# Serum CD30 and its Relationship to Breast Implant Illness

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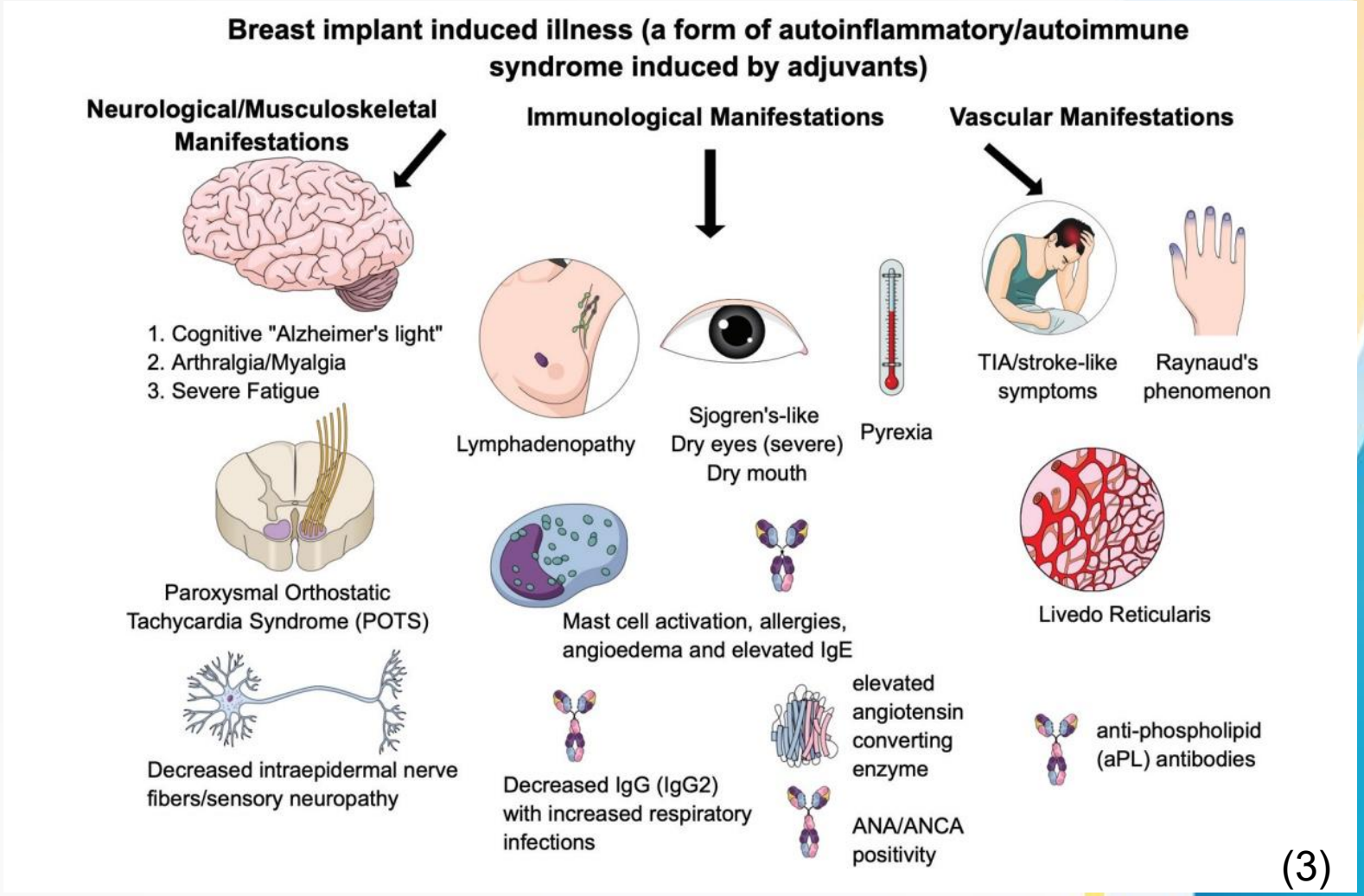
# Breast Implant Illness (BII)

- a term used to describe a constellation of systemic symptoms thought to be caused by breast implants [(1)]
- symptoms appear at fluctuating times after implantation surgery and range in severity [(1)]
- include but are not limited to: [(3)]
  - Fatigue
  - Anxiety
  - Headaches
  - Dizziness
  - brain fog
  - chronic pain
  - peripheral nervous system dysfunction
  - vascular dysfunction



