the type of research that manufacturers would need to submit to obtain approval of any breast implants in the future. A major focus of the guidance document was the need to determine why breast implants break, how long they last, and the health consequences of broken and leaking implants.

In 2005, the FDA held another Advisory Panel meeting to consider new research on silicone breast implants that had been submitted by two companies, Inamed (now called Allergan) and Mentor (now a subsidiary of Johnson & Johnson).[11] Their studies only followed women for three years, which was not responsive to the FDA guidance asking that they determine how long implants last or the health consequences of leaking or broken implants.

Meanwhile, controversies regarding implant safety continued. In late 2005, the FDA Office of Criminal Investigation started an investigation of Mentor, interviewing former Mentor employee about the sale of defective implants by the company. One employee admitted that executives

ordered him to destroy documents related to a high rupture rate of Mentor implants and admitted that some implants were contaminated with fleas.[12]

Despite the short-term studies and the investigation of Mentor, in November 2006 the FDA approved silicone gel breast implants by Mentor and Inamed (now Allergan) as "reasonably safe" for women who are 22 or older. This was the first time that FDA had approved silicone gel implants, and because of serious concerns about safety, the FDA required each of the two implant makers continue their 2-3-year studies for a total of 10 years each, and also start new studies of at least 40,000 women with breast implants for 10 years, in order to prove long-term safety.[13] The purpose of these larger, long-term trials was specifically to determine if there was a statistically significant risk of connective tissue or autoimmune diseases.

The required studies were an acknowledgement that previous studies had been too small or too short-term to determine if implants caused these systemic diseases, as well as to determine the long-term risk of documented problems such as implant breakage and breast pain. With few exceptions, almost all the published data were studies funded by implant companies, plastic surgeons, or silicone manufacturer Dow Corning. Although the required studies would still be funded by and conducted by the implant companies, the FDA had input into the scientific design of the studies to address the short-comings of previous research.

The required studies were conducted, but 5 years after silicone gel implants were approved, neither the companies nor the FDA had made any of the results publicly available. Requests from the National Center for Health Research to make the data public received no response. At that point, Congresswoman Rosa DeLauro (D-CT), who chaired the FDA Appropriations committee in the House of Representatives, requested that FDA hold a public meeting,[14] and the FDA did so in August 2011. The data were provided on the FDA web site in June 2011 and discussed at the August meeting.[13] In addition to invited presentations by the implant companies and FDA officials, several hours were set aside for public comments.

The data in the FDA's June 2011 report and as presented at the public meeting made it clear that most women enrolled in the required 10-year studies had dropped out within just the first few years. More than three-quarters of Mentor's 40,000 patients had dropped out, and at the meeting it was mentioned that Mentor had provided no stipend or other incentive for the patients to complete the very lengthy annual surveys describing their health issues. In contrast, Allergan had paid women $20 each to complete very similar questionnaires. Moreover, several women testified at the hearing that they were thrown out of the implant studies when they reported serious health problems from their breast implants or decided to have their implants removed.[15] It was impossible to determine how often that happened, but it raised questions about the accuracy of the data provided by the companies, as well as the possible reasons why so many women "dropped out" of the studies. Nevertheless, the FDA did not question the integrity of the data and maintained in their report that silicone implants were safe and effective.[13]

FDA states on its website that the 10-year studies of 40,000 women that FDA required of each of the two implant companies were never completed.[16] FDA reports that their Advisory Panel that met in 2011 recommended that the 10-year studies be replaced by a systematic literature review as well as re-designed studies that "have more efficient methodologies to assess rare

complications." On its website, FDA explains that "In response, FDA entered into collaboration with the American Society of Plastic Surgeons (ASPS), the Plastic Surgeons Foundation (PSF), breast implant manufacturers and patient advocate groups, to establish the National Breast Implant Registry (NBIR) and the PROFILE Registry (established to collect data on potential cases of breast-implant associated anaplastic large cell lymphoma (BIA-ALCL)). Tufts University was tasked with conducting a systematic literature review to look at rare endpoints (listed below) and silicone gel-filled breast implants. Despite the FDA's description of the panel's recommendation to replace post-market studies with a research review, the FDA's own summary of the meeting is completely different, focusing on the need for clinical trials and registries to answer important safety questions.[17]

Our analysis of the Tufts review is on page 15 of this report. It is important to note that although the FDA claimed they would include "patient advocacy groups," none of the patient advocacy groups that were most involved in the FDA's breast implant hearings were invited to participate in the registries or the Advisory Board of the Tufts Systematic literature review. In addition to being funded by implant manufacturer through a grant to the Plastic Surgeons Foundation, the Advisory Board was comprised primarily by plastic surgeons and industry representatives and its only "patient advocate" was head of an organization that had received funding from implant manufacturers.

Breast Implant Design Innovations

One of the difficulties of studying breast implants is that the implants have changed over time. The 50+-year history of silicone breast implants is a history of trying to reduce complications, especially common problems such as implant rupture or breast hardness and pain caused by capsular contracture. Although breast implants were not studied in clinical trials for the first 30 years that they were used, companies introduced design modifications that were intended to make implants safer but were later be found to be ineffective at fixing problems and caused new ones. For example, since the mid-1960s, implant modifications have included adding a Dacron patch to fix the implant in place; removing the Dacron patch; changing the thick gel to a thinner gel; changing the thinner gel to a thicker, more cohesive gel; making the silicone shell textured, covering the shell with polyurethane foam; removing the foam when it was found to break down to a carcinogen; making the shell smooth; changing the shape of the implants; and reducing "silicone bleed." Rather than being studied in clinical trials, women paid for surgery with these different types of implants. A Congressional report summarizing these changes referred to the patients as "guinea pigs."[8]

When research was finally conducted and showed problems, companies could claim that the newly designed implants were safer. For example, women were told that the new breast implants approved by the FDA in 2006 were improved but Inamed's Senior Director of Regulatory and Clinical Affairs testified to the FDA in 2003 that the implants on the market at that time, which were included in the studies "is basically the same product it was 10 years ago…it is essentially the same product.[9]

In addition to changes they made to silicone gel breast implants, implant makers sold implants that replaced silicone gel with other products. Implants made with a silicone elastomer envelope that is filled with saline (salt water), have been available for decades, but were not approved by the FDA until 2000. The companies had conducted 3-year studies of local complications such as pain, infection, hardening, and the need for additional surgery. They did not study other health problems.

In addition to saline, three other kinds of implants were made available in the 1990's, primarily outside the United States: Trilucent implants (with soybean oil filler), and Novagold and PIP hydrogel implants, which were filled with a plastic gel. Although never approved as safe in the U.S., these implants were vigorously promoted by plastic surgeons and the media as a "natural" and safer alternative to silicone or saline implants. Clinical trials, however, were apparently never conducted on humans with these implants, and all were removed from the market in 2000 due to safety concerns.[18,19,20,21] Their removal from the market serves as a reminder that the long-term risks of implants are not always obvious during the first few years of use.

In 2012, FDA approved silicone gel implants made by a third company, Silimed, without a public meeting to review the much more cohesive implants made by Silimed.[22] This was the first "gummy bear" silicone gel implant, the nickname given because the gel has a rubbery consistency like gummy bear candies. The goal of using such cohesive gel is to prevent leakage if the implant breaks. However, the metals and chemicals that are used to make it are different from other silicone and the long-term risks are unknown.[23] This very different implant should have been publicly scrutinized at an FDA Advisory Panel meeting, but it was not.

FDA has approved specific models of silicone or saline breast implants made by Inamed, Mentor, Silimed (also called Sientra), and Ideal Implant. Implants made by several other companies, such as those made by the French company PIP, have been sold in other countries but have not been available in the U.S. for over a decade. PIP silicone implants were taken off the market in Europe in 2011 because they tended to rupture sooner than other implants and because testing revealed that the silicone was not intended for use in the human body but rather was intended for use in mattresses.[3,4] Public outrage and concern was so strong in several countries, such as France, the United Kingdom, Bolivia, and Venezuela, that their governments agreed to pay for implant removal surgery for all PIP implant patients, including cosmetic patients.[24]

Frequency of Local Complications

Everyone agrees that breast implant surgery has risks. The risks associated with any type of surgery include infection, hematoma (blood or tissue fluid collecting around an implant), and the risks associated with anesthesia.

Everyone also agrees that breast implants can cause "local complications" in the breast area. The only controversy is how often these problems happen, due to the absence of long-term studies. These are the most common local complications.

Breast Pain and Capsular Contracture: All implants are "foreign bodies." A woman's body reacts to the introduction of this foreign object by forming a capsule of scar tissue around the implants. When this capsule becomes tight or hard—a common problem—it is called capsular contracture. Capsular contracture can cause the breasts to become very hard or misshapen and can cause mild discomfort or severe, chronic pain. Research submitted in support of Inamed's 2003 application to the FDA, for example, reported severe capsular contracture occurring in 16% of reconstruction patients and 8% of augmentation patients within 3 years.[9]

Comparing Inamed data on saline breast implants and silicone gel breast implants shows many of the same types of complications; however, complication rates from silicone gel implants tend to be higher. For example, 46% of silicone gel reconstruction patients and 21% of saline reconstruction patients underwent at least one additional operation within three years, 25% of silicone patients and 8% of saline patients had implants removed, and 6% of silicone patients and 16% of saline patients had breast pain. 3-year data of Mentor and Inamed analyzed by the FDA in 2000. Complications were lower but still substantial for augmentation patients.[7,9]

A study of Danish women who had breast implants for an average of 19 years found that women with implants were almost three times as likely to report breast pain compared to breast reduction patients.[25] In addition, two-thirds of the women with implants reported moderate or severe breast hardness.

There are other well-documented complications that affect the breasts that can result from breast implants. For example, some women lose sensitivity in their nipples, and others become overly sensitive. These problems can interfere with sexual intimacy. The cosmetic outcome is also sometimes disappointing, with breasts looking or feeling unnatural or asymmetrical.

Rupture: All breast implants will eventually break. When silicone gel breast implants break, there are often no symptoms, so accurate estimates of rupture rates depend on magnetic resonance imaging (MRIs). While most breakage occurs as the implants age, Inamed's study of their silicone gel implants found that 1-6% break within three years. [26] In a study conducted by researchers at the FDA, most women had at least one broken implant within 10 years, and the likelihood of rupture increased over time.[27] The women in the FDA study had not had their implants removed, did not know that their implants were broken, and were not seeking help because of implant concerns. Despite the fact that these women were "satisfied customers" rather than women seeking medical care, MRIs found that silicone had migrated outside of the breast capsule for 21% of the women in the study. Most of the women were unaware that this had happened. A Danish study reported that most silicone gel implants lasted for ten years; however, by the time the women in that study had implants for 15 years or more, a substantial percentage of the implants broke every year.[28]

Leakage: Numerous studies have shown silicone leaked into the scar capsules surrounding breast implants, even for implants that were not ruptured. More worrisome, researchers at Case Western Reserve and the Armed Forces Institute of Pathology reported finding silicone in the lymph nodes of women with breast implants, which can then migrate to other organs.[29,30] Case studies have confirmed that silicone can migrate to the lymph nodes.[31,32] Silicone in the lymph nodes can only be removed by removing the lymph nodes. Silicone in organs such as the lungs,

liver, and brain cannot be removed. The health risks associated with migrated silicone gel are unknown. However, case reports have indicated fatalities and serious health risks when liquid silicone injected in the breasts migrated to the lungs or other organs. Although silicone implants are filled with gel rather than the liquid form of silicone, the implants sometimes leak a silicone liquid or thin gel.

