P070004 - Sientra OPUS® Silicone Gel Filled Breast Implants

Briefing Document

for

General and Plastic Surgery Devices Panel Meeting

March 25-26, 2019

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EXECUTIVE SUMMARY

This Briefing Document was prepared to provide the U.S. Food and Drug Administration General and Plastic Surgery Devices Panel of the Medical Devices Advisory Committee with information regarding the long-term safety and effectiveness of Sientra's OPUS® Silicone Gel Breast Implants (the "Implants" or "Breast Implants"), emphasize Sientra's ongoing commitment to patient safety, and provide an industry perspective regarding the seven specific topics posed by the Agency for the March 25 and 26 Panel Meeting.

Sientra obtained PMA approval of its Breast Implants in March 2012 and committed to completing six postapproval studies. Four of those study requirements have been satisfied and two are still ongoing (the U.S.-PAS 10-year postapproval study with over 5,000 patients enrolled, and participation in the National Breast Implant Registry).

THEN AND NOW

- Although not a condition of PMA approval, Sientra committed to providing its Breast Implants exclusively to board-certified/board-eligible plastic surgeons and maintains that level of commitment to this day. Sientra believes that putting its products in the hands of only the most skilled surgeons leads to better patient outcomes.
- Sientra's completed 10-year Postapproval Cohort Study (PACS) - The 10-year results of Sientra's PACS confirm that its Implants continue to be safe and effective for their intended use. Importantly, the majority of patients continue to report favorable satisfaction with their Breast Implants throughout the 10-year follow-up time period.
- Based on the safety and performance of its Breast Implants, Sientra offers its Sientra Platinum20™ Warranty, the most complete warranty program in the industry, providing 20 years of coverage.
- Sientra remains at the forefront and steadfast in its dedication to furthering the body of scientific evidence regarding breast implantation surgery, driving transparency of evidence-based outcomes, advancing awareness of surgical best-practices by hosting educational activities and training for board-certified plastic surgeons, as well as, supporting peer-reviewed scientific publications. Communication is a critical part of the medical device industry, and Sientra wants to ensure that board-certified plastic surgeons have a wealth of data to help their patients make informed choices.
- Sientra offers numerous resources to help educate patients about breast implants and breast implant surgery, but also believes that full commitment to patients and their health is about more than offering clinically-proven safe and effective products and services. An example of this is the Sientra Full Circle™, a first-of-its-kind charitable program that supports nonprofits in the breast cancer community committed to making a meaningful difference in the lives of those affected by breast cancer. Sientra donates a portion of the revenue from every OPUS breast tissue expander to its Full Circle fund

LOOKING AHEAD

Below is a summary of Sientra's perspectives on the seven Panel Meeting topics, including relevant clinical data:

1. **Breast implant associated anaplastic large cell lymphoma (BIA-ALCL)**

   Sientra takes BIA-ALCL very seriously and continues to support medical research, education and all FDA initiatives to better understand BIA-ALCL and to provide women with the highest quality and safest implant options. Sientra's physician and patient labeling include the most-up-to-date information regarding BIA-ALCL. As an industry leader on this topic, Sientra has sponsored and produced several professional outreach and peer-reviewed publications, including Sientra's *Surgical Best Practices: 14-Point Plan*[1], authored by expert BIA-ALCL researchers. This resource educates surgeons on best surgical practices that reduce bacteria-related breast complications. Another feature of this publication includes BIA-ALCL Frequently Asked Questions.

   Sientra also supported and distributed the joint BIA-ALCL education statement prepared by The American Society of Plastic Surgeons (ASPS) and The American Society for Aesthetic Plastic Surgery (ASAPS), with the cooperation of The International Society of Plastic Surgery (ISAPS), to update plastic surgeons on the known risks, symptoms, diagnosis and treatment of BIA-ALCL with a treatment algorithm flowchart.

   A total of four cases of BIA-ALCL have been reported for Sientra Implants. However, two of the four patients each had previous tissue expanders and breast implants from another manufacturer prior to receiving Sientra implants. It is important to note that ALCL is not just specific to breast implants; there are numerous cases of ALCL reported with the use of a wide range of medical devices (e.g., tibial implants, dental implants, gluteal implants, chemotherapy ports, hip prostheses, and gastric bands). Multiple medical and scientific literature reports of ALCL[2],[3],[4],[5],[6],[7],[8] underscore the fact that while BIA-ALCL is an important consideration in breast implant surgery, ALCL also occurs

[1]Deva, A. K., Adams, W. P., (2017) Surgical Best Practices: 14-Point Plan, Sientra, Inc. Educational Resource, Ext-0029 R2

[2]Tibial Implant ALCL, Palraj, B., Paturi, A., Stone, R. G., Alvarez, H., Sebenik, M., Perez, M. T., & Bush, L. M. (2010). Soft tissue anaplastic large T-cell lymphoma associated with a metallic orthopedic implant: case report and review of the current literature. The Journal of Foot and Ankle Surgery, 49(6), 561-564.

[3] Dental Implant ALCL, Yoon, H. J., Choe, J. Y., & Jeon, Y. K. (2015). Mucosal CD30-positive T-cell lymphoproliferative disorder arising in the oral cavity following dental implants: report of the first case. *International journal of surgical pathology*, *23*(8), 656-661

[4] Chest Port ALCL, Engberg, A. K., Bunick, C. G., Subtil, A., Ko, C. J., & Girardi, M. (2013). Development of a plaque infiltrated with large CD30+ T cells over a silicone-containing device in a patient with history of Sezary syndrome. *Journal of Clinical Oncology*,*31*(6), e87.

[5] Total hip arthroplasties ALCL, Kellogg, B. C., Hiro, M. E., & Payne, W. G. (2014). Implant-associated anaplastic large cell lymphoma: beyond breast prostheses. *Annals of plastic surgery*,*73*(4), 461-464

[6] Shoulder Repair ALCL, Tuck, M., Lim, J., Lucar, J., & Benator, D. (2016). Anaplastic large cell lymphoma masquerading as osteomyelitis of the shoulder: an uncommon presentation. *Case Reports*, *2016*, bcr2016217317

[7] Lap Band ALCL, Manikkam Umakanthan, J., McBride, C. L., Greiner, T., Yuan, J., Sanmann, J., Bierman, P. J., & Bociek, R. G. (2017). Bariatric Implant–Associated Anaplastic Large-Cell Lymphoma. *Journal of oncology* practice,13(12), 838-839

[8] Gluteal Implant ALCL, Shauly, O., Gould, D. J., Siddiqi, I., Patel, K. M., & Carey, J. (2019). The First Reported Case of Gluteal Implant-Associated Anaplastic Large Cell Lymphoma (ALCL). Aesthetic surgery journal.

with other medical devices, and additionally, occurs in the general population irrespective of medical implants. The incidence of ALCL diagnosis in women is approximately 1/500,000 per year[9].

2. **Systemic symptoms reported in patients receiving breast implants**
   A wealth of literature and meta-analyses over the past two decades has not established a cause-and-effect relationship between breast implants and systemic symptoms. Sientra's completed 10-year PACS study submitted to FDA revealed risks of connective tissue disease (CTD) ranging from 0.7% to 3.2% across the four study cohorts. Patient self-reported CTD and neurological signs and symptoms were also collected in this study. After 10 years of follow-up, no significant increases were found in any of the 13 CTD signs and symptom categories.

3. **The use of registries for breast implant surveillance**
   Sientra fully supports the use of registries to collect safety and effectiveness data on breast implants, and supports The National Breast Implant Registry (NBIR), not only financially, but also as a member of the NBIR Steering Committee. Also, while not a registry per se, Sientra provides funding to the Aesthetic Neural Network (ANN), an ASAPS data collection platform. ANN is designed to automatically and retrospectively extract data from surgeons' medical records databases for analysis to help surgeons achieve better outcomes for their patients.

4. **Magnetic resonance imaging screening for silent rupture of silicone gel filled breast implants**
   Sientra's patient and physician labeling contain the FDA-required recommendations regarding magnetic resonance imaging (MRI) screening for silent rupture in women with silicone gel implants. While MRIs are effective in detecting silent rupture, there may be logistical constraints that potentially limit their value as a routine periodic silent rupture screening technique.

[9] Altekruse SF, Kosary CL, Krapcho M, Neyman N, Aminou R, Waldron W, Ruhl J, Howlader N, Tatalovich Z, Cho H, Mariotto A, Eisner MP, Lewis DR, Cronin K, Chen HS, Feuer EJ, Stinchcomb DG, Edwards BK (eds). SEER Cancer Statistics Review, 1975-2015, National Cancer Institute. Bethesda, MD, https://seer.cancer.gov/csr/1975_2015/browse_csr.php Table 19.28, based on November 2009 SEER data submission, posted to the SEER website, 2010

5. **The use of surgical mesh in breast procedures such a breast reconstruction and mastopexy**
   The use of surgical mesh in breast procedures impacts not only the breast implant industry, but also the surgical mesh industry. Use of surgical mesh not specifically indicated for use in breast procedures continues, which supports a clinical need in real-world practice. Moving forward, Sientra recommends that FDA have an open forum with all key stakeholders to discuss not only its concerns (regulatory and scientific), but also to discuss the type and extent of data (nonclinical and clinical) that would be appropriate to support an indication for mesh in breast use, with and without breast implants. An outcome of this process would be the eventual release of a guidance document.

