Breast Implant Illness: A Way Forward

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Summary: The link between breast implants and systemic disease has been reported since the 1960s. Although many studies have looked at either supporting or refuting its existence, the issue still persists and has now been labeled "breast implant illness." The rise of patient advocacy and communication through social media has led to an increasing number of presentations to plastic surgeons. This article summarizes the history of breast implants and systemic disease, critically analyzes the literature (and any associated deficiencies), and suggests a way forward through systematic scientific study. (*Plast. Reconstr. Surg.* 143: 74S, 2019.)

When analyzing the imperfections of the current state of the art, we must not succumb to pseudo-science, or jump to unsupported conclusions. Better controlled sophisticated research is required but at the time of this writing certain properties of the implant are still immeasurable. Meanwhile, we must not substitute our intuition, or other fancies, for a true scientific evaluation of the facts.[1]

—Garry S. Brody, MD, 1977

The emergence of a group of women who present with a collection of systemic symptoms thought to be related to breast implants has been now collectively termed breast implant illness (BII). This review summarizes the background of implant-related systemic disease, the previous scientific evaluation in this area and proposed a way forward to begin to evaluate the many factors at play.

HUMAN ADJUVANT DISEASE

An adjuvant is a nonspecific stimulating agent of the immune system, which increases the response of either the cellular or humoral immune systems to the presence of an antigen. Known adjuvants are oil emulsifications (Freud's adjuvant, paraffin oil, processed petroleum jelly), minerals (silicon dioxide, beryllium, aluminum, calcium compounds), or bacterially derived (*Staphylococcus, Nocardia, Salmonella, Mycobacterium*).[2]

Adjuvant disease was first described in an animal model in 1954[3,4] and then by Pearson[5] in 1956 who induced arthritis by a single injection of dried heat killed microorganisms (mycobacteria, corynebacteria, streptococci) in a rat model. The observed condition had similarities to rheumatoid arthritis in humans.[6]

The term "Human Adjuvant Disease" describes potential autoimmune connective tissue disorders arising from injection of paraffin, processed petroleum products, and silicone-containing injections. It was first described as an association with augmentation mammaplasty in the Japanese literature in 1964[7] and then more broadly through Asia and Europe.

A potential link between injectable paraffin, polydimethylsiloxane (PDMS), and processed petroleum jelly and scleroderma was explored by Kumagai et al.[8] in 1979.

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Another report in 1982 of human adjuvant disease in association with breast implants was reported in a series of 3 Australian patients,[9] and this was followed by US cases the following year in 1983.[2,10] From the onset, it was felt that it was unlikely that silicone acted as a primary antigen but likely as an adjuvant and could be associated with subclinical infection as an antigen source.[2]

CHEMISTRY OF SILICON AND SILICONE

Silicon is the second most abundant element of earth; it exists in nature as crystalline silica composed of silicon dioxide or in silicates such as talc and asbestos.[11] Crystalline silica is known to be a powerful activator of the immune system and is associated with autoimmune disease associated with progressive systemic sclerosis in stonemasons and silicotic patients. Silicone does not exist in nature and is created from silica first by reducing it with methyl chloride and then it is hydroxylated forming PDMS (Fig. 1). Medical grade silicone generally exists in 1 of 3 chemical forms and differs from other forms of silicone due to the absence of antioxidants, accelerators (such as platinum), dyes, and plasticizers during synthesis.[12]

Silicone gel is lightly cross-linked with branching polymers of varying grades resulting in variation in the gel consistency. Elastomers/rubbers are heavily cross-linked polymers of PDMS joined by side branching in combination with a filler which is predominantly silicon dioxide and metallic oxides.[13] A range of other substances can be isolated in small quantities from cross-linked PDMS resulting from the manufacturing process. The presence, quantification, and significance of these impurities require further study.

TERMINOLOGY

Human adjuvant disease (1964), silicone-induced human adjuvant disease, autoimmune/inflammatory syndrome induced by adjuvants (2011),[14] and silicone implant incompatibility syndrome (2013)[15] are a few terms that have been used to link systemic disease to silicone and other adjuvants. In this age of social media, the term BII has been loosely applied to include this entity and sometimes more broadly to encompass all complications related to silicone breast implants. Dush[16] delineated the psychological factors surrounding breast implants and illness using a behavioral medicine model to assess the interaction of physical and psychological influences. Table 1 summarizes the range symptoms reported by women with BII.