Mammography: Breast implants interfere with the detection of breast cancer because implants can obscure the mammography image of a tumor. Implants therefore have the potential to delay the diagnosis of breast cancer. Although special techniques are designed to minimize the interference of the implants, research indicates that 55% of breast tumors may still be obscured, compared to 33% obscured in women without implants in the same study.[33] Mammograms tend to be less accurate if the woman has capsular contracture. In addition, women with implants may be reluctant to undergo mammograms because of fear of rupture, and a study by FDA scientists indicates that silicone or saline implants sometimes rupture when women undergo mammograms.[34] The alternative, undergoing a regular breast coil MRI to check for cancer, is prohibitively expensive for many women at $2,000 each time.

Although there is no research evidence that implants cause breast cancer, a delay in diagnosis could have serious health implications and decrease women's options for breast-conserving surgery. Such delays have been reported by patients but not in studies. Although breast cancer rates tend to be lower in women with breast implants, that is thought to be related to the lower BMI and smaller breasts typical of women who undergo augmentation.

Breastfeeding: Women who have had any kind of breast surgery, including breast implant surgery, are up to three times more likely to have an inadequate milk supply for breastfeeding.[30] Concerns about the chemicals from the implants passing to infants through breastfeeding have also been raised, with conflicting evidence and insufficient research information available to make a determination on this risk.

Cancers, Lymphoma, and Lung Disease

In January 2011, the FDA announced that women with breast implants seem to be more likely to develop ALCL (anaplastic large cell lymphoma), a rare cancer of the immune system. This apparent link was confirmed, and the WHO and NCCAN both recognized "Breast Implant Associated ALCL (BIA-ALCL) in 2016. The risk of developing ALCL is very low, but much higher in women with implants than it is in the general population. For women with implants, ALCL has been found in fluid surrounding the implant and in the scar capsule; ALCL is not usual in the breast area for women who do not have breast implants. There is evidence that ALCL is more likely in implants with textured surfaces than with smooth surfaces.[35] The FDA is now requesting that physicians report cases of ALCL in women with breast implants to determine how great the risk is compared to women without implants and to talk with patients about the benefits and risks of textured-surface vs. smooth-surface implants.[36]

Although not announced to the public until 2011, there were published case studies of BIA-ALCL as early as 2008, and plastic surgeons were discussing their concerns about it with each other but not with patients. Why did it take more than 50 years to confirm this link to cancer? Implant manufacturers and plastic surgeons continued to state that breast implants did not cause cancer even after they suspected that implants could cause ALCL.

There is clear evidence that ALCL can develop within a few years of a woman getting breast implants; however, most cancers take many years to develop after an exposure. A study by scientists from the NCI found that women with breast implants were more likely to die from brain cancer, lung cancer, and other respiratory diseases, compared with other plastic surgery patients.[37] The NCI study compared augmentation patients to other plastic surgery patients, who were very similar in socio-economic status, health status, and health habits (including smoking). All the women in the study who had implants had them for at least 12 years. Although this is not a long enough follow-up period for a conclusive cancer study, it is considerably longer than most other implant studies, and it has an appropriate comparison group of other plastic surgery patients.

A second NCI study found a 21% overall increased risk of cancer for women with implants, compared with women of the same age in the general population.[38] The increase was primarily due to an increase in brain cancer, respiratory tract cancers, cervical cancer, and vulva cancer. Swedish and Danish studies also found a significantly increased risk of lung cancer among augmentation patients, but those studies did not control for smoking.[39,40]

The Main Controversy: Autoimmune, Connective Tissue Disease, and Breast Implant Illness

The greatest controversy regarding the risks of breast implants concerns the question of whether they increase the risk of autoimmune disease and connective tissue disease. This issue has gained more recent attention now that it is clear that implants can cause ALCL, a cancer of the immune system. If implants can cause cancer of the immune system, does that mean implants can cause other immune disorders?

As noted earlier in this report, more than 50,000 women have joined two Facebook groups of women who say their breast implants cause symptoms that they refer to as “breast implant illness.” Doctors classify many of the symptoms they are reporting as connective tissue or autoimmune symptoms, but in many cases the women are not diagnosed with a specific autoimmune or connective tissue disorder (CTD).

Nevertheless, plastic surgeons and implant manufacturers have consistently claimed that there is “no evidence” that breast implants cause autoimmune or connective tissue problems. Our scientific scrutiny of the research has determined that these claims of “no evidence” are inaccurate. The remainder of this report will examine the evidence that is quoted by implant

manufacturers and plastic surgeons, as well as the studies and results that they have often ignored.

We will start with a review of a few of the studies that indicate that breast implants are associated with autoimmune or connective tissue symptoms, whether or not they are associated with classic disease diagnoses such as Rheumatoid Arthritis (RA), scleroderma, Sjögren's Syndrome, and other specific diseases. We will not perform a traditional systematic review of the literature or a meta-analysis, because such efforts too often focus on important standards such as controlled clinical trials while ignoring the even more important flaws that are unique to the issues under investigation. For example, a study that relies on hospitalization records as a way to diagnose autoimmune disease is not appropriately designed to analyze the health effects of breast implants, especially not for women who had those breast implants for a short period of time. Instead our report will scrutinize what the previous systematic reviews and meta-analyses have failed to consider, by examining the extent to which the individual studies included in previous analyses are or are not adequate to determine the systemic, long-term symptoms and conditions caused by breast implants.

A large retrospective study published by Watad *et al* in 2018 reported a statistically significant 22% increase in several autoimmune or rheumatic disorders, although the prevalence of Sjögren's syndrome, MS, and sarcoidosis each increased by at least 60%. That analysis was based on almost 11,500 Israeli women with breast implants confirmed by medical records and almost 46,000 matched women who had no breast implants. The analyses of diseases were based on diagnoses made after the women got breast implants that were included in medical records during a period up to 20 years.[41]

Another large study published concluded that "silicone implants are associated with an increased risk of certain rare harms" and that further study is needed "to inform patient and surgeon decision-making."[42] The study is described as an analysis of almost 100,000 women with Mentor or Allergan silicone gel breast implants, but 80% of approximately 50,000 Mentor patients dropped out before their self-reported questionnaire data were collected 7 years after getting implants. Allergan's data were based on physicians' diagnoses of 60% of their patients two years after their implant surgery.

Despite these shortcoming, it is important to note that the researchers reported that the risks of certain autoimmune diseases increased significantly for women with implants; for example, there was an 800% increase in Sjogren syndrome, 700% increase in scleroderma, and 600% increase in arthritis among women with Mentor breast implants compared to the general population of women of the same age and demographics. Allergan patients had double the rates of many of the same diseases, but there were fewer diagnoses since they were based on physicians' diagnoses after only 2 years.

These two large studies documenting a link between breast implants and autoimmune or connective tissue diseases confirms what older, much smaller studies also reported. For example, a study conducted by FDA scientists during the 1990's found a statistically significant link between breast implants and fibromyalgia, as well as several connective tissue diseases.[43] The study included women who had silicone breast implants for at least six years and found that

women with leaking silicone implants were significantly more likely to report a diagnosis of painful and debilitating diseases such as fibromyalgia, dermatomyositis, polymyositis, Hashimoto's thyroiditis, mixed connective tissue disease, pulmonary fibrosis, eosinophilic fasciitis, and polymyalgia. The risk of fibromyalgia remained even after controlling for patient's age, implant age, and implant manufacturer. Extracapsular leakage was evaluated in the study using an MRI.

Around that same time, scientists at the National Cancer Institute (NCI) found a statistically significant increase in reported connective tissue diseases among breast augmentation patients; the women in their study had implants for at least seven years. They also found that many of the women made errors in their self-reported diagnoses.[44] For example, many women who reported having rheumatoid arthritis actually had osteoarthritis according to their medical records. The findings suggest that there are increased symptoms among women with breast implants, but it is not clear if there is an increase in specific diagnoses. Although the researchers concluded that the associations between breast implants and arthritis, scleroderma, Sjögren's syndrome, and other connective tissue diseases need further study, they did not consider an alternative hypothesis: perhaps implants cause symptoms that do not precisely fit the criteria of these diseases.

As noted in the study conducted by the National Center for Health Research (pg. 2), the reasons why women decide to have their implants surgically removed and not replaced is often due to symptoms of autoimmune and CTDs, rather than diagnoses. The women and their doctors often report a constellation of symptoms that do not fit the exact criteria of known diseases. A major weakness of most breast implant studies funded by implant manufacturers and plastic surgeons is that they only evaluated diagnosed diseases rather than symptoms. This shortcoming is exacerbated when the studies include women who have had breast implants for relatively short periods of time, since the women's symptoms are likely to be apparent for years before a diagnosis is made.

Fortunately, as part of the applications submitted to the FDA by Mentor and Allergan for approval for their silicone gel implants in 2005, they submitted data comparing the signs and symptoms of connective tissue diseases before and two years after patients got breast implants. The companies reported that these signs and symptoms increased significantly over those two years, although they blamed the changes on age.

Nevertheless, scientists who wrote the official FDA Summary for Inamed/Allergan patients stated that there was evidence in the research literature that implants were associated with an increase in some connective tissues diseases and that in Inamed's own data, "the increases in the following CTD categories occurred despite age": general issues, muscle weakness, joint pain, and skin symptoms.[11]

For Mentor implants, the FDA reported statistically significant increases in fatigue, exhaustion, joint swelling, frequent muscle cramps, joint pain, and fibromyalgia among augmentation patients, which the FDA concluded were not due to age.

In the one other study comparing symptoms before and after women had their breast implants removed, Aziz *et al* examined 95 women who had silicone gel-filled breast implants and diagnosed rheumatologic symptoms. These researchers found that the symptoms improved in 42 (97%) of the 43 women who had their breast implants removed and not replaced.[45] In contrast, rheumatologic symptoms worsened in 50 (96%) of the 52 women who did not have their implants removed.

A study by Brieting *et al* stands out because it reported statistically significant increases in connective-tissue and autoimmune problems for women with breast implants and yet concluded that exposure to breast implants "does not appear to be associated with" autoimmune "symptoms or diseases."[25] This study of Danish women who had breast implants for an average of 19 years found that they were significantly more likely to report fatigue, Raynaud-like symptoms (white fingers and toes when exposed to cold), memory loss, and other cognitive symptoms than women of the same age in the general population. Ten percent of the women with implants had already had their implants removed and not replaced, which might have reduced these symptoms for those women in the study. Despite stating that women with implants were between two and three times more likely to report those symptoms, the researchers concluded that there was no apparent link between breast implants and these "symptoms or diseases." In addition, the women with breast implants were at least six times as likely to be taking antidepressants as breast reduction patients and at least four times as likely as women in the general population. The increase in antidepressants and sedatives were even higher for women who had their implants replaced at least once. As we will note later, that inaccurate conclusion is often quoted, whereas the results are not. The authors of this study include the director of the International Epidemiology Institute, which was funded by silicone manufacturer Dow Corning.

Depression is not usually included in the studies of breast implants and autoimmune diseases, most of which focus on connective tissue diseases (many of which are also autoimmune diseases. For that reason, we did not focus on data on depression in this report. However, studies conducted in numerous countries consistently indicate an increase in suicides among women with breast implants,[46] and depression should be studied in future research.