6. **The use of real-world data and patient perspectives in regulatory decision making**
   Registries and other real-world data can play a larger role in the Total Product Life Cycle (TPLC) of medical devices, leading to a more efficient premarket review process. Collaboration is key (with FDA, other manufacturers, professional societies and other key stakeholders).

7. **Best practices for informed consent discussions between patients and clinicians.**
   Sientra is committed to excellence regarding the patient informed-consent process, including informative and readable patient labeling. The FDA-approved patient educational brochures, which include an *Acknowledgement of Informed Decision* form in each brochure to be signed by both the patient and her surgeon, are extremely comprehensive, but many patients and patient advocacy groups do not believe that patients are fully being informed of the risks. More specific information regarding the challenges in this process is necessary in order to address this critical step in the decision-making process.

INTRODUCTION

1.1. Purpose of this Briefing Document

The U.S. Food and Drug Administration (FDA) has convened the General and Plastic Surgery Devices Panel of the Medical Devices Advisory Committee (the "Panel") to "discuss and make recommendations regarding the benefits and risks of breast implants indicated for breast augmentation and reconstruction"[10] as they relate to seven specific topics encompassing patient outcomes, postmarket surveillance and regulatory decision-making. This document is intended to provide the Panel members with information regarding Sientra's long-term clinical study and Sientra's perspectives regarding these topics.

Sientra has a sound safety record regarding its Implants and has been and remains committed to improving patient outcomes by mitigating the potential for breast implant-specific complications through a robust Quality System and a variety of formal and informal surgeon training programs. In addition, Sientra routinely produces patient educational materials to increase patient awareness and encourage dialogue with their healthcare providers, as well as appropriately provides patients with contact information for healthcare resource groups.

Sientra's products are guided by science, and to that end, Sientra appreciates the opportunity to present its long-term clinical experience with Sientra OPUS® Breast Implants and its perspectives on the seven topics of interest, to FDA and to the Panel. Sientra anticipates a productive Panel discussion regarding the benefits and risks of breast implants and looks forward to the Panel recommendations regarding these seven topics.

1.2. Key Regulatory History

FDA granted approval of PMA P070004 for the Sientra Silicone Gel Breast Implants on March 9, 2012. Additional Breast Implant models were approved under subsequent PMA supplements.

Sientra added a tradename to its portfolio of Breast Implants in 2017. The new tradename of Sientra OPUS® Silicone Gel Breast Implants was approved on December 1, 2017, under P070004/S010. The new tradename is reflected throughout this Briefing Document.

FDA granted approval of a new manufacturing site for Sientra Implants under P070004/S009 on January 30, 2018. Sientra's Implants were previously manufactured by Silimed Ltda. in Rio de Janeiro, Brazil, but based on Sientra's January 2018 PMA Supplement approval, Sientra's Implants are manufactured at Vesta, Inc. in Franklin, Wisconsin.

1.3. Device Description and Indications for Use

Sientra OPUS Silicone Gel Breast Implants are composed of a silicone elastomer shell, which is thin and soft, and a filler made of clear, high-strength silicone gel. The silicone elastomer used in the Breast Implant shell is composed of a compound of dimethyl polysiloxane and a dimethyl fluoro silicone copolymer, catalyzed by a platinum compound. The high-strength gel filler is silicone gel catalyzed by a platinum-containing compound. The Breast Implants are sterilized by dry heat.

[10] https://www.fda.gov/AdvisoryCommittees/Calendar/ucm631324.htm

There are 25 Sientra models currently approved for use in the U.S. The models comprise: two versions of gel; smooth and textured shells; round and shaped profiles; and volumes that range from 80-700cc.

As stated in the approval order, the Sientra OPUS Silicone Gel Breast Implants are indicated for:

- **Breast augmentation for women at least 22 years old.** Breast augmentation includes primary breast augmentation as well as revision surgery to correct or improve the result of primary breast augmentation surgery.
- **Breast reconstruction.** Breast reconstruction includes primary reconstruction to replace breast tissue that has been removed due to cancer or trauma or that has failed to develop properly due to a severe breast abnormality. Breast reconstruction also includes revision surgery to correct or improve the results of a primary breast reconstruction surgery.

Labeling provided with the Implants contains, among other information, a description of the Implants, instructions for use, contraindications, warnings and precautions to aid in appropriate patient selection, and a specific section on *Information to be Discussed with the Patient*. In addition, consistent with the 2011 and 2016 updated information regarding BIA-ALCL and FDA-recommended verbiage, Sientra's FDA-approved physician and patient brochures include this updated information, as described below in the discussion on BIA-ALCL in Section 3. Patient brochures also provide information on treatment options and the benefit/risk profile of Sientra's Implants to assist patients in making informed decisions regarding their augmentation or reconstruction options. Sientra wants women to feel confident in Sientra Breast Implants and in their decision to have breast augmentation or reconstructive surgery.

1.4. P070004 Conditions of Approval

As per the March 9, 2012 approval order for P070004, there are six conditions of approval (COAs). The table below provides the status of Sientra's COAs.

Table 1: Overview of P070004 Conditions of Approval

Study Name	Purpose	Status
Post-Approval PMA Cohorts Study (PACS)	10-year follow-up of the premarket cohorts from the IDE study. Data were collected from 1,788 patients via annual physician follow-up evaluations with MRIs at years 6, 8, and 10.	The 10-year data were reviewed by FDA and the Final Report closed-out. Updated labeling that reflects the 10-year PACS results is currently under FDA review.
Post-Approval Continued Access Study (PACAS)	Continued follow-up of 2,497 patients enrolled in the Continued Access Study arm through 5 years. The Final Report with 5-year data was submitted to FDA in 2013 and reviewed and closed-out by FDA.	Completed

Study Name	Purpose	Status
U.S. Post-Approval Study (US-PAS)	Newly enrolled U.S. cohort designed to evaluate long-term clinical performance under general conditions in the postmarket environment (i.e., "real-world" study). The study involves 5,197 Sientra patients and 301 control patients followed annually through 10 years.	Data out to 2 years of follow-up have been submitted to FDA, with the third year of data being submitted in March 2019.
Post-Approval Case-Controlled Studies (PACCS)	On 8/7/15, FDA issued a letter stating that a Tufts University study[11] (discussed below in the section on systemic signs and symptoms) "showed insufficient evidence of association between silicone gel-filled breast implants and lymphoma, brain cancer, cervical cancer, rare connective tissue diseases (CTDs), or rare neurological events." Thus, "using case-control studies to study these rare events would not provide additional value." Therefore, "FDA is no longer requiring silicone gel breast implant manufacturers to conduct case-control studies to study lymphoma, brain cancer, cervical cancer, rare connective tissue diseases (CTDs), or rare neurological events." However, FDA also noted that the association between breast implants and lung cancer, rheumatoid arthritis, and suicide would be captured by data collected through the US-PAS. In addition, Sientra was expected to continue participation as a stakeholder in the development of the National Breast Implant Registry.	Terminated by FDA
Focus Group Study	To determine if the augmentation and reconstruction patient labeling (brochures) effectively communicates the risks and benefits of breast implant surgery.	Completed
National Breast Implant Registry (NBIR)	Participate as a stakeholder in developing the NBIR and contribute data from [Sientra's] U.S. Post-Approval Study to the Registry upon its implementation (which has since been implemented).	Ongoing

1.5. Sientra Commitment to Patients and Board-Certified Plastic Surgeons

Although not required by FDA as a condition of approval, true to Sientra's commitments to patient safety and the plastic surgery specialty, OPUS Breast Implants are offered exclusively to board-certified or board-eligible plastic surgeons. Sientra believes that putting its products in the hands of only the most skilled surgeons leads to better patient outcomes. Sientra is committed to making a positive difference in patients' lives by offering products to enhance body image, cultivate self-esteem and enrich confidence. The Company has developed a broad portfolio of products with technologically differentiated characteristics, supported by independent laboratory testing and strong clinical trial outcomes.

[11] Balk, E. M., Earley, A., Avendano, E. A., & Raman, G. (2016). Long-term health outcomes in women with silicone gel breast implants: a systematic review. *Annals of internal medicine*, 164(3), 164-175.

1.5.1. Science, Innovation and Surgeon Education to Maximize Patient Outcomes

Sientra's Lab and Innovation Center of Excellence (SLICE)
Sientra's Lab and Innovation Center of Excellence (SLICE) focuses on driving the development, research and innovation of surgical products, services and solutions. SLICE acts as a formal collaboration initiative to regularly connect Sientra's experienced Research and Development and Clinical teams with Sientra's Medical Advisory Board, board-certified surgeons, technical experts and consultants. This group of trusted experts helps advance solutions and brings meaningful improvements regarding key clinical products and practices to board-certified surgeons.