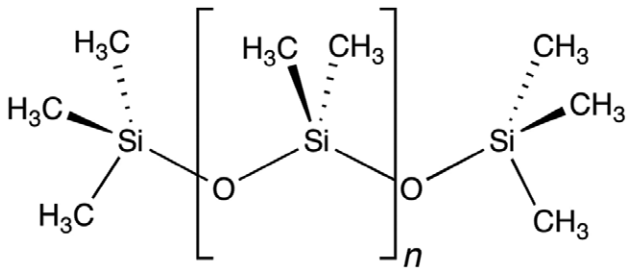

Fig. 1. Chemical structure of PDMS.

GENESIS OF THE FOOD AND DRUG ADMINISTRATION–MANDATED MORATORIUM

In the 1980s, following the report of cases of human adjuvant disease related to silicone gel implants, there were an abundance of case reports and small series followed by a rush of media attention.[2,9,10,17] The majority of patients had no abnormality in serological tests and nonspecific symptoms.[18] Attempts to look at association have been hampered by small sample size, insufficient duration of follow-up, variation in documentation, and diagnosis with some reports linking occurrence up to 20 years postimplantation.

CLINICAL STUDIES FOLLOWING THE MORATORIUM

In the 1990s, concerns built regarding a potential association between silicone and autoimmune or rheumatic diseases and the Food and Drug Administration (FDA) issued a moratorium that severely limited use of silicone breast implants. Selection bias continued to hamper efforts as recruitment of patients with implant-related illness focused on symptomatic patient referrals to rheumatology clinics[19,20] or utilized self-reporting of symptoms/illness.[13]

A prospective randomized study from the MD Anderson Cancer Center compared patients undergoing breast reconstruction randomly assigned to implant-based or autologous reconstruction. Comparison of the 2 groups showed no difference in the incidence of autoimmune-like disease but acknowledged short follow-up.[21] Peters et al.[13] (1994) analyzed the likelihood of finding a positive antinuclear antibody among 200 patients with breast implants, 100 age-matched controls, and 29 patients with known implant rupture. The assumption that if there was an association between silicone and human adjuvant disease, then a higher incidence would be

Table 1. Systemic Symptoms Associated With Silicone Breast Implants

Body System	Symptoms
Central nervous	Brain fog, memory loss, vertigo, headaches, migraines, tinnitus
Musculoskeletal	Muscle/joint pain, sore and aching joints, numbness/tingling in upper and lower limbs, fibromyalgia, neuralgia/burning pain, discoloration of hands/feet, slow muscle recovery after activity
Immune/inflammatory	Autoimmune disease – Raynauds, Hashimotos, RA, sclerodermal, SLE, Sjogrens, MCTD, MS, recurrent infections, toxic shock, fevers night sweats, slow healing and easy bruising, chronic fatigue, persistent infections, sudden food intolerance and allergies, tender lymph nodes
GI/genitourinary	Frequent urination, liver and kidney problems, reduced libido, UTI, reflux, gastritis, weight loss/gain, sudden dehydration, liver dysfunction, leaky gut, IBS, metallic tastes, choking, difficulty swallowing, pancreatitis, gallbladder disease
Integument	Hair loss, dry skin, dry hair, skin rashes
Psychological	Anxiety, depression, panic attacks, feeling of impending death
Cardiorespiratory	Shortness of breath, heart palpitations, arrhythmia, heart pain, cough, throat clearing

RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; MCTD, mixed connective tissue disease; MS, multiple sclerosis; UTI, urinary tract infection; IBS, irritable bowel syndrome.

observed in patient with rupture. They found the relative incidence in these groups as 26.5%, 28% and 17.2% with no statistical difference.[13] Gabriel et al.[22] (1994) reported a large population-based retrospective study examining the risk of a variety of connective tissue diseases and other disorders in women and found that there was no association found when they compared 749 women who received breast implants followed for a mean of 7.8 years compared with 1498 community controls followed for a mean of 8.3 years.[22] Sánchez-Guerrero et al.[23] analyzed data from the Nurses Health Study cohort of 87,501 women and also showed no association between silicone breast implants and connective tissue disease.

The importance of methodology was illustrated in a pair of connected articles in 1996 and 1999.[24,25] An initial retrospective cohort study of almost 400,000 female health professionals 45 years old or older from the Women's Health Study included 10,830 who self-reported having breast implants and 11,800 who reported some type of connective tissue disease using completed return-mail questionnaires. Of this group, 220 women with breast implants self-reported connective tissue disease and were then compared with matched controls from a random sample of 879 women without breast implants who also self-reported connective tissue disease. The rate of connective tissue disease confirmed according to medical records was only 22% of that self-reported in women with breast implants and 24% in those without implants.