In addition to the examples above, it is important to note that former FDA researchers have reported that silicone stimulates an immune response, and their cellular analyses indicate that these responses are associated with atypical forms of connective tissue disease.[47]

Does Research Prove that Breast Implants Don't Cause These Diseases?

How is it that despite these and other studies indicating significant increases in autoimmune or CTD diseases or symptoms among women with implants, the research reviews conducted by the FDA and others instead claim there is not such evidence? There are numerous reasons, but one is that the research reviews tend to rely on early studies of women who had implants for a relatively short time, ranging from a few months to a few years.

These flawed studies comprised most of the studies evaluated in two influential reports: 1) A report by the Institute of Medicine (IOM) and 2) A meta-analysis published in the *New England Journal of Medicine* that was based on an analysis prepared for Judge Pointer's National Science Panel.[48,49] These reports are based on overlapping 17-20 studies that were published prior to 1999, most of which were funded by Dow Corning at a time when the company was being sued by patients harmed by breast implants. Since many connective tissue and autoimmune diseases are relatively rare and most take many years to develop and be diagnosed, these small, short-term studies were not appropriately designed to answer questions about long-term breast implant safety. Most notably, the largest study

Their major flaws are as follows:

- The case-control studies relied on women accurately telling a stranger whether they had breast implants, and most included very few women who admitted to having breast implants. The accuracy of their responses was not verified.
- The studies include substantial numbers of women who had implants for just a few months or years. Very few of the studies included women who had implants for an average of 8 years or more, and some included few if any women who had implants for that long. Compared to the women in the current study of the National Center for Health Research (page 1), these women were exposed to implants for a much shorter period of time. As a result, these studies could not conclusively evaluate the long-term increased risk of disease.
- Almost all the studies relied on disease diagnoses rather than symptoms. The diagnoses were based on hospital records or self-report, not medical exams. Several studies had an even greater flaw: Disease diagnosis was based on hospital records rather than medical diagnoses. Most women with autoimmune symptoms or diseases are not treated in hospitals.

For example, among the studies reviewed by the IOM, only one study, by Schusterman et al, included a diagnosis based on a previously recorded medical exam, and all the women in that study had implants for less than two years — too short a time to meaningfully evaluate disease risk. In addition, several European studies (Friis *et al*; Nyren *et al*) that found an increased risk of CTDs among women with breast implants inaccurately concluded that they had not found such an increase.[50,51] Their misleading conclusions were based on comparing CTD diagnosis among breast augmentation patients to breast reduction patients, which did not differ significantly. However, the articles clearly stated that both breast surgery groups had a higher proportion of women with these diseases than expected based on the general population of women of that age. Therefore, the interpretation of "no increased risk" was inaccurate, since both types of breast surgery patients were apparently more likely to develop CTDs. Although the increase might have been due to the surgery rather than the breast implants per se, what is important to patients is that breast implant surgery significantly increases their chances of developing those diseases.

In summary, the claim that there is "no evidence" of a link between breast implants and CTDs or autoimmune health issues diseases is not accurate. Research results regarding these symptoms and diagnoses are inconsistent for a variety of reasons that we will scrutinize below. Self-reports

tend to show significant increases in health risks, whereas studies that rely on diagnoses in medical records and hospitalization are less likely to show significant increased risks. In industry-funded studies, even when studies indicate an increase in symptoms or diseases among women with implants, the authors sometimes conclude that there is no evidence of increased health problems.

To fully explore this controversy, we will examine the history of research on breast implants: Who conducted it, who paid for it, who publicized the results, and how that information influenced physicians, patients, and the public.

As noted earlier in this report, breast implants were sold starting in the 1960's, but there were no published scientific studies until after Congressional hearings received widespread media coverage in 1990 and 1991. The studies that were conducted in the 1990's were almost entirely funded by Dow Corning, conducted by a core group of researchers at the International Epidemiology Institute, which received substantial funding from Dow Corning and other industry groups that needed research evidence to defend their products. The Dow-funded studies were used by Dow to defend the company from liability from their silicone implants and the silicone they sell to other companies.

We will now review the studies used as the basis of 3 key reports: The IOM report and *New England Journal of Medicine* (NEJM) meta-analysis mentioned above, and a report by Tufts Center for Clinical Evidence Synthesis that the FDA has cited as evidence that post-market clinical trials are not needed to study the impact of implants on autoimmune or connective tissue diseases.

The studies cited in the IOM and NEJM reports overlap almost completely: 15 of the 17 studies cited by IOM comprise 75% of the 20 cited in the meta-analysis. The 390-page Tufts review funded by implant manufacturers that was published 16 years later includes 114 research citations on a wide range of diseases, not just CTDs and autoimmune diseases.[52] However, they do not go into any depth on those 114 studies. For that reason, our analysis will focus on the article the Tufts authors published in medical journal based on the same report but focused on the studies that the authors consider most scientifically sound. That published article focused on 32 studies of a wide range of diseases; 9 of the 22 studies of CTD and autoimmune diseases that were the focus of the Tufts article were included in the IOM and/or NEJM meta-analysis.[53] All 3 reports concluded that the studies do not indicate an association between silicone breast implants and connective-tissue disease, although the Tufts analysis is focused primarily on silicone gel implants rather than all breast implants.

Since the overlap in studies is so substantial for the IOM and NEJM reviews, we will focus on those studies first. A careful review of the 22 studies that were included in the IOM report and/or the meta-analysis reveals that most of those studies have a number of major flaws. The accuracy of any report, meta-analysis, or review depends on the quality of the studies included in that analysis but also on how contradictory findings are explained. However, the NEJM authors also made an unusual statistical decision: When the meta-analysis indicated that the Hennekens study was largely responsible for the significant increase in several diseases among women with breast implants, the authors excluded the Hennekens study from the meta-analysis. They

justified the exclusion on the basis of the fact that the diagnoses were self-reported, even though the patients making the reports were health professionals. The NEJM authors then focused on the lack of statistically significant findings of the meta-analysis when the Hennekens study was excluded, and concluded that implants did not cause disease.

Because the NEJM meta-analysis was prepared for Judge Pointer as part of a major law suit, the decision to exclude the Hennekens study has enormous implications for patients. It made it impossible for implanted women who developed autoimmune diseases or CTDs to be compensated or to have their health insurance policies pay for explant surgery. And yet, when we scrutinized these 22 studies, we found numerous studies with much greater flaws than the Hennekens study.

Here are the shortcomings of the 22 studies:

- Twelve studies compared women with specified CTD to women without, to determine if more women with CTD had breast implants. In most of these studies, between 1-10 women had breast implants, making it impossible to determine if implants cause disease.
- Four studies cited were not published in peer-reviewed journals. Instead they were papers presented at scientific meetings or unpublished doctoral dissertations, with limited information on methodology available to evaluate the validity of the study designs.
- Of the 22 studies, only three evaluated the symptoms frequently reported by breast implant patients, such as joint or muscle pain, chronic fatigue, mental confusion, or general body pain.
- Two of the 19 studies that excluded symptoms evaluated diagnoses based on hospitalization, not outpatient treatment. This is an enormous flaw, since few women who were healthy enough to undergo cosmetic surgery are likely to be hospitalized for CTD or autoimmune diseases unless the disease has progressed for many years.
- Only one of the studies required patients to undergo a comprehensive medical exam as part of the research, as well as including patient-reported health issues.
- At least six of the studies included women who had implants for a year or less. Unfortunately, most of the studies did not include information about the minimum number of years the women had implants, the number of years of exposure would obviously influence the development of symptoms or diseases. Symptoms or diseases might also be more likely after a silicone gel implant ruptures and leaks, which usually occurs after 7-10 years. Therefore, a well-designed study would include women who had implants for at least 7-10 years. Only one of the 10 cohort studies included women who had implants for an average of 10 years or more.
- Most of the studies did not evaluate mastectomy patients separately to determine if the results were relevant to them.
- Almost all of the samples are too small to study these relatively rare diseases, and thus, have limited power to detect increases in the rates of disease, even increases as large as 50-200 percent.
- In at least one of the studies, women were included in study even if they had their breast implants removed shortly after they got them. The majority of the studies failed to mention whether women who were identified by medical records as having implants still had them throughout the years that their data were analyzed. Those omissions potentially

bias the findings because women who had implants removed do not have the same amount of exposure as women who have implants continuously.

- The funding of most of these studies involved financial conflicts of interest. At least 10 of the 22 studies were funded by Dow Corning or the authors had served as paid expert witnesses defending Dow or another implant company. At least one of the studies was funded by the Plastic Surgery Foundation, which receives support from implant manufacturers and at least 3 other studies were conducted by plastic surgeons who were studying patients treated at their practice or Department.

The following summaries include basic information, including methodological shortcomings, about the studies included in the three key reports that concluded that breast implants do not cause autoimmune or connective tissue disease (CTD). The first 20 summaries are for the studies included in the often-quoted meta-analysis published in the *New England Journal of Medicine*. Fifteen of these studies were also included in the Institute of Medicine report and 9 of these studies (Burns et al, 1996,[54] Edworthy et al, 1998,[55] Friis et al, 1997,[50] Gabriel et al, 1994,[56] Giltay et al, 1994,[57] Nyrén et al, 1998,[51] Park et al, 1998,[58] Schusterman et al, 1993,[59] and Wells et al, 1994[60]) were also a focus of the Tufts analysis that has been cited by the FDA as proof that breast implants do not cause autoimmune problems or CTD.

Unless otherwise noted, the following 20 studies that were included in the meta-analysis were also included in the IOM report and Tufts report.

Cohort Studies in the Meta-Analysis

Cohort studies compare women with breast implants to a group of women who are similar in terms of age, race, and health who did not have breast implants.

A Clinical Study of the Relationship between Silicone Breast Implants and Connective Tissue Disease (Edworthy et al. 1998)[55]

This study included 1576 Canadian breast augmentation patients and 727 women with classic connective-tissue disease were evaluated based on medical records; patients were not directly examined. The average length of times with implants was 13.5 years; no minimum number of years was stated.

Women with breast implants were 44% more likely to have a diagnosis of rheumatoid arthritis (relative risk: 1.44), but that difference was not statistically significant. When interviewed about their health, women with implants were significantly more likely to have difficulty solving thought problems, have numbness in their extremities, muscle pain, headache, and hand pain. The analysis was measured by relative risk however, those symptoms were not included in the meta-analysis.

Connective Tissue Disease and Other Rheumatic Conditions Following Breast Implants in Denmark (Friis et al. 1997)[50]

This study included 2,570 Danish augmentation or reconstruction patients compared to 11,023 women who underwent breast reduction or mastectomy without implants. Only women who were hospitalized with classic connective-tissue disease or with "other and ill-defined rheumatic conditions" were diagnosed. The average length of times with implants was 7 years for reconstruction and 8 years for augmentation; women who had implants for less than one year were included.

According to the authors, the study had only limited power to detect an increased risk of any specific connective-tissue disease. The authors found an increase in rheumatic complaint in all of the groups and therefore concluded that breast surgery increases the risk of connective-tissue disease, and that the implants themselves do not cause connective-tissue disease.

This study was funded by Dow Corning.