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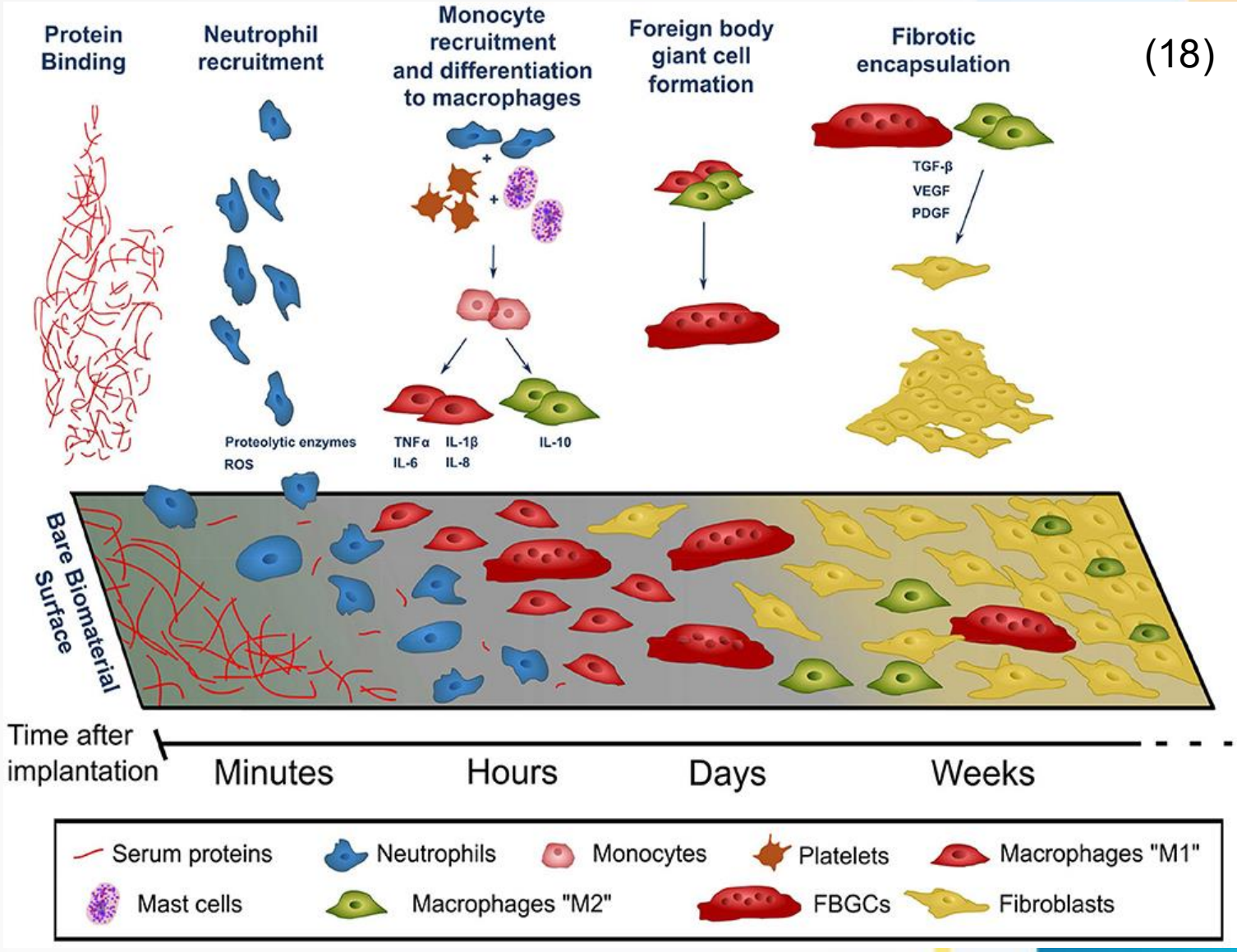
# What the literature shows:

- FDA database 2002 to 2020 = the most frequent patient-reported symptoms were fatigue, joint pain (arthralgia), hair loss, and/or a hypersensitivity/rash [6]
- In Canada, Edworthy reported = (study of 1576 Canadian patients who underwent breast augmentation)
  - systemic symptoms such as cognitive impairment and myalgia's were significantly more frequent in comparison to patients who underwent other cosmetic surgeries [8]
- US FDA study (2019) = followed nearly 100,000 women with implants = found these women were more likely to be diagnosed with an autoimmune disease after getting breast implants
  - **eight times** more likely to develop Sjögren syndrome.
  - **six times** more likely to get rheumatoid arthritis
  - **seven times** more likely to develop scleroderma [9]
- However, BII remains a diagnosis of exclusion due to:[5]
  - Inconsistencies and biases amongst studies
  - no diagnostic testing available for BII
  - no known pathophysiologic explanation for why some women get BII and others do not
- As of now experts think it is the body having an uncontrolled immune reaction in response to the implants, the potential release of substances from the implants and/or the presence of biofilm. [4]