Surgeon Education
Sientra also advances surgeon education in the form of Surgical Preceptorships. Surgical Preceptorships are surgical training sessions designed to ensure that plastic surgeons receive first-hand training from veteran/expert board-certified plastic surgeons on Sientra products, as well as to review patient informed-decision training and gain hands-on guidance of plastic surgery best-practices within a highly experienced Plastic Surgery Practice.

Peer-Reviewed Publications
Sientra is committed to driving transparency of evidence-based outcomes and advancing education of best-practices, and partners with expert, thought-leader plastic surgeons to regularly produce peer-reviewed publications and achieve these objectives[12], [13], [14], [15], [16], [17], [18], [19]. These publications focus on topics such as: robust complication analysis to determine surgical, patient and device factors that impact outcomes, appropriate patient and implant selection guidance; and *in-vitro* testing of our Implants to understand how the features of the Implants may relate to *in-vivo* clinical performance. These publications are a combined effort that reflects our commitment to using our long-term data to continue driving transparency and improvement in Implant safety and patient outcomes.

[12] Stevens, W. G., Nahabedian, M. Y., Calobrace, M. B., Harrington, J. L., Capizzi, P. J., Cohen, R., d'Incelli, R. C., Beckstrand, M. (2013). Risk factor analysis for capsular contracture: a 5-year Sientra study analysis using round, smooth, and textured implants for breast augmentation. *Plastic and reconstructive surgery*. 132(5), 1115-1123.
[13] Calobrace, M. B., Stevens, W. G., Capizzi, P. J., Cohen, R., Godinez, T., & Beckstrand, M. (2018). Risk factor analysis for capsular contracture: a 10-year Sientra study using round, smooth, and textured implants for breast augmentation. *Plastic and reconstructive surgery*, *141*(4S), 20S-28S.
[14] Haws, M. J., Schwartz, M. R., Berger, L. H., Daulton, K. L. (2014). Sientra portfolio of Silimed brand shaped implants with high-strength silicone gel: a 5-year primary augmentation clinical study experience and a postapproval experience—results from a single-surgeon 108-patient series. *Plastic and reconstructive surgery*, 134(1S), 34S-46S.
[15] Haws, M. J., Alizadeh, K., Kaufman, D. L. (2015). Sientra primary and revision augmentation rupture trending and analysis with magnetic resonance imaging. *Aesthetic surgery journal*, 35(S1), S33-S42.
[16] Kinney, B. M., Jeffers, L. L. C., Ratliff, G. E., Carlisle, D. A. (2014). Silicone gel breast implants: science and testing. *Plastic and reconstructive surgery*. 134(1S), 47S-56S.
[17] Schwartz, M. R., Haws, M. J., & Phillips, G. (2018). Results of the Postmarket Clinical Study of the Sientra 207 Highly Cohesive Gel Breast Implants in Primary and Revision Augmentation. *Plastic and reconstructive surgery*, *141*(4S), 40S-48S.
[18] Schwartz, M. R., Capizzi, P. J., Movassaghi, K., Talmor, M. (2015). Sientra high-strength cohesive shaped technique: roundtable discussion. *Aesthetic surgery journal*, 35(S1), S22-S32.
[19] Stevens, W. G., Calobrace, M. B., Cohen, R., Fiorillo, M. A., Kortesis, B. G. (2015). Sientra high-strength cohesive textured round implant technique: roundtable discussion. *Aesthetic surgery journal*, 35(S1), S11-S21.

For example, Kinney et al (2014)[20] conducted research on silicone gel implants performed at independent laboratories that included four tests: gel elasticity (the gel's ability to retain its shape), gel compression fracture (the resistance to permanent gel deformation), gel-shell peel (the integration of the gel with shell as a cohesive unit), and morphological analysis. Among shaped implants, the Sientra HSC+ Implant experienced the most gel elasticity (4.270 mm). Sientra's round (36.32 lbf) and shaped (44.16 lbf) Implants demonstrated the highest resistance to gel fracture. For the gel-shell peel test, Sientra's round Implant required over 26%-35% greater force to separate the gel from the shell than other tested devices. Sientra's shaped Implants required more than double the peel force than other tested devices (119%-130% greater). Morphological results showed Sientra's Implants preserved structural integrity (−1.10% change).

As part of an interim analysis in an ongoing, prospective, multicenter evaluation of outcomes using the Sientra style 207 high-strength cohesive-plus (HSC+) silicone gel Breast Implants,. Schwartz et al (2018)[21] reports the Sientra 207 round Breast Implants demonstrated excellent surgeon and patient satisfaction scores. Successful outcomes in the high proportion of postpartum women in the study indicate particular utility with this device for the management of postpartum superior pole involution.

Two publications have described roundtable discussions involving Sientra Implants. In the first publication, Schwartz et al (2015)[22] depicted their experience with a panel of board-certified plastic surgeons that discussed their respective experiences with the Sientra High-Strength Cohesive (HSC+) shaped silicone gel Breast Implants. The authors implanted a combined total of over 700 patients. Preoperative planning, surgical techniques, and practice integration tips were reviewed. The surgeons also presented breakthrough cases and described how the Sientra HSC+ textured Implants helped achieve a successful outcome. In the second publication, Stevens et al (2015)[23] recounts how a panel of board-certified plastic surgeons discussed their respective experiences with the Sientra High-Strength Cohesive (HSC) Textured Round silicone gel breast Implants. The authors had implanted a combined total of approximately 2100 patients. Surgical pearls, complication avoidance, and practice integration tips were reviewed. The surgeons presented challenging cases and described how the HSC textured Implants helped to achieve a successful outcome.

[20] Kinney, B. M., Jeffers, L. L. C., Ratliff, G. E., Carlisle, D. A. (2014). Silicone gel breast implants: science and testing. *Plastic and reconstructive surgery*. 134(1S), 47S-56S.
[21] Schwartz, M. R., Haws, M. J., & Phillips, G. (2018). Results of the Postmarket Clinical Study of the Sientra 207 Highly Cohesive Gel Breast Implants in Primary and Revision Augmentation. *Plastic and reconstructive surgery*, *141*(4S), 40S-48S.
[22] Schwartz, M. R., Capizzi, P. J., Movassaghi, K., Talmor, M. (2015). Sientra high-strength cohesive shaped technique: roundtable discussion. *Aesthetic surgery journal*, 35(S1), S22-S32.
[23] Stevens, W. G., Calobrace, M. B., Cohen, R., Fiorillo, M. A., Kortesis, B. G. (2015). Sientra high-strength cohesive textured round implant technique: roundtable discussion. *Aesthetic surgery journal*, 35(S1), S11-S21.

Sponsorship of Plastic Surgery Journal Supplements
In addition, Sientra has supported and funded multiple educational supplements in the two premier plastic surgery journals, *Plastic and Reconstructive Surgery* (PRS) and *Aesthetic Surgery Journal* (ASJ):

- PRS "Sientra Shaped and Round Cohesive Gel Implants", July 2014
- ASJ "Sientra High-Strength Cohesive Gel Implants", May/June 2015
- PRS "Sientra Shaped and Round Cohesive Gel Implants", April 2018
- PRS "Advances in Breast Reconstruction", December 2017
- PRS "A Review of Breast Implant- Associated Anaplastic Large Cell Lymphoma", March 2019
- ASJ "Current Controversies in Breast Implant-Associated Anaplastic Large Cell Lymphoma", March 2019

These research and training efforts are designed to bolster the safety and efficacy of the breast implantation procedure and improve patient outcomes.

1.5.2. Patient Safety and Education

In addition to the breast augmentation and breast reconstruction Educational Brochures that are part of Sientra's labeling, Sientra offers numerous resources to help educate patients about breast implants and breast implant surgery. Sientra is the only company that makes its Implants available exclusively through board-certified (or board-eligible) plastic surgeons, whose intense specialty training helps them elevate their surgical skills and aesthetic judgment. As such, through various patient educational mediums, Sientra advises patients to ask the following questions of surgeons they are considering and to consult with more than one surgeon to help them choose the plastic surgeon who best meets their needs:

- Are you board-certified (or board-eligible) by The American Board of Plastic Surgery? (Board membership status is located at abplsurg.org)
- How many breast implant surgeries do you perform each year?
- How many years have you been doing breast implant surgeries?
- What is the most common complication you encounter with breast implants?
- What is your reoperation rate for breast implant patients? What is the most common reoperation you perform?
- Do you have before and after photos of similar procedures that I can review?
- Are you licensed to practice surgery in this state?