Risks of Connective-Tissue Diseases and Other Disorders after Breast Implantation (Gabriel et al. 1994)[56]

This study included 749 Minnesota augmentation or reconstruction patients who received some treatment at the Mayo Clinic, compared to 1,498 women served by the Mayo Clinic around the same time but who did not have breast implants, some of whom had undergone mastectomies. Diagnoses of classic connective-tissue diseases, Hashimoto's thyroiditis, cirrhosis, or sarcoidosis were based on medical records. The average length of times with implants was 8 years; women who had implants for less than one year were included.

Women with breast implants had a 35% higher rate of arthritis, which was not statistically significant (relative risk: 1.35). Morning stiffness was 81% higher for implant patients, which was significantly higher than for women without implants (relative risk: 1.81). The authors estimated that they would need to have studied 62,000 women with implants for an average of 10 years to detect a substantial increase in rare diseases such as scleroderma.

This study was funded by the Plastic Surgery Educational Foundation.

Silicone Breast Prostheses and Rheumatic Symptoms: A Retrospective Follow Up Study (Giltay et al. 1994)[57]

This study included 235 implant patients, only 56 of whom were reconstruction patients, compared to 210 women who had undergone other cosmetic surgery not involving silicone. Rheumatic complaints, use of anti-rheumatic drugs, and medical consultations regarding rheumatic symptoms were asked in a patient questionnaire; for those reporting rheumatic symptoms, a rheumatologist made an assessment of the likelihood of a rheumatic disease. The average length of times with implants was 6.5 years; the minimum was 2 years.

Women with silicone breast implants reported significantly more rheumatic complaints than controls, but there was no evidence of increased prevalence of common rheumatic diseases, such as fibromyalgia, rheumatoid arthritis, or Sjögren's disease. Augmentation and reconstruction patients were not evaluated separately.

This study was conducted by plastic surgeons and apparently included their own patients.

Self-Reported Breast Implants and Connective-Tissue Diseases in Female Health Professionals (Hennekens et al. 1996)[61]

This study included 10.830 augmentation or reconstruction patients compared to more than 380,000 other women; all were health professionals. Classic connective-tissue disease or mixed connective tissue disease were self-reported. The average length of times with implants was not provided but ranged from 1 year to more than 10.

Implant patients had a 25% higher rate of connective-tissue disease, whether they were reconstruction or augmentation patients (relative risk: 1.25). This was statistically significant, and the researchers concluded that there is a small increased risk of connective-tissue disease among women with implants. Although it is a cohort study, this study was analyzed with case-control and cross-sectional studies in the meta-analysis because information about the disease and the patient's exposure to silicone breast implants was gathered at the same time.

This is one of the very few Dow-funded studies that reported an increase in connective tissue diseases.

The significant findings in this large study resulted in the NEJM meta-analysis concluding that breast implants were associated with several CTDs. The NEJM authors then excluded the Hennekens *et al* findings from the meta-analysis and concluded that breast implants do not increase the risk of CTD.

This study was not analyzed in the Tufts report.

Risk of Connective Tissue Disease and Related Disorders Among Women with Breast Implants: A Nation-Wide Retrospective Cohort Study in Sweden (Nyren et al. 1998)[51]

This study included 7,442 Swedish augmentation or reconstruction patients compared to 3,352 women who underwent breast reduction. Only women who were hospitalized with classic connective-tissue disease or "related disorders" were diagnosed. The average length of times with implants was 6 for reconstruction and 10 for augmentation; women who had implants for at least one month were included.

According to the authors, the study had only limited power to detect an increased risk of any rare connective-tissue disease, such as scleroderma. The authors found a 10% increase in connective-tissue disease for women with breast implants and 30% increase for breast reduction patients, in both cases compared to the general population. They concluded that breast surgery rather than

implants causes the increase and concluded "no evidence of an association between breast implants and connective tissue disease."

This study was funded by Dow Corning.

Silicone Gel-Filled Breast Implants and Connective Tissue Diseases (Park et al. 1998)[58]

This study included 317 Scottish implant patients, 207 of whom were reconstruction patients, compared to 419 women who had undergone other outpatient cosmetic surgery or were from the maternity ward. Women were interviewed and received a medical examination to determine signs and symptoms of connective tissue disease. The average length of times with implants was 6 years for reconstruction patients and 5 years for augmentation patients; no minimum was specified.

Because the sample size was so small, the authors acknowledge that a health risk would have to exceed 320% for reconstruction patients and 1600% for augmentation patients in order to be statistically significant. The fact that many of the women had implants for a relatively short period of time also undermines the credibility of the results, as does the fact that this study is conducted by plastic surgeons apparently studying their own patients.

Silicone Breast Implants and the Risk of Connective-Tissue Diseases and Symptoms (Sanchez-Guerrero et al. 1995)[62]

This study included 1,183 augmentation and reconstruction patients, compared to 86,318 other women; all were participants in the U.S. Nurses' Health study who completed questionnaires asking whether they had breast implants and whether they had any classic connective-tissue diseases. Women with milder or atypical cases were excluded. The average length of times with implants was 10 years (see below for problems with that statistic), and the minimum amount of time with implants was one month.

According to the authors, the study does not exclude small health risks of implants that would be of public health importance. The study was designed to minimize "reporting bias" of health problems by implant patients by excluding any health problems diagnosed after May 1990, which was six months before the major media coverage of implant problems. The researchers did not minimize bias in the opposite direction; for example, they included women who only had implants for one month as well as women who reported having breast implants since 1952 to 1961, although breast implants had not yet been invented. For a random sample of 100 women, they verified whether the women had breast implants by looking at her medical records.

This study was not analyzed in the Tufts article.

Incidence of Autoimmune Disease in Patients after Breast Reconstruction with Silicone Gel Implants vs. Autogenous Tissue: A Preliminary Report (Schusterman et al. 1993)[59]

This study included 250 reconstruction patients with implants compared to 353 women who underwent breast reconstruction with autogenous tissue. Patients were considered to have rheumatic disease if they had been seen by a physician who made the diagnosis on clinical grounds with corroborating laboratory evidence and had prescribed therapy. Only one woman with CTD was diagnosed in each group, but the number of patients was too small, and the length of follow-up was too short to be meaningful. The authors state that the report must be considered preliminary because the onset of autoimmune disorders could occur two to 21 years after implantation. Also, important to note that Friis et al and Nyren et al each concluded that any breast surgery patient would be at increased risk for an autoimmune disease.

This study was conducted by plastic surgeons apparently studying their own patients.

The Health Status of Women Following Cosmetic Surgery (Wells et al. 1994)[60]

This study included 222 Florida augmentation and reconstruction patients, compared to 80 women who underwent other cosmetic surgery. Women completed questionnaires that asked about 23 symptoms as well as the diagnosis of classic connective tissue diseases; unfortunately, more than half the women contacted did not participate. The women reported having implants for an average of 4 years, with no minimum reported.

The women with implants averaged 10 years younger than the other cosmetic surgery patients. Tender and swollen glands under the arm were seven times as likely in implanted women. Symptoms that were more frequent in implanted women but did not achieve statistical significance were: easily tired, muscle pain, swollen and tender glands in the neck, change in hand color with cold, weight gain, swollen and painful joints, and general stiffness. Arthritis was present in 5% of implanted women and 3% of controls. One implanted woman reported Raynaud's disease; none of the women reported having scleroderma or lupus. The authors acknowledged that the small sample size could explain why the differences did not achieve statistical significance.

Case-Control or Cross-Sectional Studies in the Meta-Analysis

These studies compare women suffering from a particular disease (cases) to those who are healthy (controls) and determine whether breast implants are more common in the ill women.

Burns, Lacey, and Laing were co-authors that each were listed as first author of a study that was not peer reviewed.

The Epidemiology of Scleroderma Among Women: Assessment of Risk from Exposure to Silicone and Silica (Burns et al. 1996)[54]

This study compared 274 Michigan women with scleroderma to 1,184 identified by random digit dialing who were matched by age, race, and geography. Medical information for the scleroderma patients were based on medical records, and for controls based on telephone interviews (accuracy of breast implant reporting was found to be 94%).

This small study revealed a nonsignificant 30% increased risk of scleroderma for women with silicone gel breast implants and the same risk for women with silicone chin implants. The increased risk was slightly higher but still nonsignificant for other silicone implants, such as shunts and artificial joints. In contrast, there was a statistically significant increase in scleroderma for women exposed to silicone through their jobs, suggesting that silicone exposure may be associated with scleroderma.

This study was funded by Dow Corning.

This study was not included in the Tufts published article.

Silicone Breast Implants and Risk for Rheumatoid Arthritis. (Dugowson et al. 1992)[63]

This study compared 300 women with rheumatoid arthritis to 1,456 other women matched on age. All women completed a questionnaire asking if they had breast implants. They reported no link between RA and implants, but the sample is very small, and information is lacking about the research methods or analyses. The results were reported at a scientific meeting in the form of an abstract that was not peer reviewed.

This study was not analyzed in the IOM study or the Tufts report.

Scleroderma and Augmentation Mammoplasty — A Casual Relationship? (Englert et al. 1996)[64]

This study compared 287 Australian women with scleroderma to 371 women who had visited randomly selected general practitioners. Women were interviewed by telephone. This small study revealed no increased likelihood that women with scleroderma reported having silicone breast implants, although the authors acknowledged that the study lacked the power to detect an increased risk if it were lower than 150-200%. The implant data were provided by the women and most were verified by plastic surgeons.

This study was funded by Dow Corning.

This study was not analyzed in the Tufts report.

Breast Implants, Rheumatoid Arthritis, and Connective Tissue Diseases in a Clinical Practice (Goldman et al. 1995)[65]

Instead of comparing sick women to healthy women, all of the women in this study were patients in a rheumatology practice. They compared 721 Atlanta women with connective tissue disease

(CTD) to 3,508 Atlanta women with other rheumatology complaints, and medical records determined that 1.7% of the CTD women had implants compared to 3.9% of the other rheumatology patients. However, the women who had breast implants were significantly younger than those who did not have implants. The authors acknowledged that since the study took place in the practice of a single clinician, there is the potential for referral or selection bias. Also, many patients were seen for only a single assessment, and the researchers acknowledged that losing women to follow up could have resulted in a selection bias.

This study was funded by Dow Corning.

This study was not analyzed in the Tufts report.

Lack of Association Between Augmentation Mammoplasty and Systemic Sclerosis (Scleroderma) (Hochberg et al. 1996)[66]

This study compared 837 Pittsburgh women with scleroderma to 2,507 women who were identified by random dialing and matched for age and race. Women with scleroderma completed a self-administered questionnaire and the other women were interviewed by telephone. This study revealed no increased likelihood that women with scleroderma reported having silicone breast implants, although the authors acknowledged that the study lacked the power to detect an increased risk. The implant data were unverified.

At least one of the authors of this study was paid as an expert witness for an implant manufacturer prior to publication.

This study was not analyzed in the Tufts report.

Reply to Letter: Epidemiology of Scleroderma Among Women: Assessment of risk from exposure to silicone and silica. (Lacey et al 1997)[67]

This study of 189 Ohio women with scleroderma and 1, 043 healthy women was briefly described in a letter to the editor in the *Journal of Rheumatology*. It was not peer-reviewed, which is why this is one of the 5 studies included in the meta-analysis that were not included in the IOM report. In a telephone interview, researchers asked women who were diagnosed with scleroderma about their exposure to silicone (including silicone gel breast implants) and compared the likelihood with similarly aged controls. One case and 10 controls reported having silicone breast implants. In addition to the information about implants being unverified and the lack of information about the study design and analysis, this study lacks the statistical power to determine if women with scleroderma are more likely to have breast implants.