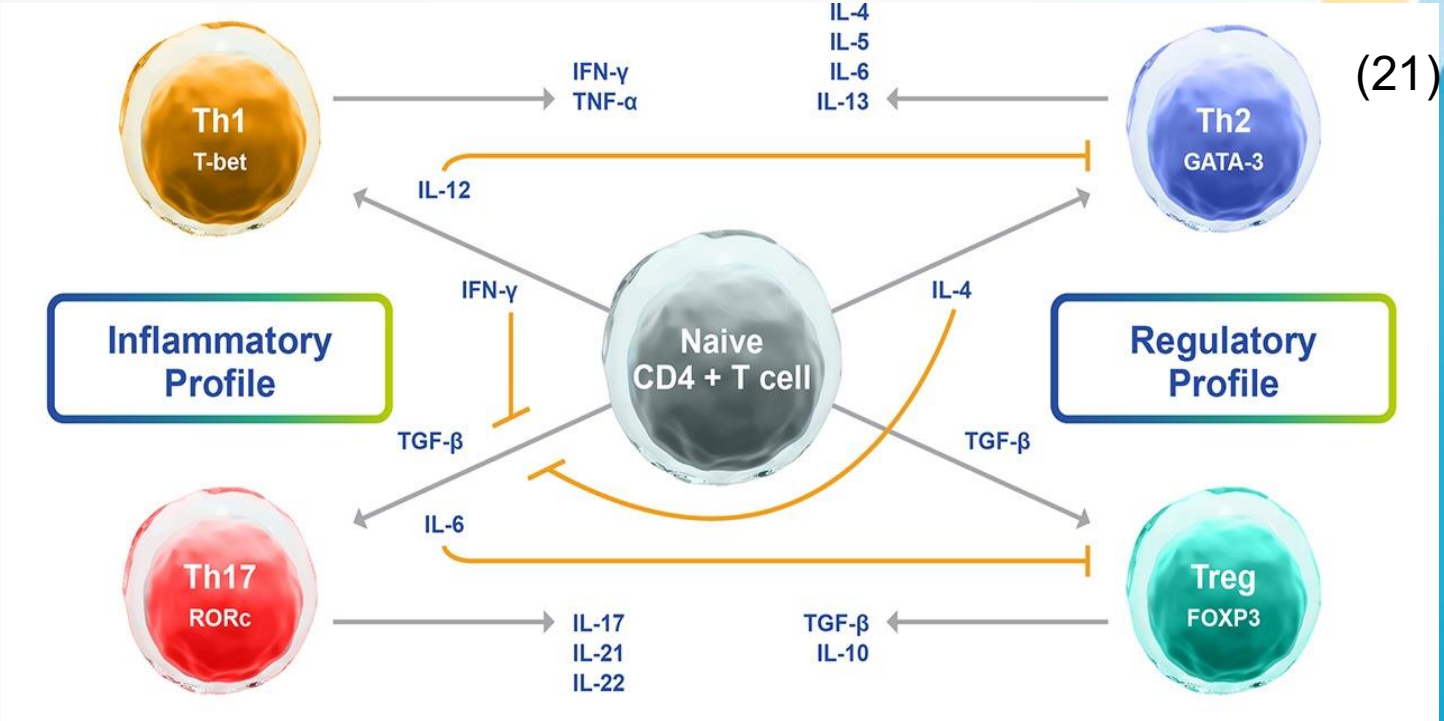
# Inflammatory Process

- Acute inflammatory process
- Chronic inflammatory process
- Foreign body response = because the material is not broken down
  - macrophages join together into foreign body giant cells to try to break down the biomaterial
  - and when that doesn't work, the remaining macrophages are supposed to differentiate into their M2 anti-inflammatory phenotypes and signal for fibroblasts that will come in and create a fibrous capsule = wall off the "invader"[12]
- Multiple studies show that the macrophages and fibroblasts are the most significantly present cell types in the frontier layer of the fibrous capsule, regardless of the age of the implant, followed by CD4+ T cells. [13] [14] [15] [16] [17]



- T cells predominantly produced the following cytokines: interleukin-17, interleukin-6, interleukin-8, transforming growth factor-β1, and interferon-γ = suggesting a TH1/TH17–weighted local immune response [17][19]
- Th1 and Th17 are both CD4+ T cell subsets = play crucial roles in the immune system, but with different focuses:
  - Th1 = help the body fight infections; produce cytokines like interferon gamma and interleukin 2; implicated in certain autoimmune diseases such as MS and type 1 DM
  - Th17 = involved in the immune response against extracellular pathogens; produce cytokines like interleukin 17 and interleukin 22 which recruit neutrophils and promote inflammation; implicated in various autoimmune and inflammatory diseases such as psoriasis, rheumatoid arthritis, IBS, and asthma. [20]

- Th1 and Th17 responses can sometimes work against each other = an overactive Th1 response can suppress Th17, and vice versa. [20]
- The balance between the two is crucial for maintaining a healthy immune system and preventing excessive inflammation or autoimmune disease. [20]