The 10-year results of Sientra's Core Study support a comprehensive safety and effectiveness profile of Sientra's portfolio of round and shaped Breast Implants.[24] Because Sientra trusts in the

[24] Stevens, W. G., Calobrace, M. B., Alizadeh, K., Zeidler, K. R., Harrington, J. L., & d'Incelli, R. C. (2018). Ten-year Core Study Data for Sientra's Food and Drug Administration–Approved Round and Shaped Breast Implants with Cohesive Silicone Gel. *Plastic and reconstructive surgery*, *141*(4S), 7S-19S.

safety and performance of its Breast Implants, Sientra offers its Sientra Platinum20™ Warranty[25], the most complete warranty program in the industry, and is the first company to provide 20-year coverage. Sientra's extensive warranty coverage is designed to give surgeons and patients the same level of confidence. Any type of surgery carries inherent risks, and Sientra takes that very seriously. That's why Sientra entrusts patient safety and satisfaction to only the most highly trained, board-certified and board-eligible plastic surgeons in our industry, who are also patients' most important resource when it comes to breast implant surgery.

1.5.3. Recognition and Philanthropy

Sientra believes that full commitment to patients and their health is about more than offering products and services. Full commitment requires giving back, so that philanthropies focused on improving the experience of patients with breast cancer can receive the support they need. Sientra Full Circle™ is a first-of-its-kind charitable program that supports nonprofits in the breast cancer community that are committed to making a meaningful difference. As part of supporting these philanthropies, Sientra donates a portion of revenue from every OPUS® breast tissue expander sold to the Full Circle fund.

With the Full Circle program, Sientra is proud to support nonprofits in the breast cancer community dedicated to aid, research, patient outreach and advocacy and prevention. In 2018, Sientra announced the recipients of its inaugural Sientra Full Circle grant program, which included eight U.S.-based nonprofit breast cancer organizations with missions to support breast cancer aid, research, patient outreach, advocacy, and/or prevention.

1. Adelphi NY Statewide Breast Cancer Hotline & Support Program: Funds provide information for individuals diagnosed with breast cancer, their families and practitioners through breast cancer forums.
2. Breast Cancer Angels: Funds help cover non-medical living expenses for individuals undergoing breast cancer treatments.
3. Breast Cancer Assistance Group of Monterey County: Funds help cover non-medical living expenses for breast cancer patients undergoing breast reconstruction.
4. Breast Cancer Resource Center of Santa Barbara: Funds help cover costs of support services, such as patient navigation and peer counseling services.
5. Breast Care for Washington: Funds help cover the cost of 3-D mammography for uninsured women.
6. Jill's Wish Foundation: Funds help cover non-medical living expenses for patients with newly-diagnosed or terminal breast cancer.
7. Sharsheret: Funds provide peer support, patient navigation, and cancer prevention genetics information.
8. Integrated Breast Center at St. John's: Funds increase awareness of new cancer center and support new programs for breast cancer patients.

[25] http://sientra.com/feelgood/implants-warranty

Sientra is also supporting breast cancer patients and breast cancer research by other philanthropic endeavors. For example:

- Sponsor of the American Society of Plastic Surgeons (ASPS) Plastic Surgery Foundation (PSF) Breast Reconstruction Awareness Campaign
- The inaugural Industry sponsor for the Breast Reconstruction Awareness (BRA) Day USA event in 2012, with annual participation in BRA Day events
- Flagship Sponsor of Making Strides Against Breast Cancer Walk
- Team TBG Triathlon Group sponsorship
- Sponsorship of several regional breast cancer events annually, including participating in patient education at these events

2. SIENTRA LONG-TERM CLINICAL DATA

2.1. Overview of 10-Year Postmarket Cohort Study (PACS)

Sientra's Breast Implants are effective in restoring or enhancing breast shape and self-esteem for both cosmetic and reconstructive patients. The patient benefits are demonstrable and clinically relevant. Subjective success rates and quality-of-life improvements, as part of ensuring clinically meaningful outcomes of breast implant surgery, are high to very high 10 years post-implantation with Sientra Implants. The vast majority of patients report continued satisfaction with their Implants and their decision to undergo breast implantation.

Furthermore, a long-term safety profile has been established with no unexpected or significant increases in complications over time. Based on the 10-year data, Sientra's Implants demonstrate long-term benefits with no additional safety risks (Table 2).

Table 2
Kaplan-Meier Risk Complications through Year 3 and Year 10, by Patient

Key Complication	Primary Augmentation (N=1,116)		Revision-Augmentation (N=363)		Primary Reconstruction (N=225)		Revision Reconstruction (N=84)	
	3-Year	10-Year	3-Year	10-Year	3-Year	10-Year	3-Year	10-Year
Breast Pain	0.8%	1.2%	1.2%	2.5%	3.1%	4.5%	1.3%	3.1%
Capsular Contracture III/IV	5.9%	12.9%	6.2%	13.7%	9.7%	15.8%	7.9%	14.3%
Infection	0.8%	0.9%	1.2%	1.5%	5.1%	5.1%	1.2%	1.2%
Rupture (MRI Cohort)*	0.0%	8.5%	0.0%	6.8%	0.0%	16.5%	0.0%	0.0%
Rupture (Overall)*	1.6%**	7.8%	1.1%**	5.2%	1.4%**	9.8%	0.0%**	NR
Reoperation	12.8%	24.0%	20.9%	38.8%	35.6%	48.2%	39.4%	56.7%

*Rupture rate includes suspected, indeterminate and confirmed ruptures.
**Reflects 4-Year Overall rupture results.
NR: Some rates are not reported because the number of remaining patients/implants at timepoint is < 10.

Sientra's Silicone Gel Breast Implant Clinical Study (the "Study") is a prospective, 10-year, multicenter clinical study conducted to examine the long-term safety and effectiveness of Sientra's OPUS Silicone Gel Breast Implants in patients undergoing primary augmentation, primary reconstruction, revision-augmentation, and revision-reconstruction of the breast. The Study consists of data from the primary augmentation and revision-augmentation cohorts of Sientra's CORE study, as well as pooled data from Sientra's CORE and Continued Access (CA) studies for the primary reconstruction and revision-reconstruction cohorts. The Study has been completed and the Final Report of 10-year data has undergone FDA review and been closed-out.

There were 1,788 patients who participated in the Study. A total of 1,116 patients underwent primary augmentation, 363 patients underwent revision-augmentation, 225 patients underwent primary reconstruction (152 CORE and 73 CA) and 84 patients (52 CORE and 32 CA) underwent revision-reconstruction with Sientra Implants. Of these patients, 398 primary augmentation patients, 115 revision-augmentation patients, 48 primary reconstruction patients, and 10 revision-reconstruction patients (for a total of 571 patients) were assessed for implant rupture by MRI at 3, 4, 6, 8, and 10 years. A total of 37 investigators (including transfer follow-up investigators) followed patients in the four cohorts.

Study patients were expected to complete annual follow-up visits for safety and effectiveness through 10 years. Assessment of the long-term safety of the Study Implants was based on the incidence, severity, method of resolution and duration of all complications, including device failures and adverse device effects, on a per-implant and per-patient basis. The rate of asymptomatic or "silent" rupture was assessed via MRI at regular intervals for all study patients. Other potential complications of the breast implant surgery assessed by the Study include possible systemic effects (e.g., autoimmune and/or rheumatologic effects). In addition, all secondary procedures related to the breast, including explant surgery with or without replacement, were recorded. Assessment of long-term effectiveness was based on changes in bra size/chest circumference taken at Years 1 and 2, and patient-reported satisfaction and quality-of-life (QOL) outcomes, including the Short Form Health Survey (SF-36), the Rosenberg Self-Esteem Scale, and the Body Image Scale assessed through 10 years.

The final, 10-year results of the Study demonstrate that the Implants continue to be safe and effective for use in primary augmentation, revision-augmentation, primary reconstruction, and revision-reconstruction of the breast. The long-term safety profile has been established with no unexpected or significant increases in complications over time in both Sientra smooth and textured devices, which has also been substantiated in the peer-reviewed *Long Term Safety of Textured and Smooth Breast Implants*[26]. Additionally, the effectiveness outcomes demonstrate that the majority of subjects continue to report favorable satisfaction and QOL results. Based on the 10-year data, Sientra's Implants demonstrate long-term benefits without additional safety risks.

Final 10-year data from the Study are available for 67% of the eligible primary augmentation patients, 62% of the eligible revision-augmentation patients, 65% of the eligible primary reconstruction patients, and 58% of the revision-reconstruction patients, for an overall final Study follow-up compliance of 65%. Sientra's overall follow-up compliance meets the expected minimum 65% follow-up compliance rate stipulated in the Study protocol for a long-term study

[26] Calobrace, M.B., Schwartz, M.R., Zeidler, K.R., Pittman, T.A., Cohen, R, Stevens, W.G. (2018). Long-term safety of textured and smooth breast implants. *Aesthetic surgery journal*. 38(1), 38–48.

duration of 10 years. The PACS Study is a large, robust sample size with adequate statistical power to estimate important health-related endpoints.