LITIGATION IN THE ABSENCE OF EVIDENCE

The pursuit of scientific evidence was outstripped, however, by growth in litigation. There were approximately 400,000 women participating in a class action lawsuit against several manufacturers of breast implants and an additional 20–30,000 who elected to litigate individually. In 1996, US District Court Judges in Oregon and Alabama appointed independent scientific panels to review evidence to determine what constituted scientific knowledge derived from the scientific method.[26,27] In Oregon, the judge was able to rule that the plaintiffs "scientific" experts did not offer opinions on causation, were not based on tested hypotheses, and their analysis of experimental studies involved an extrapolation that represented a "leap of faith." A similar verdict was returned in Alabama.

LARGER POPULATION-BASED ANALYSES

In 1999, further extensive reviews that were performed by The Institute of Medicine (US) Committee on the Safety of Silicone Breast Implants[28] made a clear distinction between local complications and systemic health concerns concluding that there was no evidence of systemic health effects such as autoimmune disease. Tugwell et al.[29] (2001) reported on a further systematic review of published studies on the association between silicone breast implants and systemic connective tissue disorders that they felt the National Science Panel established by the US District Court did not fully assess. They also found no evidence to support an association between silicone breast implants and connective tissue diseases.

Janowsky et al.[30] (2000) published a meta-analysis after 3 prior meta-analyses had failed to demonstrate increased risk of connective tissue and autoimmune diseases after implantation of the silicone breast prostheses. Yet again, no evidence of association between breast implant and a significant increase in the summary-adjusted relative risk of individual connective tissue and autoimmune diseases could be demonstrated.[30]

REINTRODUCTION OF SILICONE IMPLANTS

In 2003, the U.S. FDA convened an advisory panel to consider specific aspects regarding breast augmentation and breast implant devices. This included methods of monitoring and managing symptoms or symptom complexes that may or may not be associated with connective tissue disease or other undefined symptom complexes.[31] When silicone breast implants were reintroduced to the American market in 2006, the FDA-stipulated manufacturers conduct large postapproval studies recognizing that there were limited data on rare events and long-term outcomes.

The immunology and rheumatology literature has brought much of the publications supporting an association between been silicone breast implants and systemic disease.[14,15,32,33] Watad et al.[33] (2018) recently published a cross-sectional study in attempt to overcome some of the weaknesses of previous studies. They looked at 24,651 silicone breast implant recipients and compared this to 98,604 age-matched controls from the electronic database of Maccabi Healthcare Services which included up to 20 years of data on 2 million members and representing 25% of the Israeli population. They believe that they demonstrated a relationship between silicone breast implants and autoimmune/rheumatic disease; evidence of a causal effect is lacking. Coroneos et al.[34] recently performed a retrospective cohort review of the prospectively collected data from the FDA large postapproval studies performed by Allergan Inc. (55,279 women including 39,069 with silicone breast implants) and Mentor Corp. which together represented almost 100,000 women. Their findings showed a higher rate of Sjogren's syndrome, scleroderma, rheumatoid arthritis, stillbirth, and melanoma when compared with normative data.

Unfortunately, this article is hampered by its limitations as has been outlined in an editorial in the same journal and a statement released by the FDA.[35,36] This is a secondary analysis of summarized data without access to the methodology or raw data. Each company collected data using a different protocol. For both studies, there was a significant loss to follow-up such that of 99,993 patients, data analysis was limited to <34,000, which introduces study bias and limits the interpretation of the study results. An increased incidence of rare systemic harms was noted in the Mentor data, which was patient reported, whereas the Allergan data that were physician-reported did not show this association. This unadjusted analysis tended to emphasize patient-reported data from 8,437 Mentor patients compared with 25,219 physician-reported Allergan patients. We have previously seen a <25% correlation between self-reported and medical diagnosis for connective tissue disease and autoimmune disease in women with and without implants.[24,25] In addition, there was insufficient control for confounding factors with no matched cohort design to calculate the standardized incidence ratios of the reported rare systemic harms. Nevertheless, the mistaken attempt to pool these data resulted in significant media attention and reignition of the issue of systemic breast implant–related illness. One of the difficulties in assessing the incidence of BII is a lack of correlation of the true incidence of these symptoms to the number of implants being inserted in a given population. This similar lack of an accurate denominator has hampered the risk calculation for breast implant–associated anaplastic large cell lymphoma (BIA-ALCL).[37] In spite of this, there are still patients who are not comfortable with their breast implants and present for the consideration of implant removal.