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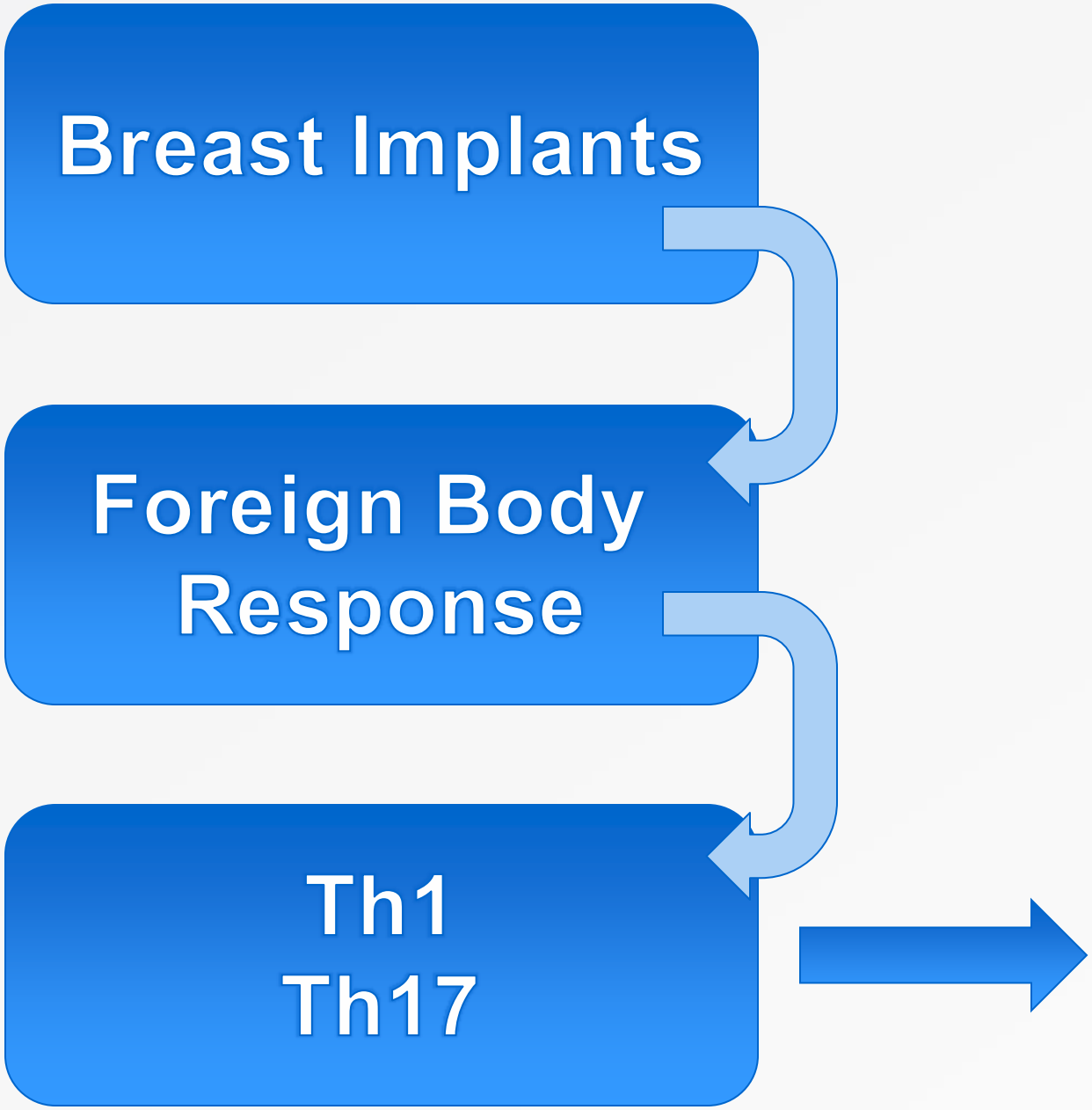
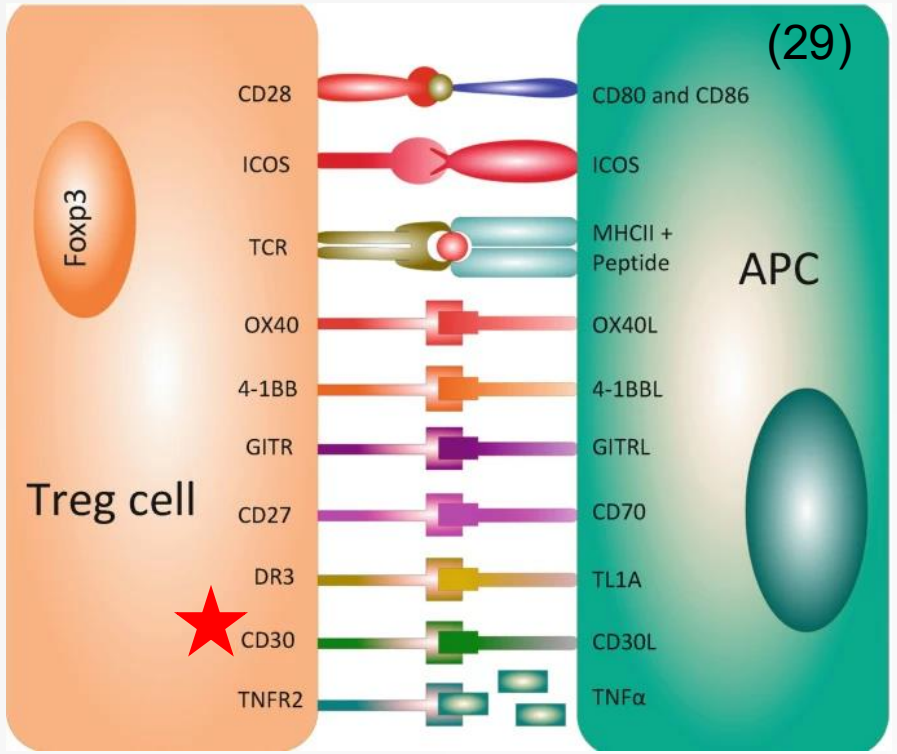
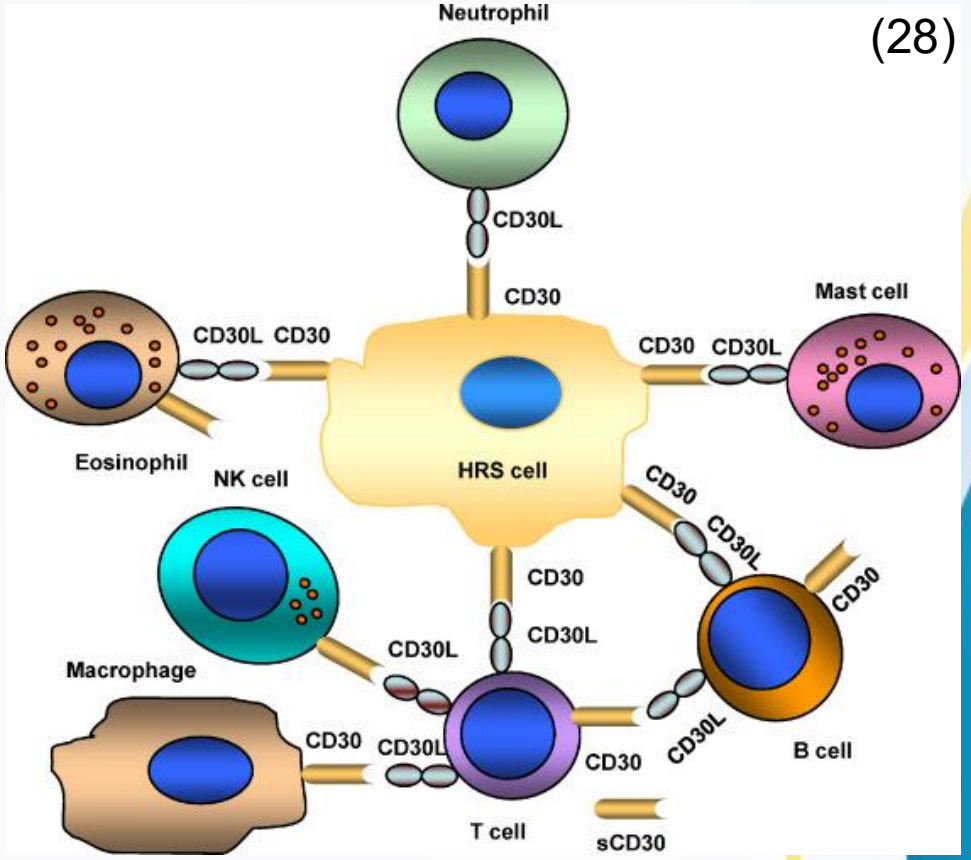