Study strengths include the fact that the Study is a multicenter, prospective long-term (10-year) study with a large, robust sample size and adequate statistical power to estimate important health-related endpoints. Patient follow-up at 10-years met the FDA compliance requirement for a long-term study. Other Study strengths include a Study design with a representative mix of Sientra's various Implant styles (smooth/textured, round/shaped). Further strengths include the datum that safety endpoints were assessed and collected by the plastic surgeons during physical examination of their patients at follow-up office visits (rather than unconfirmed or indirect patient-reported outcomes).

The use of more recent surgical tools and techniques, including surgical mesh, acellular dermal matrix (ADM), insertion devices, etc., together with the Breast Implants, was not studied as part of Sientra's Silicone Gel Breast Implant Clinical Study. This could be viewed as a Study limitation. However, this is consistent with any 10-year, long-term study that was based on state-of-the art best practices during the Study enrollment time period.

Demographic information for the Study with regard to race is as follows: 92% of the Study patients were Caucasian; 3% were Hispanic; 2% were Asian, 2% were African American; less than 1% were Indian and less than 2% were other or unknown. The median age at surgery was 36 years for primary augmentation patients, 42 years for revision-augmentation patients, 46 years for primary reconstruction patients, and 51 years for revision-reconstruction patients. Approximately 59% of the Study patients were married. Approximately 74% had some college education. Table 3 presents the Study population demographics at baseline by cohort.

Table 3
Patient Demographics by Cohort

Characteristic	Primary Augmentation N=1,116	Revision Augmentation N=363	Primary Reconstruction N=225	Revision Reconstruction N=84
Age (years)				
≤ 21	47	3	9	0
22-25	102	12	5	0
26-39	566	128	55	8
40-49	335	139	67	26
50-59	57	63	62	29
60-69	8	18	17	14
70 & over	1	0	10	7
Median Age	36	42	46	51
Marital Status				
Single	317	92	47	14
Married	641	217	142	59
Widowed	9	9	6	5
Divorced	126	42	26	6

Table 3 Patient Demographics by Cohort				
Characteristic	**Primary Augmentation N=1,116**	**Revision Augmentation N=363**	**Primary Reconstruction N=225**	**Revision Reconstruction N=84**
Separated	21	3	1	0
Not Provided	2	0	3	0
Race				
Caucasian	1,014	338	204	80
Black	12	7	5	2
Hispanic	37	7	10	1
Asian	29	8	1	0
Indian	1	0	1	0
Other	22	2	2	1
Not Provided	1	1	2	0
Education				
Less than 12 years	8	4	5	1
High School Graduate	187	68	71	24
Some College	368	95	52	24
College Graduate	399	150	61	22
Post Graduate	94	26	18	6
Not Provided	60	20	18	7

With respect to surgical approach, for primary augmentation patients, the majority of Implants (62%) were placed through an inframammary incision; 34% of Implants were placed through a periareolar incision, 3.9% were placed through a transaxillary incision and 0.9% included a mastopexy procedure. The placement was submuscular in 57% of Implants and subglandular in 43% of Implants. Round Implants represented 89% of total Implants and shaped Implants represented 12% of total Implants. Smooth Implants represented 58% of Implants and textured Implants represented 42% of Implants.

For revision-augmentation patients, the majority of Implants (61%) were placed through an inframammary incision; 33% of Implants were placed through a periareolar incision, 3.3% were placed through a transaxillary incision, 2.2% were placed through a mastopexy procedure and 0.3% were placed through a mastectomy or other scar incision. The placement was submuscular in 61% of Implants and subglandular in 39% of Implants. Round Implants represented 86% of Implants and shaped Implants represented 14% of Implants. Smooth Implants represented 47% of Implants and textured Implants represented 53% of Implants.

For primary reconstruction patients, the most commonly used surgical approach for Implant placement (45%) was through a mastectomy or other scar, 28% were placed through an inframammary incision, 17% of Implants were placed through a periareolar incision, 6.6% were

placed through a mastopexy procedure and 3.2% were placed through a transaxillary incision. The placement was submuscular in 73% of Implants and subglandular in 27% of Implants. Round Implants represented 88% of Implants and shaped Implants represented 12% of Implants. Smooth Implants represented 46% of Implants and textured Implants represented 54% of Implants.

For revision-reconstruction patients, the majority of Implants (57%) were placed through a mastectomy or other scar, 34% were placed through an inframammary incision; 7% of Implants were placed through a periareolar incision, 2% were placed through a transaxillary incision and 0.7% were placed through a mastopexy procedure. The placement was submuscular in 90% of Implants and subglandular in 10% of Implants. Round Implants represented 88% of Implants and shaped Implants represented 12% of Implants. Smooth Implants represented approximately 40% of Implants and textured Implants represented 60% of implants.

The following two tables represent Implant placement and surgical approach by cohort (Table 4) and breast Implant style by cohort (Table 5).

Table 4
Breast Implant Placement & Surgical Approach by Cohort

Surgical Characteristic	Primary Augmentation N=2,230	Revision Augmentation N=725	Primary Reconstruction N=412	Revision Reconstruction N=139
Implant Placement				
Submuscular	1,273	440	300	125
Subglandular	957	285	112	14
Total	2,230	725	412	139
Surgical Approach				
Inframammary	1,374	441	117	47
Mastectomy scar	0	2	187	79
Mastopexy	20	16	27	1
Periareolar	748	242	68	9
Transaxillary	88	24	13	3
Total	2,230	725	412	139

Table 5 Breast Implant Style by Cohort				
Product Style/Projection[1]	**Primary Augmentation N=2,230**	**Revision Augmentation N=725**	**Primary Reconstruction N=412**	**Revision Reconstruction N=139**
Round Styles				
Style 10512 (Smooth)/MP	716	136	79	20
Style 10521 (Smooth)/HP	572	204	110	36
Style 20610 (Textured)/LP	99	36	28	3
Style 20621 (Textured)/MP/HP	587	248	144	63
Shaped Styles				
Style 20645 (Textured)/LP	54	12	10	11
Style 20646 (Textured)/HP	0	0	1	3
Style 20676 (Textured)E/MP	202	89	40	3

[1]Projections include: LP=Low Profile, MP or E=Moderate Profile, HP=High Profile

Information on the benefits and safety of Sientra Implants is presented below and organized by indication.

2.2. Effectiveness Outcomes

The benefits of Sientra OPUS Silicone Gel Breast Implants were determined by measuring bra size/chest circumference change (primary augmentation only) and assessing patient satisfaction using patient-reported quality-of-life (QOL) outcomes, including the Short Form Health Survey (SF-36), the Rosenberg Self-Esteem Scale, and the Body Image Scale. The information was collected before implantation and at scheduled follow-up visits.

Primary Augmentation Patients

For primary augmentation patients, 91% of patients increased their bra cup size by at least one cup size. Eighty-two percent (82%) of patients increased their bra cup size by one to two cups, while 10% gained more than two cup sizes.

The majority of primary augmentation patients were satisfied with their results through 10 years of follow-up. The Study showed that most patients agreed their Breast Implants make them feel more feminine (89%) and more attractive (86%). In addition, the majority of women indicated that their Breast Implants made them feel better about themselves (77%).

For the primary augmentation cohort, prior to implantation and continuing afterwards, the mean SF-36 (Health Survey) QOL scores were significantly higher for the Study population compared to the general female population. For primary augmentation patients, comparisons of Baseline QOL scores to scores at Year 10 showed no clinically significant changes. There were a number of statistically significant decreases in the quality of life scales. However, the magnitude of

changes and/or the effect sizes were small or very small and the observed changes were not clinically relevant, and the 10-year scores were still higher than the general female population.

For primary augmentation patients, mean total self-esteem scores on the Rosenberg Self-Esteem Scale at Baseline and Year 10 remained above 25. Scores between 15 and 25 are considered to be within normal range, with higher scores indicating more positive feelings.

Mean scores on the Body Esteem Scale and subscales showed no clinically significant changes from Baseline to Year 10 among women in the primary augmentation cohort. Scores were relatively high at baseline and remained high postoperatively.

Revision-Augmentation Patients

Through 10-years of the Clinical Study, the majority of revision-augmentation patients continued to be satisfied with their results. The Study showed that most patients agreed that their Breast Implants make them feel more feminine (87%) and more attractive (83%). In addition, the majority of women indicated that their Breast Implants made them feel better about themselves (78%).

For the revision-augmentation cohort, prior to implantation and continuing afterwards, the mean SF-36 (Health Survey) QOL scores were significantly higher for the Study population compared to the general female population.

For revision-augmentation patients, comparison of baseline QOL scores to scores at Year 10 showed no clinically significant changes. There were a number of statistically significant decreases in the quality of life scales. However, the magnitude of the changes and/or the effect sizes were small or very small and therefore the observed changes were judged not to be clinically relevant, and the 10-year scores were still higher than the general female population.

For revision-augmentation patients, mean total scores on the Rosenberg Self-Esteem Scale at Baseline and Year 10 remained above 25. Scores between 15 and 25 are considered to be within normal range, with higher scores indicating more positive feelings.