This study was not analyzed in the IOM report or Tufts report.

The Association Between Silicone Exposure and Undifferentiated Connective Tissue Disease Among Women in Michigan and Ohio (Laing et al. 1996)[68]

The results of this study of 206 women with undifferentiated connective tissue disease and 2,239 controls. In a telephone interview, researchers asked women with undifferentiated connective-tissue disease about their silicone exposure and compared the exposure with similarly aged controls. The authors state that women with undifferentiated connective-tissue disease were significantly more likely to report having all types of implanted devices, including breast implants, artificial joints, pacemakers, and non-CNS shunts. Although women with scleroderma were 127% more likely to report having breast implants, that specific difference was not statistically significant. These results were reported on a non-peer-reviewed abstract from a conference.

This study was funded by Dow Corning.

This study was not analyzed in the IOM report or Tufts report.

Breast Silicone Implants and Risk of Systemic Lupus Erythematosus (Strom et al. 1994)[69]

The very small study based on phone interviews with 133 Philadelphia women with lupus and 100 friends of those patients included only one lupus patient with implants and none among their friends. The authors then compared the lupus women to a control group from another study and reported an odds ratio of 4.5 (a 450% increase). However, the results are meaningless because the study lacked statistical power.

This study was not analyzed in the Tufts report.

A Population-Based Case-Control Study of Risk Factors for Connective Tissue Diseases (Teel et al. 1997)[70]

This non-peer-reviewed doctoral dissertation included 427 Washington state women with connective tissue diseases and 1,577 other women matched on age and race. Only 6 of the 427 women had breast implants and there was no statistically significant difference in this study, which was too small to draw conclusions. No information about the study design is publicly available.

This study was not analyzed in the IOM report or Tufts report.

Silicone Breast Implants and the Risk of Fibromyalgia and Rheumatoid Arthritis (Wolfe et al. 1995)[71]

This study was described in a non-peer-reviewed abstract from a conference. It compared 533 Kansas patients with fibromyalgia and 637 with rheumatoid arthritis to 479 with osteoarthritis and 655 women randomly selected from the general population and statistically adjusted for age. Only 14 women reported having breast implants, the differences were not statistically significant, and the study lacked statistical power to draw conclusions. The information on whether the women had implants was self-reported and unverified. Patients were asked to fill out

questionnaires asking if they had breast implants and the healthy controls were questioned on the telephone.

This study was not analyzed in the IOM report or Tufts report.

Additional Studies in the IOM Report

Of the 17 articles in the IOM report, 15 were also in the NEJM meta-analysis (see above) and two were not.

Both were co-authored by Michael Weisman, who was acknowledged as serving as an expert witness defending implant companies in litigation. Those two articles are as follows:

Connective-Tissue Disease Following Breast Augmentation: A Preliminary Test of the Human Adjuvant Disease Hypothesis. (Weisman et al, 1988)[72]

One-third (125) of augmentation patients from a private practice agreed to participate in a study based on a survey asking about health-related issues since the surgery, including joint pain or lupus. There was no control group. All 38 women who replied "yes" were interviewed on the phone; 16 were thought to have a localized condition. Only the 22 who were thought to have a systemic inflammatory disease were asked and agreed to a medical visit. Three were diagnoses with fibromyalgia and since none were diagnosed with classic RA, lupus, scleroderma, or other CTDs, the authors concluded that there is no evidence that implants cause CTD. However, they acknowledge that the study was too small to conclusively identify a 10-fold or even 100-fold increase of rare diseases such as scleroderma.

Breast Implants in Patients with Differentiated and Undifferentiated Connective Tissue Disease (Williams et al, 1997)[73]

Of 410 patients enrolled in a study of patients with early-onset CTD, 323 were women. Most have had signs and symptoms that satisfied criteria for RA, lupus, scleroderma, or polymyositis/dermatomyositis (PM//DM). The rest had undifferentiated disease. Women were asked if they had breast implants; only 3 reported having breast implants, 2 of which were prior to CTD. The authors admit several shortcomings of the study and also conclude that due to the lack of statistical power of this study, it could not identify any increase in CTD due to implants that was under 300%.

Neither of these two articles was included in the Tufts analysis.

Additional Studies from the 2016 Tufts Report Prepared with FDA Guidance

When the FDA determined that the 10-year studies they had required of Mentor and Inamed had lost between 50-80% of the patients in just the first few years, it became clear that there was no point in completing them. The FDA apparently decided to instead rely on a systematic review funded by the Plastic Surgery Foundation, which was in turn funded by the three-major breast implant manufacturers and written by scientists from Tufts' Medical Center.[53] The report's Advisory Board included representatives from the implant manufacturers, plastic surgeons, and the FDA; the one women's health advocate was a non-scientist whose organization has received funding from implant manufacturers.

Like the IOM report and NEJM meta-analysis, this systematic review relies on industry-funded studies with substantial flaws. And while the report specifies when the studies do not have the statistical power to adequately determine if implants are associated with diseases or symptoms, the Tufts review fails to focus on other major flaws of the studies it includes it is analysis:

➢ **Studies that include women with implants for too short a period of time to develop a diagnosed disease.** At least 6 of the 22 studies summarized above and 3 of the studies summarized below included women who had implants for a year or less. Even when some of the women had implants for 5 years or more, it would be important to specify how many had implants for a period that is too short to develop a diagnosable disease. Nowhere in the 390-page report or the published summary is that shortcoming mentioned. Similarly, studies that relied on hospitalization for autoimmune or CTD diseases should not have been considered, since few women are hospitalized for CTD unless they have had the disease for a long time.

➢ **The number of years that women were "followed" was misreported.** For the Mentor and Allergan studies, for example, the Tufts report noted that women had been followed for 9 years. However, as previously noted, three out of four patients had dropped out long before 9 years, making an analysis of 9-year data meaningless. In fact, most Mentor patients dropped out within 3 years. The high drop-out rate was never mentioned by the Tufts researchers, and those studies were included in the analysis with no caveats about that major shortcoming.

Their analysis of 32 studies and over 50 publications rely on many studies that conclude that there is no evidence that implants cause CTD or autoimmune diseases, despite clear caveats that the studies have design flaws that make it impossible to draw conclusions about the link between implants and the symptoms that so many women with implants have been reporting.

A closer look at the 2016 review analysis reveals that despite having numerous studies showing a statistically significant risk of rheumatoid arthritis, lupus, Sjögren syndrome, Raynaud's syndrome, and fibromyalgia among women with breast implants, the authors downplay this association. The authors conclude that there is inconclusive evidence to make a claim between breast implants and long-term health outcomes.

The nine published studies that we reviewed because of their inclusion in the IOM and NEJM analyses include very old studies by Burns et al, 1996,[54] Edworthy et al, 1998,[55] Friis et al, 1997,[50] Gabriel et al, 1994,[56] Giltay et al, 1994,[57] Nyrén et al, 1998,[51] Park et al, 1998,[58] Schusterman et al, 1993,[59] and Wells et al, 1994.[60] Since we have critiqued the problems with these studies above, we will not do so again here.

Below we will analyze the quality of the data of the other 12 studies of autoimmune and CTD symptoms or diseases that were included in the 2016 review from the past two decades, we see a similar pattern in terms of bias and poorly modeled study design. Looking more closely at the newer studies that focused exclusively on CTD and autoimmune disorders, it is apparent that the report relied on a small number of studies in addition to the older studies mentioned above, and that those studies had inconsistent findings. They include Berner et al 2002,[74] Breiting et al 2004,[25] Brinton et al 2004,[44] Collado Delfa et al 1998,[75] Fryzek et al 2001,[76] Fryzek et al 2007,[77] Kjøller et al 2004,[78] Laing et al 2001,[79] Lee et al 2011,[80] Mentor post approval study,[81] Oberto et al 1993,[82] Rubin et al 2010.[83]

Comparative Examination of Complaints of Patients with Breast-Cancer With and Without Silicone Implants (Berner et al, 2002)[74]

This study compared 32 mastectomy patients with breast implants to 1,100 mastectomy patients without implants. Reconstruction patients were more likely to undergo radiation; most women in both groups did not take hormone treatment. The women completed questionnaires that asked about symptoms such as swelling, general pain, muscle pain, joint pain, numbness or tingling sensations in extremities, or dry eyes. The women had implants for an average of almost 7 years. Women with implants had statistically significant increases in fatigue (41% vs. 25%), insomnia (47% to 38%), depression (34% to 20%), numbness/tingling (59% vs. 38%) and swelling of fingers (31% vs. 13%). The authors noted that these were symptoms rather than diagnosed diseases and were not able to categorize the symptoms as a diagnosis for any classic connective tissue disorders and therefore concluded that middle aged women have the types of symptoms evaluated whether or not they have breast implants. This study was funded by Dow Corning.

Long-Term Health Status of Danish Women with Silicone Breast Implants (Breiting et al 2004)[25]

This study compared 190 Danish women with breast augmentation to 186 women with breast reduction and 149 women from the general population. The women had implants for an average of 19 years, according to their medical records. The women underwent a clinical exam, had a blood test, and completed a questionnaire regarding weight and height, health habits, medication use, and symptoms and diseases such as allergies, hypertension, anemia, cancer, diabetes, connective tissue disorders, breast pain, cognitive symptoms, joint pain, muscle pain, skin rash, and hair loss. The researchers adjusted for BMI, smoking, alcohol, education, marital status, parity and age at first pregnancy.

Relative risk analysis indicated that women with more than two sets of breast implants had a 2-fold increased risk in cognitive symptoms, 4-fold increased risk of Raynaud-type symptoms, 3-fold increased risk of fatigue, a 6-fold increased risk for antidepressant use and a 6.6-fold

increased use of sedatives compared to women in the general population. Despite the dramatic and sometimes statistically significant differences for women with implants, the researchers conclude that, other than breast pain and capsular contracture, long-term use of silicone breast implants are not related to "other symptoms, diseases, or autoimmune reactivity." They also conclude that the excess use of medications for depression and anxiety "may warrant further investigation."

This study was funded by Dow Corning.

Risk of Connective Tissue Disorders Among Breast Implant Patients. (Brinton et al 2004)[44]

This study compared 10,778 American women who underwent breast augmentation to 3,214 women who had other types of cosmetic surgery. The women completed questionnaires that asked about autoimmune diagnoses such as rheumatoid arthritis, scleroderma, lupus, Sjögren syndrome, other arthritis, Raynauds, fibromyalgia, vasculitis, chronic fatigue syndrome, and MS. All augmentation patients had implants for more than 20 years. The researchers reported that 5% of augmentation patients and 3% of the other cosmetic surgery patients reported a diagnosis of at least one of four major CTDs (rheumatoid arthritis, scleroderma, systemic lupus erythematosus, or Sjögren's syndrome). They reported a statistically significant 100% increase for women with breast implants for scleroderma, Sjögrens, and RA combined an increase as well 30% increased for RA alone.