- CD30L/CD30 signaling is involved in Th1 cell response and associated diseases, such as diabetes. (23)
- CD30L/CD30 signaling plays a critical role in Th17 cell differentiation. (23)
- CD30L/CD30 signaling plays a role in the regulatory T cell response in a graft-versus-host disease model (23)
- Thus, CD30L/CD30 appears to be important for amplification and/or activation of any CD4+ T cell subsets. (23)

# CD30/CD30L

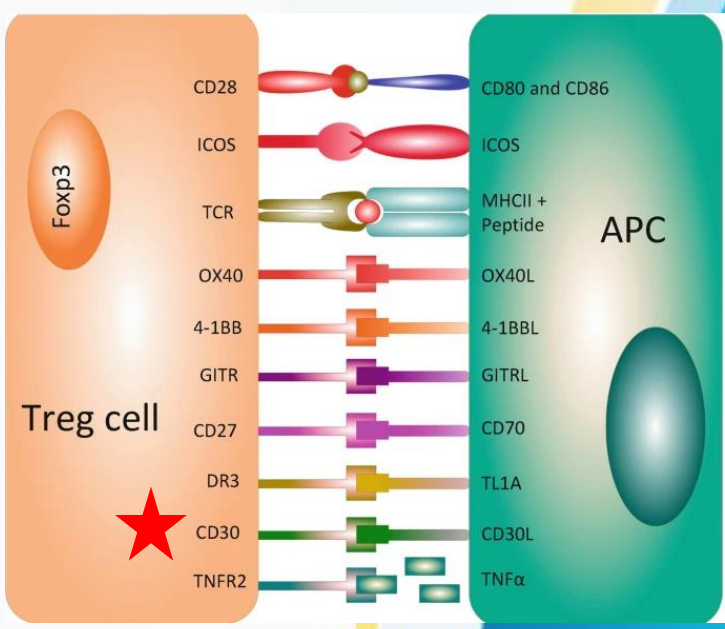
- CD30 = receptor found on B and T lymphocytes and NK cells; some expression reported for activated monocytes and eosinophils [28]
- CD30 signaling pathway = activation of signals (MAP kinases and NF-κB) = capable of promoting cell proliferation and survival or anti-proliferative responses and cell death [28]
  - depending on the cell types communicating and the co-stimulatory signals involved



# Serum CD30

- Circulating serum CD30 = A product of proteolytic cleavage (sCD30); released into the bloodstream as a soluble protein - can be measured [22,26,28]
    - Cleaved by metalloprotease
    - Binds to CD30L = blocks cell to cell interaction/signaling
- Elevated concentrations of circulating serum CD30 have been reported to correlate with autoimmune disease activity in patients with:
    - SLE
    - Sjogren's
    - Granulomatosis with polyangiitis
    - Rheumatoid arthritis
    - Grave's disease
    - Hashimoto's thyroiditis [22] [23] [24] [25] [26] [27]
- Researchers propose that serum CD30 may serve as a diagnostic marker in various autoimmune disorders [22, 23, 24, 25, 26, 27, 28]
- Purpose of our study: determine relationship between BII and serum CD30



# Methods

*Participants and Setting*

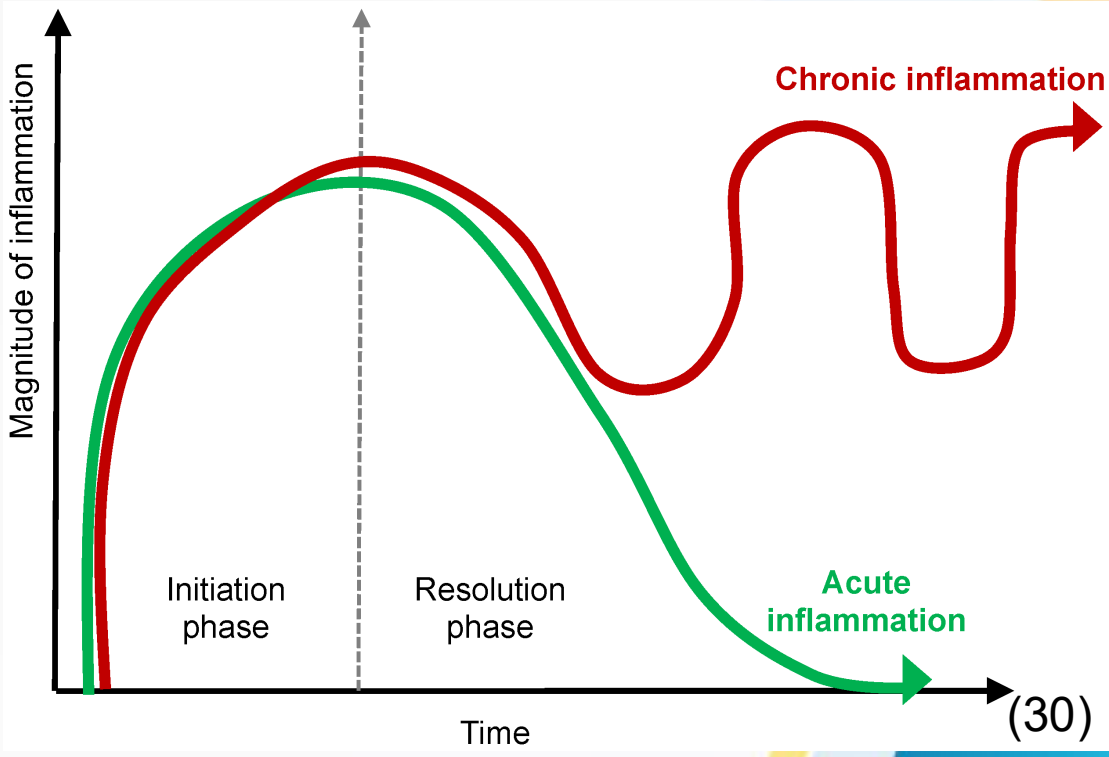
- Thirteen patients total were followed from their BII consultation to 3 months postoperatively after they had their implants removed via en-bloc/total capsulectomy explantation surgery at Pryor Health.
- Patients with silicone implants or saline implants were included.
- Patients with a current diagnosis of an autoimmune disease and/or were currently pregnant were excluded from the study.