Mean scores on the Body Esteem Scale and subscales showed no clinically significant changes from Baseline to Year 10 among women in the revision-augmentation cohort. Scores were relatively high at baseline and remained high postoperatively.

Primary Reconstruction Patients

The majority of primary reconstruction patients in this Study were satisfied with their results. The Study showed that most women felt their Breast Implants make them feel more feminine (77%) and more attractive (71%). In addition, the majority of women indicated that their Breast Implants made them feel better about themselves (69%).

For the primary reconstruction cohort, prior to implantation and continuing afterwards, the mean SF-36 (Health Survey) QOL scores were higher for the Study population compared to the general female population. For primary reconstruction patients, comparison of baseline QOL scores to scores at Year 10 showed no clinically significant changes. There were a small number of statistically significant decreases in the quality of life scales. However, effect sizes were small or very small and therefore the observed changes were judged not to be clinically relevant, and in most cases the 10-year scores were still higher than the general female population.

For primary reconstruction patients, mean total scores on the Rosenberg Self-Esteem Scale at Baseline and Year 10 remained above 25. Scores between 15 and 25 are considered to be within normal range, with higher scores indicating more positive feelings.

Mean scores for the Body Esteem Scale and subscales showed no clinically significant changes from Baseline to Year 10 among women in the primary reconstruction cohort. Scores were relatively high at baseline and remained high postoperatively.

Revision-Reconstruction Patients
The majority of revision-reconstruction patients in this Study were satisfied with their results. The Study showed that most women felt their Breast Implants made them feel more feminine (92%) and feel more attractive (84%). In addition, the majority of women indicated that their Breast Implants made them feel better about themselves (85%).

For the revision-reconstruction cohort, prior to implantation and continuing afterwards, the mean SF-36 (Health Survey) QOL scores were at least comparable and in most cases higher for the Study population compared to the general female population. Comparisons of Baseline QOL scores to scores at Year 10 showed no clinically significant changes. Only one scale showed a statistically significant decrease in the quality of life scales. However, the median change from baseline was small and therefore, the difference was judged to be clinically irrelevant.

For revision-reconstruction patients, mean total scores on the Rosenberg Self-Esteem Scale at Baseline and Year 10 remained above 25. Scores between 15 and 25 are considered to be within normal range, with higher scores indicating more positive feelings.

Scores for the Body Esteem Scale and subscales showed no clinically significant changes from Baseline to Year 10 among women in the revision-reconstruction cohort. Scores were relatively high at baseline and remained high postoperatively.

2.3. Safety Outcomes

The safety of Sientra Implants was determined by assessing the incidence of complications, including device failures.

2.3.1. Key Complications

Primary Augmentation Patients
Table 6 describes the Kaplan-Meier risk of key complications experienced for the primary augmentation patients in the Study through 10 years.

Table 6 Kaplan-Meier Risk of Complications for Primary Augmentation Patients through 10 Years (N=1,116 Patients)		
Key Complications	**KM Risk**	**95% CI**
Reoperation	24.0%	(21.4%, 26.8%)
Capsular Contracture (Baker Grade III/IV)	12.9%	(10.8%, 15.2%)
Implant Removal with Replacement	12.2%	(10.3%, 14.5%)
Implant Rupture (MRI cohort)[1]	8.5%	(5.8%, 12.4%)
Implant Removal without Replacement	4.7%	(3.5%, 6.4%)

[1] Implant rupture was reported at a risk rate of 6.3% (3.9%, 10.1%) in the non-MRI cohort.

Revision-Augmentation Patients

Table 7 describes the Kaplan-Meier risk of complications for the revision-augmentation patients in the Study through 10 years.

Table 7 Kaplan-Meier Risk of Complications for Revision-Augmentation Patients through 10 Years (N=363 Patients)		
Key Complications	**KM Risk**	**95% CI**
Reoperation	38.8%	(33.6%, 44.6%)
Implant Removal with Replacement	18.7%	(14.7%, 23.7%)
Capsular Contracture (Baker Grade III/IV)	13.7%	(10.2%, 18.4%)
Implant Removal without Replacement	9.4%	(6.4%, 13.7%)
Implant Rupture (MRI cohort)[1]	6.8%	(3.1%, 14.7%)

[1] Implant rupture was reported at a risk rate of 3.5% (1.1%, 10.4%) in the non-MRI cohort.

Primary Reconstruction Patients
Table 8 describes the Kaplan-Meier risk of complications for the primary reconstruction patients in the Study through 10 years.

Table 8
Kaplan-Meier Risk of Complications for Primary Reconstruction Patients through 10 Years
(N=225 Patients)

Key Complications	KM Risk	95% CI
Reoperation	48.2%	(41.5%, 55.4%)
Implant Removal with Replacement	28.8%	(22.8%, 35.9%)
Implant Rupture (MRI cohort)[1]	16.5%	(6.3%, 39.1%)
Capsular Contracture (Baker Grade III/IV)	15.8%	(11.0%, 22.5%)
Implant Removal without Replacement	11.1%	(7.2%, 17.1%)

[1] Implant rupture was reported at a risk rate of 6.6% (2.1%, 19.3%) in the non-MRI cohort.

Revision-Reconstruction Patients
Table 9 describes the Kaplan-Meier risk of complications for the revision-reconstruction patients in the Study through 10 years.

Table 9
Kaplan-Meier Risk of Complications Reported for Revision-Reconstruction Patients through 10 Years
(N=84 Patients)

Key Complications	KM Risk	95% CI
Reoperation	56.7%	(45.4%, 68.5%)
Implant Removal with Replacement	40.5%	(29.1%, 54.4%)
Implant Removal without Replacement	18.9%	(11.0%, 31.6%)
Capsular Contracture (Baker Grade III/IV)	14.3%	(7.5%, 26.4%)
Implant Rupture (MRI cohort)[1]	0.0%	0.0%

[1] No ruptures were reported in the revision-reconstruction MRI cohort; however, 5 patients (2 confirmed and 3 unconfirmed) were reported as ruptures in the non-MRI cohort.

2.3.2. Reasons for Reoperation

Primary Augmentation Patients
There were 291 reoperations performed in 236 primary augmentation patients through 10 years following implantation. Table 10 provides the primary reasons for reoperation. The most common reasons for reoperation through 10 years in these patients were capsular contracture (25%) and patient request for change in the size or style of the implant (21%).

Table 10 Main Reasons for Reoperation through 10 Years for Primary Augmentation Patients (N=291 Reoperations)	
Reasons for Reoperation through 10 Years[1]	**n (%)**
Capsular Contracture	72 (24.7%)
Patient Request for Size/Style Change	60 (20.6%)
Ptosis	31 (10.7%)
Hematoma/Seroma	23 (7.9%)
Implant Malposition	20 (6.9%)
Suspected Rupture	19 (6.5%)
Asymmetry	10 (3.4%)
Scarring/Hypertrophic Scarring	10 (3.4%)
Mass/Lump/Cyst	9 (3.1%)
Unknown	9 (3.1%)
Infection	7 (2.4%)
Wrinkling/Rippling	6 (2.1%)
Breast Cancer	5 (1.7%)
Delayed Wound Healing	3 (1.0%)
Nipple-Related Complications	3 (1.0%)
Implant Extrusion	1 (0.3%)
Pain	1 (0.3%)
Palpability/Visibility	1 (0.3%)
Upper Pole Fullness	1 (0.3%)
[1] Some reoperations were performed for multiple reasons; only the primary reason is provided in the table.	

Revision-Augmentation Patients

There were 172 reoperations performed in 123 revision-augmentation patients through 10 years following implantation. Table 11 provides the main reasons for reoperation. In this population, the most common reasons for reoperation through 10 years were patient's desire for a change in the size or style of their Implants (17%) and capsular contracture (16%).

Table 11 Main Reasons for Reoperation through 10 Years for Revision-Augmentation Patients (N=172 Reoperations)	
Reasons for Reoperation through 10 Years[1]	**n (%)**
Patient Request for Size/Style Change	30 (17.4%)
Capsular Contracture	28 (16.3%)
Implant Malposition	14 (8.1%)
Ptosis	13 (7.6%)
Wrinkling/Rippling	12 (7.0%)
Asymmetry	11 (6.4%)
Pain	11 (6.4%)
Scarring/Hypertrophic Scarring	11 (6.4%)
Unknown	8 (4.7%)
Mass/Cyst/Lump	7 (4.1%)
Delayed Wound Healing	5 (2.9%)
Hematoma/Seroma	5 (2.9%)
Breast Cancer	4 (2.3%)
Infection	4 (2.3%)
Suspected Rupture	4 (2.3%)
Implant Extrusion	1 (0.6%)
Implant Palpability/Visibility	1 (0.6%)
Necrosis	1 (0.6%)
Nipple-Related Complications	1 (0.6%)
Other[2]	1 (0.6%)

[1] Some reoperations were performed for multiple reasons; only the primary reason is provided in the table.
[2] Patient reported back pain from the weight of the Implants.