The Prevalence of Systemic Autoimmune Diseases in Women Reconstructed with Silicone Breast Implants after Mastectomy. A Comparative Study (Collado et al 1998)[75]

This study compared 81 mastectomy patients reconstructed with silicone breast implants with 72 women reconstructed with autologous tissue or who did not have reconstruction (N = 72). The average period of exposure to silicone was 4.4 years. A medical history, physical examination, general laboratory tests, level of antinuclear antibodies, antithyroid antibodies, and rheumatoid factor were performed on each woman. In no case was connective tissue disease recognized, and the prevalence of the autoantibodies studied did not differ significantly between the two groups. As noted earlier, the follow-up of 4.4 years may have been too short and the number of women with implants was too small to provide definitive results.

Self-Reported Symptoms Among Women After Cosmetic Breast Implant and Breast Reduction Surgery (Fryzek et al 2001)[76]

This study compared 1,546 Swedish women who underwent breast augmentation with allopathic breast implants to 2,496 women who had breast reduction surgery. Women who had connective tissue disease or cancer prior to surgery were excluded. The women completed questionnaires that asked about symptoms such as painful or swollen joints, burning eyes, mouth ulcers, muscle pain, tingling numbness, skin abnormalities, memory difficulties, hair loss, and unexplained fevers. All augmentation patients had implants for at least one year and ranging up to more than

18 years. Despite showing statistically significant increases in the reporting of 16 of the 28 symptoms by women with breast implants, and nonsignificant increases in most of the other symptoms, the authors concluded there is no relationship between the symptoms and breast implants because the symptoms did not vary according to "dose response" — the type, size, or number of years the women had implants.

This study was funded by Dow Corning.

A Nationwide Study of Connective Tissue Disease and Other Rheumatic Conditions Among Danish Women with Long-Term Cosmetic Breast Implantation (Fryzek et al, 2007)[77]

This study is a 5-year extension of a previously published study (Kjoller et al 2001) and compares 2,761 Danish augmentation patients with 8,807 women who underwent breast reduction and other types of cosmetic surgeries, and also compares with general population data. The women completed questionnaires that asked about polymyositis, lupus, scleroderma, and Sjögren syndrome, and reported diagnoses were verified in medical records. Augmentation patients had implants for at least one year and for an average of 13.4 years. Compared to the general population, they reported a statistically significant 90% increase in the reporting of "unspecified rheumatism" (fibromyalgia symptoms) among women with breast implants and a significant 50% increase among other cosmetic surgery patients. They also reported nonsignificant increases in RA, polymyositis, scleroderma, Sjögren's, and fibromyalgia. The authors conclude that there is no association between breast implants and connective tissues diseases.

This study was funded by Dow Corning.

Self-Reported Musculoskeletal Symptoms Among Danish Women with Cosmetic Breast Implants. (Kjøller et al 2004)[78]

This study compared 688 Danish women who underwent breast augmentation to 688 other cosmetic surgery patients of the same age from the same clinics, and 400 women from the general population. The women completed questionnaires that asked about symptoms that had lasted for at least 3 months since surgery, such as joint pain, muscle pain or weakness, abnormal skin tightness, or dry eyes. The implanted women had their implants for 0-24 months. Women with breast implants were more than twice as likely to report joint stiffness and finger swelling; these were statistically significant. Other symptoms were non-significantly higher or lower for women with breast implants. The women had implants for such a short period of time that any CTD or autoimmune symptoms would not be expected, and these results cannot be considered conclusive. However, the authors concluded that mild, moderate and severe rheumatic symptoms were less likely for women with breast implants compared to other cosmetic surgery patients.

This study was funded by Dow Corning.

Women's Health After Plastic Surgery (Englert et al, 2001)[84]

This study compared 458 Australian women who underwent breast augmentation to 687 women who had other kinds of cosmetic surgery such as abdominoplasty and rhinoplasty. The women completed questionnaires that asked about past surgical history, complications, and their subjective ranking of the influence of surgery on their health and body image. All women underwent a standardized clinical examination, as well as lab tests that were used to validate their self-reports. All augmentation patients had implants for at least 12-15 years. Women with implants were three times as likely to report rheumatoid arthritis developing in the years after surgery, but this difference is not statistically significant.

This study was funded by Dow Corning.

Potential Risk Factors for Undifferentiated Connective Tissue Disease among Women: Implanted Medical Devices (Laing et al, 2001)[79]

This study compared 205 Midwestern women who had undifferentiated CTD and 2,095 randomly selected women without CTD to compare the percentage with breast implants or other types of implants. The women completed questionnaires that asked about Raynauds phenomenon, Sjögren syndrome, and joint pain. Duration of breast implantation was not mentioned. The researchers reported a statistically significant almost 3-fold increase in any type of silicone implants among women with CTD compared to the general population; the 2-fold increase in breast implants was not statistically significant. However, the CTD women also were more likely to have implants made without silicone, such as orthopedic screws. When the researchers replicated the study replacing undifferentiated CTD patients with 600 scleroderma patients, the increase in all types of implants, including those made without silicone, remained statistically significant for women with scleroderma.

This study was funded by Dow Corning.

Prospective Cohort Study of Breast Implants and the Risk of Connective-Tissue Diseases (Lee et al, 2011)[80]

This study started with 3,950 American women with breast implants and 19,897 without. All had participated in the Women's Health Study. Women with implants completed an additional questionnaire that asked about their implants, reporting that they had implants for a median of 17 years. All women who had reported a CTD in the Women's Health Study were asked to complete another questionnaire focused on CTD, and that was completed by 91 women with breast implants and 287 women without breast implants. The researchers reported statistically significant increases in 3 CTDs for women with implants: a doubling (RR=2.23) in self-reported Sjögren's syndrome, quadrupling in dermatomyositis/polymyositis, and a 76% increase in "other CTDs." Women with implants were also more than twice as likely to report lupus, but that was not statistically significant. Efforts were made to confirm diagnoses using medical records, but that was not always possible. The researchers concluded that the data helped "exclude the likelihood of large increases in CTD risk associated with breast implants."

This study was funded by Dow Corning.

Mentor Summary Basis of Decision (SBD) for Mentor MemoryGel CPG Breast Implants Cohesive III. Health Canada 2104.[85]

This report of Mentor data that the company submitted to Health Canada is based on a 10-year study of more than 41,000 augmentation, reconstruction, and revision patients with silicone gel breast implants. The 7-year follow-up data are provided but they do not mention that most of the women dropped out of the study prior to 7 years (80% drop-out according to other published sources). The report found a more than 6-fold increase in Sjogren's syndrome, more than 3-fold increase in scleroderma, 56% increase in Rheumatoid arthritis, 43% increase in lupus. and 18% increase in fibromyalgia. The increases in Sjogren's syndrome, scleroderma, and Rheumatoid arthritis were statistically significant. However, not all the diagnoses were confirmed, and limited information is available from this unpublished report.

Connecttiviti autoimmuni e protesi mammarie: studio controllato sulle nostre pazienti sottoposte (Oberto et al 1993)[79]

This study included 102 mastectomy patients reconstructed with breast implants compared to 102 mastectomy patients without breast implants. They determined which women had confirmed diagnoses of Raynaud's syndrome and rheumatoid arthritis. This small study included no women with Raynaud's in either the implant or non-implant group and two women with rheumatoid arthritis in each group. This study was too small to draw conclusions about the impact of implants on these two diseases.

Health Characteristics of Postmenopausal Women with Breast Implants (Rubin et al 2010)[83]

The women in this observational study were from the Women's Health Initiative observational study, conducted from 1993-98. Most of the 1,257 augmentation patients in the study had implant surgery more than 20 years prior to the study and they were compared to 86,686 women who did not have breast implant surgery. Women with a history of breast cancer were excluded. The women with implants had lower BMI and tended to be more physically active and healthier in terms of diabetes, heart disease, or cataracts; however, they were significantly likely to report a poorer emotional well-being and quality of life. They were more than twice as likely to have lupus (1.2% vs. 0.5%) but it was unknown if lupus preceded implants or developed after implants, and the diagnosis was not necessarily confirmed in medical records. Women with implants also reported higher depression scores and more likely to commit suicide (7% of deaths of women with implants compared to 0.4% in the control group.

In summary, the Tufts review relied heavily on industry-funded and plastic-surgery authored studies, many with substantial flaws. Although it included several studies indicating significant increases in autoimmune or CTD symptoms or diseases, the authors concluded that the evidence from those studies was outweighed by the studies that did not find a statistically significant association. The Tufts report stated that "For none of the outcomes was there sufficient evidence of an association" with breast implants.[52] So although the report did not conclude that there was no evidence of an association, it downplayed the evidence that supported an association. It is important to note, however, that when the authors published a summary in a peer-reviewed

medical journal, they sounded more open-minded, concluding that "the evidence remains inconclusive about any association between silicone gel breast implants and long-term health outcomes. Better evidence is needed."[53]

Conclusions

Despite the controversies about autoimmune and CTD diseases, the evidence is quite consistent; women with implants tend to have increases in symptoms and diagnoses compared to similar women in the general population. Although the strength of these associations vary greatly, mostly between 22%-800%, that is not surprising given the differences in which diseases are studied and how they are studied. When patient-reported symptoms are evaluated rather than classic diagnoses, when studies with large numbers of women with implants for 7 years or more are included, and when women with implants are compared to similar women who did not have breast surgery or other types of implants, the associations tend to be stronger and statistically significant.

In order for patients to make informed decisions and the FDA to make policy decisions regarding the regulation and use of breast implants, we need objective studies undertaken by unbiased research teams. All studies have limitations, and studies that start with small numbers of patients, that include women with implants for too short period of time, or where most patients drop out (for whatever reason) before long-term data are collected are especially inadequate to evaluate the impact of implants on systemic diseases, whether cancer, autoimmune, or connective tissue diseases. The FDA is now emphasizing the use of device registries to provide post-market data on patients with breast implants and other types of implants, but device registries are focused on counting the number of surgeries rather than evaluating symptoms or other complications. The focus on surgeries and revision surgeries omits many of the outcomes that matter most to patients, and especially patients who may not have the financial resources to undergo additional surgeries. Instead, studies are needed of women with breast implants for at least 10 years, compared to similar women who did not undergo any type of breast surgery, evaluated in terms of specific autoimmune symptoms that the women are reporting when they say they have "breast implant illness."

References:

1. ASPS. "Report of the 2017 Statistics." *American Society of Plastic Surgeons (ASPS).* 2018. https://www.plasticsurgery.org/documents/News/Statistics/2017/plastic-surgery-statistics-report-2017.pdf.
2. ASAPS. "1997 Statistics on Cosmetic Surgery." *American Society for Aesthetic Plastic Surgery (ASAPS), Inc.* 1998. http://www.surgery.org/sites/default/files/ASAPS1997Stats_0.pdf.