OUTCOMES FOLLOWING EXPLANTATION

There are, however, published data on outcomes following explantation. These outcomes give us some information on which to begin to structure our investigations on BII.

A Canadian study (1997) assessed 100 patients presenting for explantation during the silicone moratorium and compared them to 100 plastic surgery patients without exposure to breast implants.[38] They found that 42% of the capsules demonstrated colonization by bacteria; the positive rate of antinuclear antibodies was higher in the control group at 28% than in the explant group, which was 24%. They divided the group into 3. Group 1 did not meet diagnostic criteria for rheumatic or autoimmune disease and demonstrated a >80% improvement in physical symptoms and 93% improvement in psychological well being following explantation. Group 2 had a documented rheumatic disease but no autoimmune disease and tended to show a short window of improvement in symptoms all with recurrence at 6–12 months. Group 3 had a proven autoimmune disease, and these patients showed no improvement of physical symptoms or autoantibody levels and went on to have a clinical deterioration (Table 2). This stratification of BII should be considered especially as a means of studying progress following explantation.

Rohrich et al.[39] (2000) also assessed patients presenting for explantation and showed that there was statistically significant improvement in subjective health for patients who are distressed by their implants.

Interestingly, patients seemed content with the esthetic outcome following explantation with either no surgery, mastopexy, and/or conversion to autologous reconstruction for reconstructive patients.[40,41] The recent addition of fat grafting to the breast as a modality for soft-tissue augmentation presents a further tool in treatment of the explanted breast mound[42] with a valid safety record.[43]

Table 2. Proposed Stratification of BII Based on Preexisting Disease and Likely Outcome[44]

Type	Description	Prognosis
BII type A	No proven disease	Most likely will improve after explantation
BII type B	Abnormal markers but short of disease diagnosis	Short honeymoon but likely to have return of symptoms
BII type C	Proven autoimmune disease	Most likely will not improve after explantation

MODERN INFLUENCERS ON SELF-REPORTING

The growth of social media as a source of information for patients[44] and a platform for professional networking and research.[45] Patient support groups connect patients with similar concerns, offer information and emotional support,[46] allow them to share their experiences, outline their symptoms, review their medical encounters, share knowledge about their problems, and discuss best treatment strategies.[47] Anecdotally, the authors are seeing an increased referral of patients for this type of problem and yet this is precisely the type of data we need to move away from to pursue a scientific resolution.

A SUGGESTED PATH FORWARD

BII remains a challenging issue. However, the lack of robust epidemiologic evidence to support