Primary Reconstruction Patients

There were 124 reoperations performed in 99 primary reconstruction patients through 10 years following implantation. Table 12 provides the main reasons for reoperation. In this population, the most common reason for reoperation, through 10 years, was the patient's desire for a change in the size or style of the Implant (20%).

Table 12 Main Reasons for Reoperation through 10 Years for Primary Reconstruction Patients (N=124 Reoperations)	
Reasons for Reoperation1	**n (%)**
Patient Request for Size/Style Change	25 (20.2%)
Asymmetry	20 (16.1%)
Infection	10 (8.1%)
Capsular Contracture	9 (7.3%)
Unknown	8 (6.5%)
Implant Malposition	7 (5.6%)
Ptosis	7 (5.6%)
Mass/Lump/Cyst	6 (4.8%)
Hematoma/Seroma	5 (4.0%)
Nipple-Related Complications	5 (4.0%)
Suspected Rupture[2]	5 (4.0%)
Scarring/Hypertrophic Scarring	4 (3.2%)
Breast Cancer	3 (2.4%)
Delayed Wound Healing	3 (2.4%)
Implant Extrusion	2 (1.6%)
Skin Related	2 (1.6%)
Implant Palpability/Visibility	1 (0.8%)
Pain	1 (0.8%)
Wrinkling/Rippling	1 (0.8%)

[1] Some reoperations were performed for multiple reasons; only the primary reason is provided in the table.
[2] Two of the five patients were confirmed non-ruptured via explant.

Revision-Reconstruction Patients

There were 55 reoperations performed in 42 revision-reconstruction patients through 10 years following implantation. Table 13 provides the main reasons for reoperation. In this population, the most common reason for reoperation through 10 years was asymmetry (24%).

Table 13 Main Reasons for Reoperation through 10 Years for Revision-Reconstruction Patients (N=55 Reoperations)	
Reasons for Reoperation[1]	**n (%)**
Asymmetry	13 (23.6%)
Capsular Contracture	12 (21.8%)
Patient Request for Size/Style Change	9 (16.4%)
Implant Malposition	5 (9.1%)
Nipple-related Complications	3 (5.5%)
Mass/Lump/Cyst	2 (3.6%)
Pain	2 (3.6%)
Unknown	2 (3.6%)
Breast Cancer	1 (1.8%)
Hematoma/Seroma	1 (1.8%)
Infection	1 (1.8%)
Scarring/Hypertrophic Scarring	1 (1.8%)
Suspected Rupture	1 (1.8%)
Trauma	1 (1.8%)
Wrinkling/Rippling	1 (1.8%)
[1] Some reoperations were performed for multiple reasons; only the primary reason is provided in the table.	

2.3.3. Reasons for Implant Removal

Primary Augmentation Patients

The main reasons for Implant removal among primary augmentation patients through 10 years are provided in Table 14. There were 283 Implants removed from 151 patients. Of these 283 Implants, 74 % were replaced. The most common reason for Implant removal was the patient requesting a different Implant size or style (49%).

Table 14 Main Reason for Implant Removal through 10 Years for Primary Augmentation Patients (N= 283 Implant Removals)	
Reason for Removal	**n (%)**
Patient Request for Size/Style Change	139 (49.1%)
Capsular Contracture	53 (18.7)
Suspected Rupture	21 (7.4%)
Unknown	17 (6.0%)
Ptosis	14 (4.9%)
Infection	8 (2.8%)

Table 14 (cont.) Main Reason for Implant Removal through 10 Years for Primary Augmentation Patients (N= 283 Implant Removals)	
Reason for Removal	**n (%)**
Wrinkling/Rippling	8 (2.8%)
Asymmetry	7 (2.5%)
Hematoma/Seroma	5 (1.8%)
Implant Malposition	5 (1.8%)
Breast Cancer	4 (1.4%)
Delayed Wound Healing	1 (0.4%)
Implant Extrusion	1 (0.4%)

Revision-Augmentation Patients

The main reasons for Implant removal among revision-augmentation patients through 10 years are provided in Table 15. There were 144 Implants removed from 79 patients. Of these 144 Implants, most were replaced (69%). The most common reason for Implant removal was the patient requesting a different Implant size or style (44%).

Table 15 Main Reason for Implant Removal through 10 Years for Revision-Augmentation Patients (N=144 Implant Removals)	
Reason for Removal	**n (%)**
Patient Request for Size/Style Change	63 (43.8%)
Capsular Contracture	16 (11.1%)
Unknown	15 (10.4%)
Wrinkling/Rippling	11 (7.6%)
Asymmetry	7 (4.9%)
Implant Malposition	6 (4.2%)
Breast Cancer	5 (3.5%)
Suspected Rupture	5 (3.5%)
Infection	4 (2.8%)
Ptosis	4 (2.8%)
Hematoma/Seroma	3 (2.1%)
Other	2 (1.4%)
Scarring/Hypertrophic Scarring	2 (1.4%)
Pain	1 (0.7%)

Primary Reconstruction Patients

The main reasons for explantation among primary reconstruction patients through 10 years are provided in Table 16. There were 111 Implants removed from 73 patients. Of these 111 Implants, most were replaced (77%). The most common reason for Implant removal was the patient requested an Implant size or style change (36%).

Table 16
Main Reason for Implant Removal through 10 Years
for Primary Reconstruction Patients
(N=111 Explants)

Reasons for Implant Removal	n (%)
Patient Request for Size/Style Change	40 (36.0%)
Asymmetry	18 (16.2%)
Unknown	11 (9.9%)
Implant Malposition	9 (8.1%)
Infection	9 (8.1%)
Capsular Contracture	8 (7.2%)
Suspected Rupture[1]	6 (5.4%)
Scarring/Hypertrophic Scarring	3 (2.7%)
Implant Extrusion	2 (1.8%)
Wrinkling/Rippling	2 (1.8%)
Breast Cancer	1 (0.9%)
Delayed Wound Healing	1 (0.9%)
Hematoma/Seroma	1 (0.9%)

[1] Two of the 6 devices were confirmed not ruptured at explantation.

Revision-Reconstruction Patients

The main reasons for explantation among revision-reconstruction patients through 10 years are provided in Table 17. There were 50 Implants removed from 36 patients. Of these 50 Implants, most were replaced (72%). The most common reason for Implant removal was the patient requested an Implant style or size change (28%).

Table 17 Main Reason for Implant Removal through 10 Years for Revision-Reconstruction Patients (N=50 Explants)	
Reasons for Implant Removal	**n (%)**
Patient Request for Size/Style Change	14 (28.0%)
Asymmetry	9 (18.0%)
Capsular Contracture	9 (18.0%)
Implant Malposition	4 (8.0%)
Pain	4 (8.0%)
Unknown	3 (6.0%)
Trauma	2 (4.0%)
Breast Cancer	1 (2.0%)
Hematoma/Seroma	1 (2.0%)
Infection	1 (2.0%)
Suspected Rupture	1 (2.0%)
Wrinkling/Rippling	1 (2.0%)

2.3.4. Other Clinical Findings

The Study evaluated several long-term health effects that have been reported in breast implant patients. These include cancer, connective tissue disease (CTD), CTD signs and symptoms, lactation complications and reproduction complications. These endpoints, along with others, are being further evaluated as part of Sientra's US-PAS postapproval study and the National Breast Implant Registry (NBIR).

Results for cancer, lactation complications, reproduction complications, and suicide are presented immediately following this paragraph. Connective tissue disease (CTD) and CTD signs and symptoms data are presented below in the Panel topic discussion of "Systemic Symptoms Reported in Patients Receiving Breast Implants."

Cancer

For primary augmentation patients, through 10 years, there have been five cases of breast cancer identified (0.6%). Diagnoses of any other (non-breast) cancers have been reported in 12 patients (1.1%) in the augmentation cohort through 10 years. There were four cases of fibrocystic disease (0.5%) in the primary augmentation cohort through 10 years.

For revision-augmentation patients, through 10 years, there have been four cases of breast cancer (1.6%). Diagnoses of any other (non-breast) cancers have been reported in 4 patients (1.1%) in the revision-augmentation cohort through 10 years. There were five cases of fibrocystic disease in the revision-augmentation cohort through 10 years (1.8%).

One primary reconstruction patient reported breast cancer during the 10 years following implantation and three recurrent cases of breast cancer were reported (2.9%). Diagnoses of any other (non-breast) cancers have been reported in 16 patients (7.1%) in the primary reconstruction cohort through 10 years. The other types of cancer include duodenum, ovarian, pancreatic, skin, and metastatic cancers. There were no cases of fibrocystic breast disease reported through 10 years in primary reconstruction patients.

Two revision-reconstruction patients reported breast cancer through 10 years in the Study; both were recurrent cases of breast cancer. This represents a risk of 3.2%. Diagnoses of any other (non-breast) cancers have been reported in seven patients (8%) in the revision-reconstruction cohort through 10 years. The other types of cancers reported in the revision-reconstruction cohort include lung, skin and metastatic cancers. There was one case of fibrocystic disease among revision-reconstruction patients through 10 years (1.7%).