3. "L'afssaps lance l'alerte aux prothèses mammaires défecteuses." *American Family Physician.* March 31, 2010. http://www.lemonde.fr/societe/article/2010/03/31/l-afssaps-lance-l-alerte-aux-protheses-mammaires-defectueuses_1326644_3224.html.
4. Macrae F and Randall C. "Thousands of British women in dangerous breast implants alert." *Daily Mail.* June 18, 2010. http://www.dailymail.co.uk/health/article-1287564/Thousands-British-women-dangerous-breast-implants-alert.html.
5. Ashar B, Krause D, and Scudder L. "Breast Implants: The View from the FDA." July 17, 2013. https://www.medscape.com/viewarticle/807689_2.
6. Ashar, B. "Statement from Binita Ashar, MD, of the FDA's Center for Devices and Radiological Health on agency's commitment to studying breast implant safety." September 14, 2018. https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm620589.htm.
7. Allergan. "Natrelle Silicone-Filled Breast Implants and Natrelle Inspira Breast Implants." https://allergan-web-cdn-prod.azureedge.net/actavis/actavis/media/allergan-pdf-documents/labeling/natrelleus/siliconeimplants/l3889rev02_web.pdf
8. FDA. "The FDA's Regulation of Silicone Breast Implants: A Staff Report Prepared by the Human Resources and Intergovernmental Relations Subcommittee of the House Government Operations Committee." December, 1992. http://implantawareness.com/PDF/FDAReg1.pdf
9. FDA. "General and Plastic Surgery Devices Panel Transcript." October 14, 2003. http://wayback.archive-it.org/8871/20170429032345/https:/www.fda.gov/ohrms/dockets/ac/03/transcripts/3989T1.htm
10. FDA. "Breast Implants – FDA Breast Implant Consumer Handbook – 2004 – Timeline of Breast Implant Activities." https://web.archive.org/web/20170118090812/http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/BreastImplants/ucm064242.htm
11. FDA Summary Panel Memorandum. "Inamed PMA Review Team." March 2, 2005. https://web.archive.org/web/20060819041515/http:/www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4101b1_tab-1_fda-Inamed%20Panel%20Memo.pdf
12. Harris G. "Implant Maker Hid Defects, Workers Said." *New York Times*. May 22, 2005. http://www.nytimes.com/2005/05/22/national/22implant.html?_r=1
13. FDA. "Update on the Safety of Silicone Gel-Filled Breast Implants." June, 2011. https://www.fda.gov/downloads/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/BreastImplants/UCM260090.pdf
14. DeLauro, R. "DeLauro Calls for Investigation into Safety of Breast Implants." August 16, 2013. https://delauro.house.gov/media-center/press-releases/delauro-calls-investigation-safety-breast-implants
15. Dorsey, S. "Testimony at the FDA Advisory Committee panel." August 23, 2011. http://www.breastimplantinfo.org/per_stories/susand.html.
16. FDA: Post-Approval Studies (PAS). 2018. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma_pas.cfm?t_id=377695&c_id=868
17. FDA. Brief Summary of the General and Plastic Surgery Devices Panel. August 30 & 31, 2011. https://wayback.archive-it.org/7993/20170113203020/http://www.fda.gov/downloads/AdvisoryCommittees/Com

mitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/GeneralandPlasticSurgeryDevicesPanel/UCM270599.pdf
18. United Kingdom: Medical and Health Care products Regulatory Agency. "Device Alert – Breast Implants: NovaGold." http://www.mhra.gov.uk/index.htm.
19. Medicines and Health Care products Regulatory Agency. http://www.mhra.gov.uk/index.htm.
20. Laurance J. "Agonizing wait for 5,000 women told that their breast implants might leak and cause cancer." *The Independent.* June 7, 2000. http://www.independent.co.uk/story.jsp?story=5864
21. United Kingdom: Medical and Health Care products Regulatory Agency. "Device Alert: Trilucent (soya bean oil filled) breast implants." http://www.mhra.gov.uk/index.htm.
22. FDA. "News Release: FDA approves new silicone gel-filled breast implant." March 9, 2012. http://web.archive.org/web/20120419163433/http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm295437.htm
23. United States Centers for Disease Control and Prevention. "Occupational Health Guideline for Soluble Platinum Salts (as Platinum)." https://www.cdc.gov/niosh/docs/81-123/pdfs/0520.pdf
24. Jones B. "Breast Implant Scandal: What Went Wrong?" CNN. January 27, 2012. http://www.cnn.com/2012/01/27/world/europe/pip-breast-implant-scandal-explained/index.html.
25. Breiting VB, Holmich LR, Brandt B. "Long-term health status of Danish women with silicone breast implants." *Plastic and Reconstructive Surgery*. 2004. https://www.ncbi.nlm.nih.gov/pubmed/15220596
26. Zuckerman D, Santoro E, Hudak N. "Silicone Breast Implants: Illnesses and Complications, The Latest Research from Inamed's Core Study. National Research Center for Women & Families." 2003. https://breastimplantinfo.org/symptoms-silicone-gel-breast-implants-fdas-2003-inamed-implants/.
27. Brown SL, Middleton MS, Berg WA, et al. "Prevalence of rupture of silicone gel breast implants revealed on MR imaging in a population of women in Birmingham, Alabama." *American Journal of Roentgenology*. 2000. https://www.ajronline.org/doi/10.2214/ajr.175.4.1751057
28. Holmich L, Friis S, Fryzek J, et al. "Incidence of silicone breast implant rupture." *Archives of Surgery*. 2003. https://www.ncbi.nlm.nih.gov/pubmed/12860765
29. Beekman WH, Feitz R, van Diest PJ, and Hage JJ. "Migration of silicone through the fibrous capsules of mammary prostheses." *Annals Plastic Surgery*. 1997. https://insights.ovid.com/crossref?an=00000637-199705000-00001
30. Katzin WE, Centeno JA, Feng LJ. "Pathology of lymph nodes from patients with breast implants." *American Journal of Surgical Pathology.* 2005. https://www.ncbi.nlm.nih.gov/pubmed/15767806.
31. Adams ST, Cox J, GS Rao. "Axillary silicone lymphadenopathy presenting with a lump and altered sensation in the breast: a case report." *Journal of Medical Case Reports*. 2009. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2726483/
32. Dragoumis DM, Assimaki AS, Vrizas TI, Tsiftsoglou AP. "Axillary silicone lymphadenopathy secondary to augmentation mammaplasty." *India Journal of Plastic Surgery*. 2001. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3010785/

33. Miglioretti DL, Rutter CM, Geller BM, et al. “Effects of breast augmentation on the accuracy of mammography and cancer characteristics.” *Journal of the American Medical Association*. 2004. https://jamanetwork.com/journals/jama/fullarticle/198089
34. Brown SL, Todd JF, and Luu HD. “Breast Implant Adverse Events during mammography: Reports to the Food and Drug Administration.” *Journal of Women’s Health*. 2004. https://www.ncbi.nlm.nih.gov/pubmed/15195650
35. FDA. “Breast Implants: Update-Breast Implant Associated Anaplastic Large Cell Lymphoma (BIA-ALCL).” https://www.fda.gov/medicaldevices/productsandmedicalprocedures/implantsandprosthetics/breastimplants/ucm239995.htm.
36. FDA. “Breast Implant-Associated Anaplastic Large Cell Lymphoma (BIA-ALCL). Released Summary of Safety and Effectiveness Data for Saline Breast Implants.” March, 2017. https://wayback.archive-it.org/7993/20170112002119/http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/BreastImplants/ucm239996.htm
37. Brinton LA, Lubin JH, Murray MC, et al. “Mortality among augmentation mammoplasty patients: An update.” *Epidemiology*. 2006. https://www.ncbi.nlm.nih.gov/pubmed/?term=Mortality+among+augmentation+mammoplasty+patients%3A+An+updat
38. Brinton LA, Lubin JH, Burich MC, et al. “Cancer risk at sites other than the breast following augmentation mammoplasty.” *Annals of Epidemiology*. 2001. https://www.ncbi.nlm.nih.gov/pubmed/?term=Cancer+risk+at+sites+other+than+the+breast+following+augmentation+mammoplasty
Koot VCM, Peeters PHM, Granath F, et al. “Total and cause specific mortality among Swedish women with cosmetic breast implants: prospective study.” *British Medical Journal*. 2003. https://www.ncbi.nlm.nih.gov/pubmed/?term=Total+and+cause+specific+mortality+among+Swedish+women+with+cosmetic+breast+implants%3A+prospective+study.
39. Jacobsen PH, Holmich LR, McLaughlin JK. “Mortality and suicide among Danish women with cosmetic breast implants.” *Archives of Internal Medicine*. 2004. https://www.ncbi.nlm.nih.gov/pubmed/?term=Mortality+and+suicide+among+Danish+women+with+cosmetic+breast+implants
40. Watad A, Rosenberg V, et al. “Silicone breast implants and the risk of autoimmune/rheumatic disorders: A real-world analysis.” *International Journal of Epidemiology*. 2018. https://www.ncbi.nlm.nih.gov/pubmed/?term=Silicone+breast+implants+and+the+risk+of+autoimmune%2Frheumatic+disorders%3A+A+real-world+analysis
41. Coroneos CJ, et al. “US FDA Breast Implant Postapproval Studies: Long-term Outcomes in 99,993 Patients.” *Annals of Surgery*. 2018.
42. Brown SL, Pennello G, Berg WA, et al. “Silicone gel breast implant rupture, extracapsular silicone, and health status in a population of women.” *Journal of Rheumatology*. 2001. https://www.ncbi.nlm.nih.gov/pubmed/?term=Silicone+gel+breast+implant+rupture%2C+extracapsular+silicone%2C+and+health+status+in+a+population+of+women

43. Brinton LA, Buckley LM, Dvorkina O et al. “Risks of connective tissue disorders among breast implant patients.” *American Journal of Epidemiology*. 2004. https://academic.oup.com/aje/article/160/7/619/136686
44. Aziz NM, Vasey FB, Leaverton PE, et al. “Comparison of clinical status among women retaining or removing gel breast implants.” Presented at the American College of Epidemiology. 1998. https://serials.unibo.it/cgi-ser/start/en/spogli/df-s.tcl?prog_art=632112&language=ENGLISH&view=articoli
45. Zuckerman D, et al. “Breast Implants, Self-Esteem, Quality of Life, and the Risk of Suicide.” Women’s Health Issues. 2016. https://www.whijournal.com/article/S1049-3867(16)00031-1/pdf
46. O’Hanlon TP. “Restricted and shared patterns of TCR b-chain gene expression in silicone breast implant capsules and remote sites of tissue inflammation.” *Journal of Autoimmunity*. 2000. https://www.ncbi.nlm.nih.gov/pubmed/10882054
47. Janowsky EC, Kupper LL, Hulka BS. “Meta-analyses of the relation between silicone breast implants and the risk of connective tissue diseases.” *New England Journal of Medicine*. 2000. https://www.ncbi.nlm.nih.gov/pubmed/?term=Meta-analyses+of+the+relation+between+silicone+breast+implants+and+the+risk+of+connective+tissue+diseases
48. Diamond BA , Hulka BS , Kerkvliet NI , Tugwell P. “Silicone Breast Implants in Relation to Connective Tissue Diseases and Immunologic Dysfunction: A Report by a National Science Panel to the Honorable Sam C. Pointer Jr.” Coordinating Judge for the Federal Breast Implant Multi-District Litigation. 1998. http://www.fsc.gov/BREIMLIT/md/1926.htm.
49. Friis S, Mellemkjaer L, McLaughlin JK, et al. “Connective tissue disease and other rheumatic conditions following breast implants in Denmark.” *Annals of Plastic Surgery*. 1997. https://www.ncbi.nlm.nih.gov/pubmed/11295960
50. Nyren O, Yin L, Josefsson S, et al. “Risk of connective tissue disease and related disorders among women with breast implants: A nation-wide retrospective cohort study in Sweden.” *British Medical Journal*. 1998. https://www.ncbi.nlm.nih.gov/pubmed/?term=Risk+of+connective+tissue+disease+and+related+disorders+among+women+with+breast+implants%3A+A+nation-wide+retrospective+cohort+study+in+Sweden
51. Balk E, Earley A, Raman G, and Avendano E. “Systematic Review of Selected Adverse Outcomes and Symptoms in Women with Silicone Gel Breast Implants.” Tufts Center for Clinical Evidence Synthesis. 2016. https://www.brown.edu/academics/public-health/research/evidence-synthesis-in-health/sites/brown.edu.academics.public-health.research.evidence-based-medicine/files/uploads/Silicone%20breast%20implants%20Report.pdf
52. Balk EM, Earley A, Avendano EA, Raman G. “Long-Term Health Outcomes in Women With Silicone Gel Breast Implants: A Systematic Review.” *Annals of Internal Medicine*. https://www.ncbi.nlm.nih.gov/pubmed/26550776
53. Burns, C.J., Laing, T.J., Gillespie, B.W., et al. “The Epidemiology of Scleroderma Among Women: Assessment of Risk from Exposure to Silicone and Silica.” *Journal of Rheumatology*. 1996. https://www.ncbi.nlm.nih.gov/pubmed/8923364