*Procedure*

- Serum CD30 samples were collected at both time points as well as symptom severity questionnaires completed at both time points.

*Data Analysis*

- Preoperative and postoperative serum CD30 samples were analyzed using ELISA protocol.
- Preoperative and postoperative symptom severity was examined using paired t-test analysis and a bonferroni correction due to the high number of symptoms analyzed (in order to reduce likelihood of false positives).



# Signs and Symptoms of Breast Implant Illness

Pre-op ☐ Post-op ☐

Please indicate what symptoms you are experiencing by checking the associated severity box according to your illness experience. If you are not experiencing a symptom, you may leave it blank.

| Symptom | Mild | Mod | Severe | Symptom | Mild | Mod | Severe | Symptom | Mild | Mod | Severe |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Fatigue or chronic Fatigue | | | | Tingling or numbness in the arms and legs | | | | Cold and discolored hands and feet | | | |
| Cognitive dysfunction (brain fog, difficulty concentrating, word retrieval, memory loss) | | | | Estrogen/progesterone imbalance, diminishing hormones or early menopause | | | | Swollen and tender lymph nodes in the breast area, underarms, throat, neck, or groin | | | |
| Muscle aches, pain, and weakness | | | | Burning pain around the chest wall or breasts | | | | Chronic neck and back pain | | | |
| Joint pain and soreness | | | | Skin rashes | | | | Photo-sensitivity | | | |
| Hair loss | | | | Frequent urination | | | | Premature aging | | | |
| Dry skin, eyes, mouth, hair | | | | Edema (swelling) around eyes | | | | Nail changes (cracking, splitting, slow growth) | | | |
| Weight gain or loss | | | | Muscle twitching | | | | Foul body odor | | | |
| Easy bruising and slow wound healing | | | | Fevers | | | | Hypo/hyper thyroid symptoms | | | |
| Decline in vision or vision disturbances | | | | Dehydration | | | | Hypo/hyper adrenal symptoms | | | |
| Low libido | | | | Insomnia | | | | Depression | | | |
| Vertigo | | | | Temperature Intolerance | | | | Suicidal thoughts | | | |
| Night sweats | | | | Chronic Inflammation | | | | Anxiety, panic attacks | | | |

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11/3/23 through 11/2/24

| Symptom | Mild | Mod | Severe | Symptom | Mild | Mod | Severe | Symptom | Mild | Mod | Severe |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Mood swings, emotional instability | | | | Slow muscle recovery after activity | | | | Metallic taste in the mouth | | | |
| Feeling like you are dying | | | | Ringing in the ears | | | | Oral thrush (white tongue) | | | |
| Liver and kidney dysfunction | | | | Gastrointenstinal and digestive issues | | | | Smell or chemical sensitivities | | | |
| Sudden food intolerances and allergies | | | | Throat clearing, cough, difficult swallowing, choking feeling | | | | Recurring sinus, yeast, and UTI infections | | | |
| Headaches, dizziness, and migraines | | | | Symptoms or diagnosis of lyme disease | | | | Symptoms or diagnosis of fibromyalgia | | | |
| Shortness of breath or heart palpitations / difficulty breathing / chest pain | | | | New or persistent infections - viral, bacterial, and/or fungal (candida) | | | | Skin freckling, pigmentation changes (darkening or white spots), or an increase in papules (flesh colored raised bumps) | | | |

Patient ID:_____

Date:_____

# Results

- Ages ranged from 29 to 76 years old

- Average length of having their implants before presenting for their BII consultation was 16 years with a range of 3 to 36 years, and average onset of symptoms after receiving their implants was 4.56 years with a range of 30 days to 12 years.

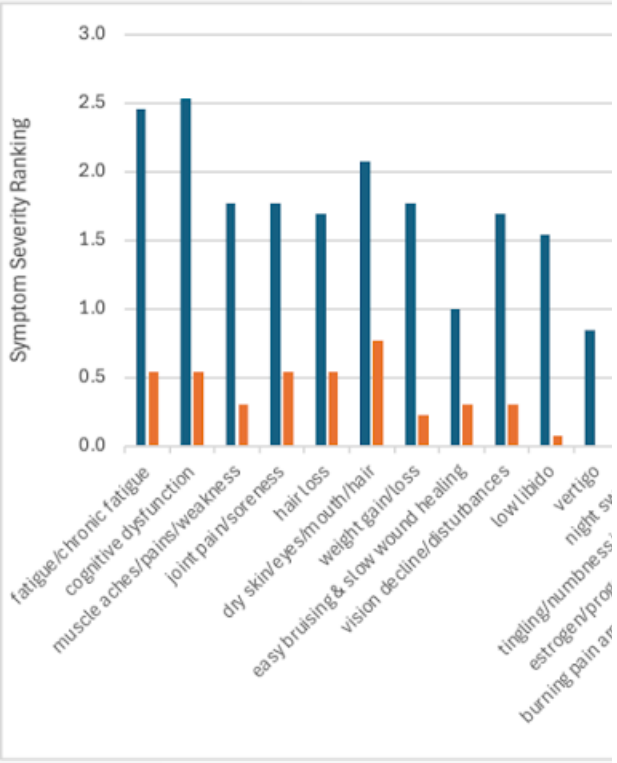
- All expressed concerns that their symptoms had worsened overtime and were requesting for their breast implants to be removed.