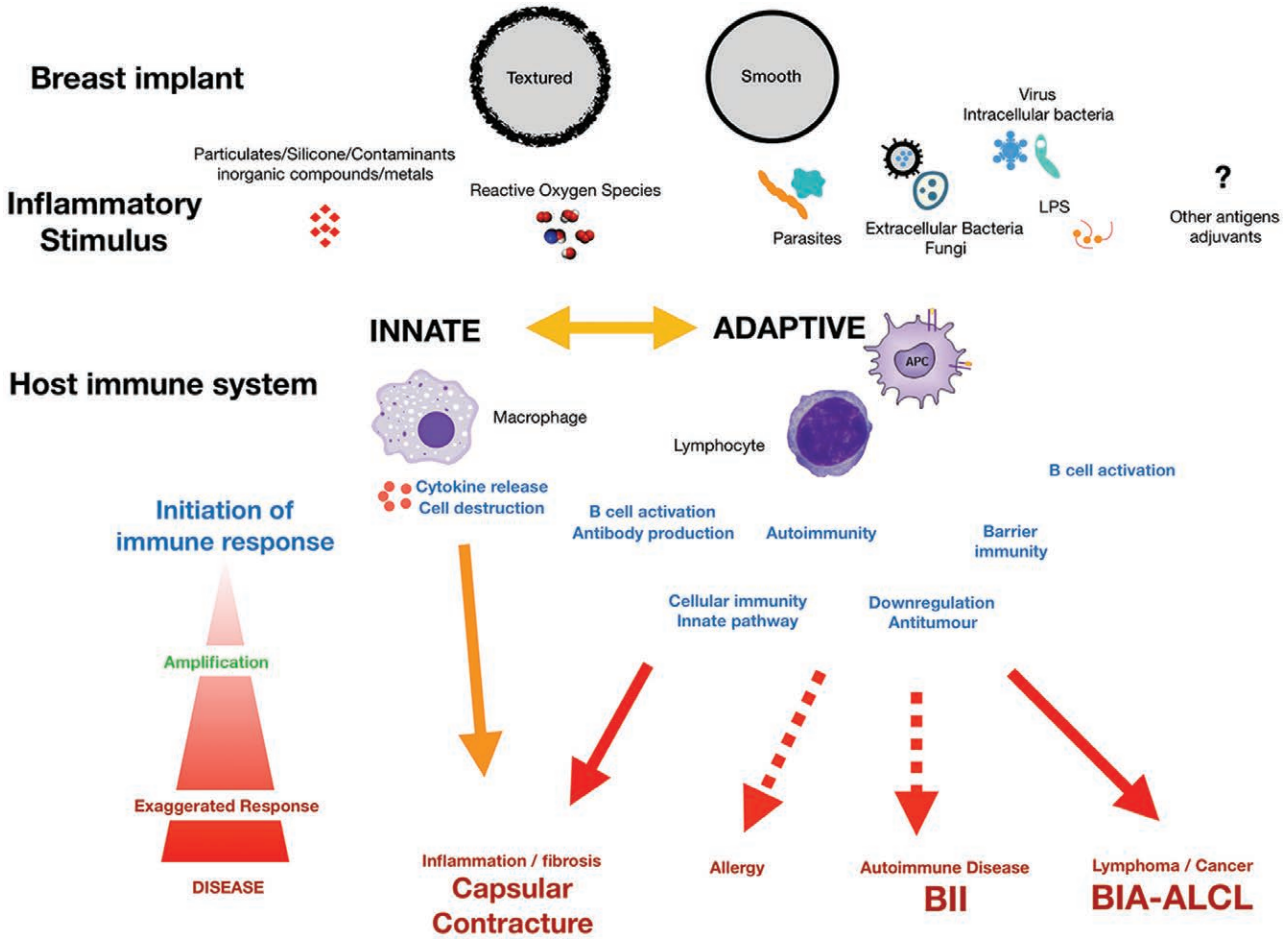

Fig. 2. Likely pathogenetic pathway for BII.

the association should not stop the pursuit of ongoing scientific evaluation. The timeline from emergence of a disease entity to characterization and identification of underlying pathogenesis can take decades and will require significant funding for both epidemiologic and laboratory investigations. The variability and broad range of symptoms, the lack of clear diagnostic criteria, the absence of long-term safety and efficacy data, and the need for better understanding of the interaction between host and implant cloud the picture. It is our responsibility to approach these patients as caregivers because a substantial number will be improved by surgical implant removal and capsulectomy. The task is to find out which patients benefit and why. The complex interaction of implant substrate, implant contents with the host immune system/genetics overlaid by bacterial antigens has been increasingly the focus of research into BIA-ALCL. Perhaps, these same parameters mix in the wrong combination for some patients and can lead to autoimmune disease and/or other associated systemic symptoms.

Figure 2 summarizes a likely pathway for implant-induced inflammation both via the innate and adaptive immune pathways to observed disease. It is interesting to note that inflammatory-driven exaggeration of the immune response can produce fibrosis, autoimmune disease, and lymphoma—all noted adverse outcomes following breast implant surgery.

A 2-pronged approach is suggested which is conditional on developing pathways for regular breast implant surveillance (Fig. 3). A new breast implant check clinic, commenced in Australia, is now scaling to 2 states and will provide an important low cost entry point for women with breast implant–related issues to be assessed both clinically and with imaging and/or pathology.[48] These clinics will serve to capture patient, surgical, implant, and outcome data. They will also serve to standardize work up for patients with potential BII. These will include wide ranging blood screening for autoimmune disease markers (Table 3) and also collect patient-reported outcome measure data with validated instruments such as the BREAST-Q[49] and modified BREAST-Q, as pertaining to cosmetic surgery. These patients will need to be followed up closely and for a period of ≥2 years to track their progress following explantation. The process of measuring the denominator, that is, number of implants deployed across a population over time will allow assessment of the risk and scale of BII. Sales data from all manufacturers have been used with success to estimate relative risk in BIA-ALCL.[50]

The true denominator, however, will be derived by the establishment and maturing of