54. Edworthy S.M., Martin L., Barr S.G., et al. “A Clinical Study of the Relationship Between Silicone Breast Implants and Connective Tissue Disease.” *Journal of Rheumatology*. 1998. https://www.ncbi.nlm.nih.gov/pubmed/9489816
55. Gabriel S.E., O’Fallon W.M., Kurland L.T., et al. “Risks of Connective-Tissue Diseases and Other Disorders after Breast Implantation.” *New England Journal of Medicine*. 1994. https://www.ncbi.nlm.nih.gov/pubmed/8190133
56. Giltay E.J., Bernelot Moens H.J., Riley A.H., et al. “Silicone Breast Prostheses and Rheumatic Symptoms: a Retrospective Follow Up Study.” *Annals of the Rheumatic Diseases*. 1994. https://www.ncbi.nlm.nih.gov/pubmed/8154939
57. Park A.J., Black R.J., Sarhadi N.S., et al. “Silicone Gel-Filled Breast Implants and Connective Tissue Diseases.” *Plastic and Reconstructive Surgery*. 1998. https://www.ncbi.nlm.nih.gov/pubmed/9462756
58. Schusterman M.A., Kroll S.S., Reece G.P., et al. “Incidence of Autoimmune Disease in Patients after Breast Reconstruction with Silicone Gel Implants Versus Autogenous Tissue: A Preliminary Report.” *Annals of Plastic Surgery*. 1993. https://www.ncbi.nlm.nih.gov/pubmed/?term=Incidence+of+Autoimmune+Disease+in+Patients+after+Breast+Reconstruction+with+Silicone+Gel+Implants+Versus+Autogenous+Tissue%3A+A+Preliminary+Report.
59. Wells K.E., Cruse C.W., Baker J.L. Jr., et al. “The Health Status of Women Following Cosmetic Surgery.” *Plastic and Reconstructive Surgery*. 1994. https://www.ncbi.nlm.nih.gov/pubmed/8134482.
60. Hennekens C.H., Lee I.M., Cook N.R., et al. “Self-Reported Breast Implants and Connective-Tissue Diseases in Female Health Professionals. A retrospective cohort study.” *Journal of the American Medical Association.* 1996. https://www.ncbi.nlm.nih.gov/pubmed/8594243
61. Sanchez-Guerrero J., Colditz G.A., Karlson E.W., et al. “Silicone Breast Implants and the Risk of Connective-Tissue Diseases and Symptoms.” *New England Journal of Medicine*. 1995. https://www.ncbi.nlm.nih.gov/pubmed/7760867
62. Dugowson C.E., Daling J., Koepsell T.D., et al. “Silicone Breast Implants and Risk for Rheumatoid Arthritis.” *Arthritis and Rheumatism*. 1992. https://www.ncbi.nlm.nih.gov/pubmed/10493686
63. Englert H.J., Morris D. et al. “Scleroderma and Silicone Gel Prostheses – The Sydney Study Revisited.” *Australia and New Zealand Journal of Medicine*. 1996. https://www.ncbi.nlm.nih.gov/pubmed/?term=Scleroderma+and+Silicone+Gel+Prostheses+%E2%80%93+The+Sydney+Study+Revisited
64. Goldman J.A., Greenblatt J., Joines R., et al. “Breast Implants, Rheumatoid Arthritis, and Connective Tissue Diseases in a Clinical Practice.” *Journal of Clinical Epidemiology*. 1995. https://www.ncbi.nlm.nih.gov/pubmed/?term=Breast+Implants%2C+Rheumatoid+Arthritis%2C+and+Connective+Tissue+Diseases+in+a+Clinical+Practice
65. Hochberg M.C., Perlmutter D.L., Medsger T.A. Jr., et al. “Lack of Association Between Augmentation Mammoplasty and Systemic Sclerosis (Scleroderma).” *Arthritis and Rheumatism*. 1996. https://www.ncbi.nlm.nih.gov/pubmed/?term=Lack+of+Association+Between+Augmentation+Mammoplasty+and+Systemic+Sclerosis+(Scleroderma)

66. Lacey, J.V. Jr., Laing, T.J., Gillespie, B.W., et al. “Reply to Letter: Epidemiology of Scleroderma Among Women: Assessment of Risk from Exposure to Silicone and Silica.” *Journal of Rheumatology*. 1997.
67. Laing T.J., Gillespie B.W., Lacey J.V. Jr., et al. “The Association Between Silicone Exposure and Undifferentiated Connective Tissue Disease Among Women in Michigan and Ohio.” *Arthritis and Rheumatism*. 1996. https://www.ncbi.nlm.nih.gov/pubmed/?term=The+Association+Between+Silicone+Exposure+and+Undifferentiated+Connective+Tissue+Disease+Among+Women+in+Michigan+and+Ohio
68. Strom B.L., Reidenberg M.M., Freundlich B., et al. “Breast Silicone Implants and Risk of Systemic Lupus Erythematosus.” *Journal of Chemical Epidemiology*. 1994. https://www.ncbi.nlm.nih.gov/pubmed/7722556
69. Teel W.B. et al. “A Population-Based Case-Control Study of Risk Factors for Connective Tissue Diseases.” Ph.D. dissertation, Seattle: University of Washington. 1997. https://digital.lib.washington.edu/researchworks/handle/1773/10893
70. Wolfe F. et al. “Silicone Breast Implants and the Risk of Fibromyalgia and Rheumatoid Arthritis.” *Arthritis and Rheumatism*. 1995. https://www.ncbi.nlm.nih.gov/pubmed/10493686
71. Weisman MH, et al. “Connective-Tissue Disease Following Breast Augmentation: A Preliminary Test of the Human Adjuvant Disease Hypothesis.” *Plastic Reconstructive Surgery*. 1988. https://www.ncbi.nlm.nih.gov/pubmed/?term=Connective-Tissue+Disease+Following+Breast+Augmentation%3A+A+Preliminary+Test+of+the+Human+Adjuvant+Disease+Hypothesis
72. Williams HJ, et al. “Breast Implants in Patients with Differentiated and Undifferentiated Connective Tissue Disease.” *Arthritis and Rheumatology*. 1997. https://www.ncbi.nlm.nih.gov/pubmed/?term=Breast+Implants+in+Patients+with+Differentiated+and+Undifferentiated+Connective+Tissue+Disease
73. Berner I, Gaubitz M, Jackisch C, Pfleiderer B. “Comparative examination of complaints of patients with breast-cancer with and without silicone implants.” *European Journal of Obstetrics & Gynecology and Reproductive Biology*. 2002. https://www.ncbi.nlm.nih.gov/pubmed/12039092
74. Collado Delfa, J, Guinot-Madridejos, A, Martinez R, Darnell-Buisan P. “The prevalence of systemic autoimmune diseases in women reconstructed with silicone breast implants after mastectomy: A comparative study.” *Cirugía Plástica Ibero-Latinoamericana*.1998. https://www.researchgate.net/publication/295631759_The_Prevalence_of_systemic_autoimmune_diseases_in_women_reconstructed_with_silicone_breast_implants_after_mastectomy_A_comparative_study
75. Fryzek JP, Signorello LB, Hakelius L, Feltelius N, Ringberg A, Blot WJ. et al. “Self-reported symptoms among women after cosmetic breast implant and breast reduction surgery.” *Plastic Reconstructive Surgery*. 2001. https://www.ncbi.nlm.nih.gov/pubmed/11176625
76. Fryzek JP, Holmich L, McLaughlin JK, Lipworth L, Tarone RE, Henriksen T. et al. “A nationwide study of connective tissue disease and other rheumatic conditions among Danish women with long-term cosmetic breast implantation.” *Annals of Epidemiology*. 2007. https://www.ncbi.nlm.nih.gov/pubmed/?term=A+nationwide+study+of+connective+tissu

e+disease+and+other+rheumatic+conditions+among+Danish+women+with+long-term+cosmetic+breast+implantation
77. Kjøller K, Hölmich LR, Fryzek JP, Jacobsen PH, Friis S, McLaughlin JK. et al. "Self-reported musculoskeletal symptoms among Danish women with cosmetic breast implants." *Annals of Plastic Surgery*. 2004. https://www.ncbi.nlm.nih.gov/pubmed/?term=Self-reported+musculoskeletal+symptoms+among+Danish+women+with+cosmetic+breast+implants
78. Laing TJ, Schottenfeld D, Lacey JV Jr, Gillespie BW, Garabrant DH, Cooper BC. et al. "Potential risk factors for undifferentiated connective tissue disease among women: implanted medical devices." *American Journal of Epidemiology*. 2001. https://www.ncbi.nlm.nih.gov/pubmed/?term=Potential+risk+factors+for+undifferentiated+connective+tissue+disease+among+women%3A+implanted+medical+devices
79. Lee IM, Cook NR, Shadick NA, Pereira E, Buring JE. "Prospective cohort study of breast implants and the risk of connective-tissue diseases." *Internal Journals of Epidemiology*. 2011. https://www.ncbi.nlm.nih.gov/pubmed/20943932
80. FDA. "Summary of safety and effectiveness data—Mentor MemoryGel Silicone Gel-Filled Breast Implants." 2006. www.accessdata.fda.gov/cdrh_docs/pdf3/p030053b.pdf on 28 July 2015
81. Oberto E, Navissano M, et al. "Connecttiviti autoimmuni e protesi mammarie: studio controllato sulle nostre pazienti sottoposte a ricostrzione protesica post mastectomia." *Rivista Italiana di Chirurgia Plastica*. 1993.
82. Rubin JP, Landfair AS, Shestak K, Lane D, Valoski A, Chang Y. et al. "Health characteristics of postmenopausal women with breast implants." *Plastic Reconstructive Surgery*. 2010. https://www.ncbi.nlm.nih.gov/pubmed/20195108
83. Englert H, Joyner E, McGill N, Chambers P, Horner D, Hunt C. et al. "Women's health after plastic surgery." *Internal Medicine Journal.* 2001. https://www.ncbi.nlm.nih.gov/pubmed/11480483
84. "Summary Basis of Decision — Mentor MemoryGel Silicone Gel-Filled Breast Implants." Health Canada. https://hpr-rps.hres.ca/reg-content/summary-basis-decision-medical-device-detailOne.php?lang=en&linkID=SBD00412