- Out of 54 symptoms assessed using the symptom questionnaire:
  - preoperatively, patients had **31.6** symptoms.
  - These symptoms were ranked as mild, moderate, severe with corresponding scores of 1, 2, and 3, respectively. The average symptom severity ranking preoperatively was **1.94**.

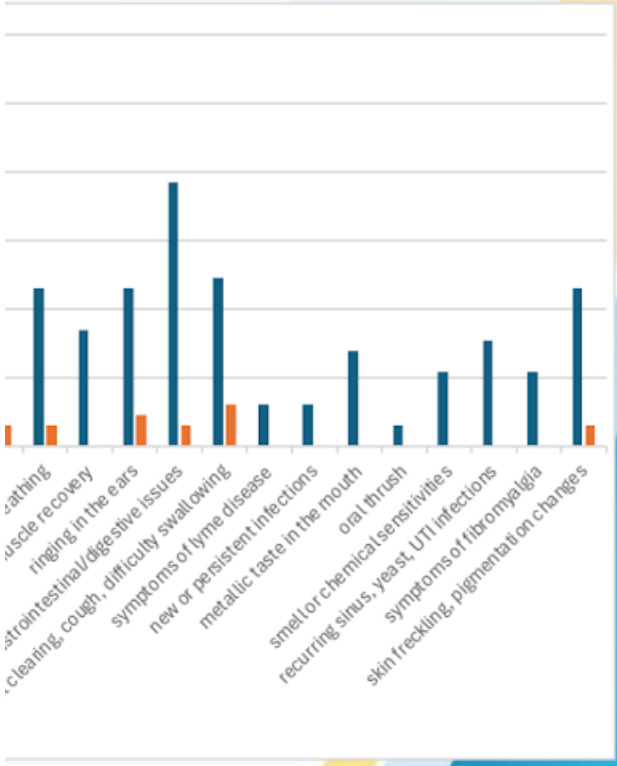
- 3-months after en-bloc/total capsulectomy implant explantation surgery:

  -The overall report of symptoms significantly **decreased** with the average number of symptoms reported being only **5.6** (p=.0000864).

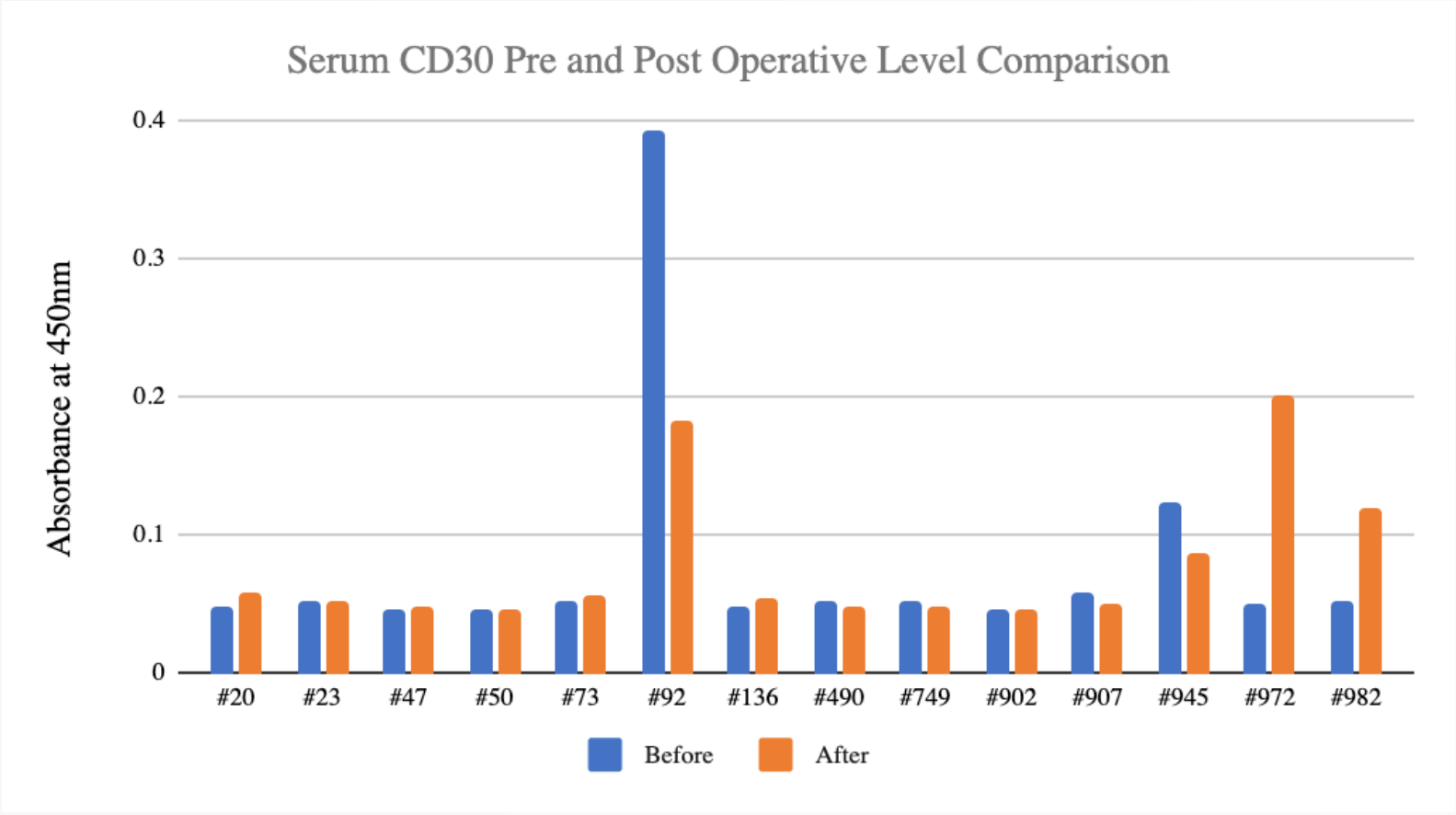
  -Overall symptom severity significantly **decreased** as well with the average severity ranking of symptoms postoperatively being 0.995 (p=.00011).