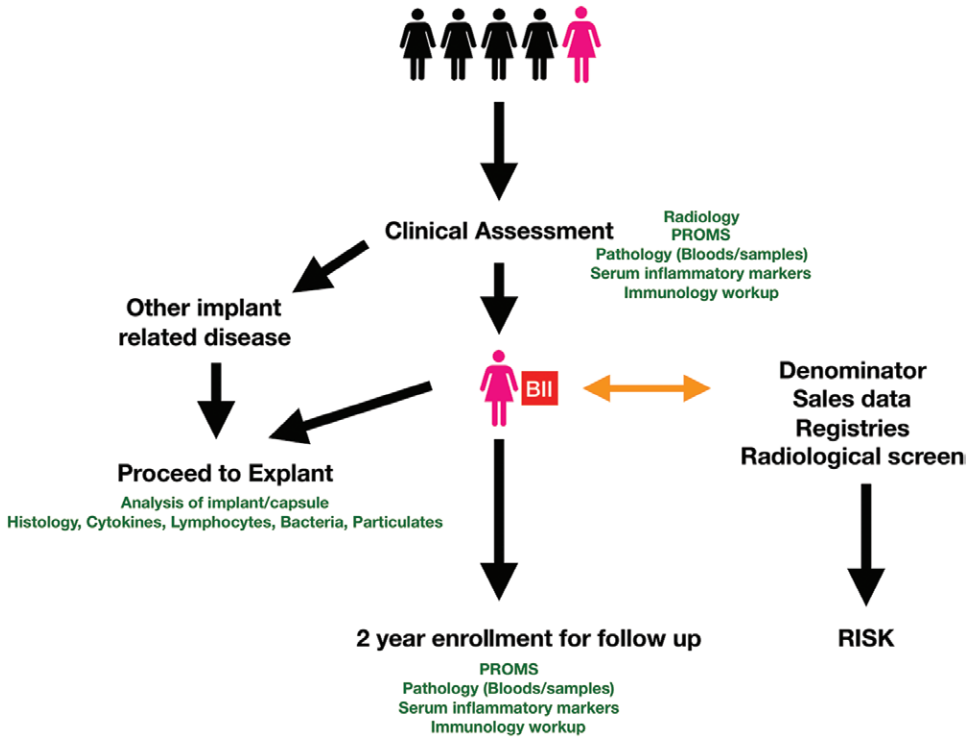

Fig. 3. Proposed study plan.

Table 3. Suggested Blood Work Up for Suspected BII

Full blood count
Urea electrolytes creatinine
Liver function tests
Thyroid function
CRP ESR
Serum IgG, IgM
Iron, ferritin
Autoimmune disease markers

Antinuclear antibody, antineutrophil cytoplasmic antibody, anti-double strand DNA, anti-Sjogren's syndrome A, anti-Sjogren's syndrome B, rheumatoid factor, anti-ribonucleic acid protein, Anti Sm, antiscleroderma antibodies, anti-TTG. CRP, C reactive protein; ESR, erythrocyte sedimentation rate; TTG, tissue transglutaminase.

national breast device registries.[51] International collaboration will also allow harmonizing and pooling of these data to generate overall risk for many breast-related complications.[52]

The second part of this approach is to closely examine the implant, capsule, and peri-implant tissues to delineate the presence of pro-inflammatory substances and their subsequent effect on local tissues. The detection and characterization of the microbiome on these implants and capsules will also be an important strategy to look for differences in measurable parameters between patients with BII and explantation for other indications, including capsular contracture, size change, intra-/extracapsular rupture, and BIA-ALCL. These patients will also need genetic sequencing to look for patterns of gene mutations and HLA type that predispose to the development of autoimmune and other systemic disease. The analysis of various implant/patient and peri-implant parameters may also provide clues and patterns as to the natural history, pathogenesis, and outcome of patients with BII. To this, we need to also consider toxicology around measuring inorganic compounds, particulates, and other implant-related substances that may precipitate activation of the immune system. Although the presence of these compounds may trigger overall activation of inflammation, the link between this and generation of immune-related disease will need to be further studied and proven. Figure 2 outlines the proposed study protocol.

CONCLUSIONS

The relationship between breast implants and systemic disease, including autoimmune disease, has been postulated, studied, and claimed since 1964, but the debate continues even today. A systematic, prospective evaluation of breast implant outcomes and study of samples from patients with BII, correlating their preoperative symptoms and morbidity to measurable postexplantation improvement is required. A way forward will require a collaborative and open approach across a range of organizations and borders.

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