| SYMPTOM | P-VALUE | MEAN DIFFERENCE (SD) |
|---|---|---|
| Fatigue or chronic fatigue | <.0001 | 1.92 (0.95) |
| Cognitive dysfunction (brain fog, difficulties concentrating, word retrieval, memory loss) | <.0001 | 2.00 (0.82) |
| Muscle aches, pains, weakness | 0.0001 | 1.46 (0.97) |
| Hair loss | 0.0002 | 1.15 (0.80) |
| Decline in vision or vision disturbances | 0.0008 | 1.38 (1.12) |
| Low libido | 0.0005 | 1.46 (1.13) |
| Night sweats | 0.0009 | 1.46 (1.20) |
| Frequent urination | 0.0002 | 1.54 (1.05) |
| Cold and discolored hands and feet | 0.0008 | 1.00 (0.82) |
| Anxiety, panic attacks | 0.0001 | 1.69 (1.11) |
| Mood swings, emotional instability | 0.0009 | 1.23 (1.01) |
| Headaches, dizziness, migraines | 0.0001 | 1.77 (1.17) |
| gastrointestinal/digestive issues | 0.0001 | 1.77 (1.17) |



- CD30 levels were analyzed similarly by comparing preoperative and postoperative levels using ELISA. Standard curves were utilized to ensure ELISA protocol accuracy. Overall, no significant difference was found after en-bloc/total capsulectomy explantation surgery (p=.9402).



# Discussion

- Our research further demonstrated the correlation between BII symptom improvement and implant removal via en-bloc/total capsulectomy explantation surgery.
  - We did the same surgery with the same surgeon to keep the study controlled.
  - Recent study in 2022 showed no statistical difference in the reduction of symptoms based on the type of capsulectomy performed (intact total, total, or partial). All showed similar symptom improvement. [31]

- Our study examined patients with both silicone and saline implants due to the prevalence of BII in patients with both implant types.
  - In a 10 year review of the U.S. Food and Drug Administration's Manufacturer and User Facility Device Experience (MAUDE) database on BII referenced reports where 60.6 percent of patients reporting had silicone implants and 39.4 percent had saline implants [2]
  - Therefore, we felt it was important to include both implant types to see if this would change data results. To our surprise, it did not. In fact, an overall significant decrease in the number of symptoms remained regardless of implant type (p=.0000864).

- When looking at symptoms independently in relation to their severity scores, there was a significant improvement seen in 13 of the 54 symptoms analyzed (24%).
  - Many non-significant symptoms were rare in our study participants to begin with, which most likely contributed to the lack of significant difference by statistical analysis.
  - Except, depression and ringing in ears = both of those symptoms were highly reported both preoperatively and postoperatively meaning that BII is most likely not causing these symptoms.

- It is arguable that many of these symptoms can be attributed to other diagnoses, especially autoimmune diseases with known criteria. However, our study excluded patients with a known diagnosis of an autoimmune disease at the time of study entry whereas many other studies in the literature do not thus increasing the likelihood that the change in symptom severity score was due to implant removal alone.

# Limitations

- We had a smaller sample size than expected due to loss to follow up. While 22 patients signed consent forms, only 13 completed all required study visits and surveys. Many were lost to follow up due to practical considerations including the need to come in for their 3 month post operative appointment in person as well as travel to another facility to get the blood work done that was not available at Pryor Health.

- All symptom severity scores were self-reported. Given that our patients specifially sought out Pryor Health to explore explantation options they may be more likely to report more severe symptoms than women with BII not seeking implant removal.

- Lastly, the questionnaire used amongst BII clinics that we adapted for this research remains very broad with some symptoms grouped together. A more precise break-down of symptoms with possible objective measures would increase the validity of studies.

# Conclusion

- BII remains a diagnosis of exclusion with no validated diagnostic marker or validated pathophysiologic explanation for the symptoms of BII. More research is needed to understand the role of both serum CD30 and signaling between CD30/CD30L in this patient population.

- Despite this, our study's findings suggest implant removal may decrease self-reported symptoms - specifically physical, emotional, GI, and cognitive symptoms – validates women's reports of symptoms experienced with their breast implants.

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# Questions?

# Enbloc removal procedure

- BII is not completely accepted as an official medical diagnosis. It is poorly understood and there are limited studies because it is a unique condition which is why there's still a fair amount of uncertainty about the best course of action along with the implant removal.
- Despite this, severe physical and psychological symptoms have been described under the umbrella of breast implant illness and have led to a patient cohort that is well versed (often via the internet and social media) with specific treatment goals = en-bloc capsulectomy (10)
- the entire scar tissue capsule and the implant are removed in one piece (10)
- According to some studies there is no statistical difference in the reduction of symptoms based on the type of capsulectomy; intact total, total, or partial all showed similar symptom improvement while some others highlight that a Total Intact Capsulectomy should be performed (11)

- all breast implant–associated anaplastic large-cell lymphoma (BIA-ALCL) cases to date are linked to textured implants (or implants of unknown surface),
  - Clemens MW, Jacobsen ED, Horwitz SM. 2019 NCCN consensus guidelines on the diagnosis and treatment of breast implant-associated anaplastic large cell lymphoma (BIA-ALCL). Aesthet Surg J. 2019;39(Suppl_1):S3-S13.
- BIA-ALCL is a rare type of non-Hodgkin lymphoma that develops around the fibrous capsule surrounding a breast implant. It's mostly associated with textured implants and usually presents as swelling, pain, or a fluid collection around the implant. The mainstay of treatment for BIA-ALCL is implant removal with En-bloc Capsulectomy
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