There were no cases of BIA-ALCL in any of the patient cohorts in the Study through 10 years of follow-up.

Lactation Complications

There were 236 primary augmentation patients experiencing at least one postoperative live birth; of these, 88% reported no difficulties with lactation after they received Sientra's Implants. Twenty-seven of the 236 patients (11%) reported postoperative lactation difficulties, such as lack of milk production, mastitis or pain. In addition, one woman (0.4%), who had experienced preoperative lactation difficulties reported postoperative difficulties as well.

There were 47 revision-augmentation patients experiencing at least one postoperative live birth; of these, 89% reported no difficulties with lactation after they received Sientra's Implants. Five of the 47 patients (11%) reported postoperative lactation difficulties, such as lack of milk production or pain.

There were 22 primary reconstruction patients who delivered a baby after reconstruction with Study Implants. None of these patients reported difficulties with lactation after they received the Implants.

There were three revision-reconstruction patients who delivered a baby after reconstruction with Study Implants; these patients reported no problems with lactation.

Reproduction Complications

Of the 1,116 patients in the primary augmentation cohort, 19 (1.7%) reported postoperative pregnancy difficulties through 10 years. In addition, four women (0.4%) who had experienced preoperative pregnancy difficulties reported postoperative difficulties as well. Of the 363 patients in the revision-augmentation cohort, six (1.7%) reported postoperative pregnancy difficulties.

Of the 225 patients in the primary reconstruction cohort, 2 (0.9%) reported postoperative pregnancy difficulties through 10 years. Of the 84 patients in the revision-reconstruction cohort, none (0%) had postoperative pregnancy difficulties.

Suicide
Although not collected as a primary endpoint, there was one report of a possible suicide in the primary augmentation cohort and no reports of suicide in the revision-augmentation, primary reconstruction or revision-reconstruction cohorts in the Study through 10 years.

3. BREAST IMPLANT ASSOCIATED ANAPLASTIC LARGE CELL LYMPHOMA (BIA-ALCL)

3.1. Background

In 2011, FDA released a report of preliminary findings and analyses regarding a possible link between breast implants and the development of anaplastic large cell lymphoma (ALCL). Although FDA considers ALCL to be "extremely rare," FDA stated its intention to continue collecting data to better characterize the possible association of ALCL with breast implants. Two of the steps that FDA identified included: (1) working with ASPS and the clinical and scientific community to pursue a registry of women with breast implants and ALCL and (2) asking industry to update their breast implant labeling.

In 2016, FDA reported that the World Health Organization designated breast implant-associated anaplastic large cell lymphoma (BIA-ALCL) as a T-cell lymphoma that can develop following breast implants. Moreover, the data suggest that this occurs more frequently with textured implants. In 2019, FDA further reported that there were 457 unique MDRs for BIA-ALCL, including 9 deaths, since November 30, 2018. FDA also noted that there was additional literature published since their 2011 report.

Regarding the ASPS registry, the Patient Registry and Outcomes For breast Implants and Anaplastic Large Cell Lymphoma (ALCL) Etiology and Epidemiology (PROFILE) registry was developed and implemented in 2011. It is currently open to all physicians who have a patient with breast implants that has a suspected or confirmed case of breast implant-associated ALCL (BIA-ALCL).

Regarding the labeling, since approval of its PMA in 2012, the Sientra patient labeling has included the FDA-recommended information regarding ALCL. In 2017 Sientra revised both its physician and patient labeling with the FDA-approved verbiage to apprise health care practitioners and patients of the updated information related to BIA-ALCL, as follows:

Updated Physician Labeling Language

<u>BREAST IMPLANT ASSOCIATED ANAPLASTIC LARGE CELL LYMPHOMA (BIA-ALCL)</u>

Based on information reported to global regulatory agencies and found in medical literature, an association has been identified between breast implants and the development of anaplastic large cell lymphoma (ALCL), a type of non-Hodgkin's lymphoma. Women with breast implants have a very small but increased risk of developing Breast Implant Associated ALCL (BIA-ALCL) in the fluid or scar capsule adjacent to the implant, with documented potential for local, regional, and distant spread of the cancer with mortality reported in rare cases.

BIA-ALCL has been reported globally in patients with an implant history that includes Sientra's and other manufacturers' breast implants with various surface properties, styles, and shapes. Most of the cases in the literature reports describe a history of the use of textured implants.

You should consider the possibility of BIA-ALCL when a patient presents with late onset, persistent peri-implant seroma. In some cases, patients presented with capsular contracture or masses adjacent to the breast implant. When testing for BIA-ALCL, collect fresh seroma fluid and representative portions of the capsule, and send to a laboratory with appropriate expertise for pathology tests to rule out ALCL, including immunohistochemistry testing for CD30 and ALK (anaplastic lymphoma kinase). If your patient is diagnosed with peri-implant BIA-ALCL, develop an individualized treatment plan in coordination with a multidisciplinary care team. Because of the small number of cases worldwide, there is no worldwide consensus on the treatment regimen for peri-implant BIA-ALCL. However, the National Comprehensive Cancer Network (NCCN) recommends surgical treatment that includes implant removal and complete capsulectomy ipsilaterally as well as contralaterally, where applicable.

Report all confirmed cases of BIA-ALCL to the FDA (https://www.fda.gov/Safety/MedWatch). In some cases, the FDA may contact you for additional information. The FDA will keep the identities of the reporter and the patient confidential.

FDA also recommends reporting cases of BIA-ALCL to the PROFILE Registry (https://www.thepsf.org/research/clinical-impact/profile.htm) where you can submit more comprehensive case data. This will help provide a better understanding of the etiology of BIA-ALCL.

For additional information on FDA's analysis and review of BIA-ALCL, please visit: http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/BreastImplants/ucm239995.htm

Updated Patient Labeling Language

Breast Implant Associated Anaplastic Large Cell Lymphoma

If you have breast implants, you have a very small, but increased risk of developing breast implant associated anaplastic large cell lymphoma, or BIA-ALCL. BIA-ALCL is not breast cancer —it is a rare type of non-Hodgkin's lymphoma (cancer of the immune system). In most cases, BIA-ALCL is found in the scar tissue and fluid near the implant, but in some cases it can spread throughout the body. In the cases that have spread beyond the scar tissue and fluid near the implant, rare cases of death have been reported.

Most patients were diagnosed with BIA-ALCL when they sought medical treatment for implant-related symptoms such as swelling, pain, lumps, or asymmetry that developed after their initial surgical sites were fully healed. In the cases known to FDA to date, BIA-ALCL was diagnosed years after the breast implant was placed. The earliest report was one year after implant placement and the latest was 23 years after the implant surgery. About half the cases occurred within the first 7 years after implant. BIA-ALCL was most often diagnosed in women who had textured implants. The textured implant may have been placed at the most recent surgery or at any other prior breast implant operation.

If you develop swelling or pain around your breast implants, be sure to talk to your health care provider. Your health care provider should consider the possibility of BIA-ALCL if after you have recovered from your breast implant operation, you later notice changes in the way your breast looks or feels — including swelling or pain around the implant. If your health care provider suspects BIA-ALCL, they will refer you to an appropriate specialist for evaluation which may involve obtaining fluid and tissue samples from around your breast implant. If a diagnosis of BIA-ALCL is confirmed, the doctor will develop an individualized treatment plan for you. Because of the small number of cases worldwide and the variety of available treatment options, there is no single defined treatment. However, if you are diagnosed with BIA-ALCL, the National Comprehensive Cancer Network (NCCN) recommends removing the implant and the surrounding tissue.

If you have breast implants, you should monitor them and follow your routine medical care. You do not need to take any additional steps. It is not necessary to remove your breast implants if you have no symptoms and you have not been diagnosed with BIA-ALCL.

If you are diagnosed with BIA-ALCL, you can help the FDA understand the disease and the effectiveness of treatment.

You or your doctor should report all confirmed cases of BIA-ALCL to the FDA ((https://www.fda.gov/Safety/MedWatch/). In some cases, the FDA may contact you for additional information. The FDA will keep the identities of the reporter and the patient confidential.

In addition, if you are diagnosed with BIA-ALCL, talk to you doctor about reporting it to the PROFILE Registry (https://www.thepsf.org/research/clinical-impact/profile.htm).

Every case of BIA-ALCL should be reported to the PROFILE Registry because this helps provide a better understanding of the disease.

If you are considering breast implant surgery, you should discuss the risks and benefits with your health care provider. You may also visit the FDA's Breast Implants website for additional information https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/BreastImplants/ucm064106.htm.

For additional information on FDA's analysis and review of BIA-ALCL, please visit:

http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/BreastImplants/ucm239995.htm

3.2. Sientra-Specific Data

Although Sientra has not received any reports of breast implant associated anaplastic large cell lymphoma (BIA-ALCL) for the PACS (completed 10-year study) or US-PAS (ongoing study) populations, two cases of BIA-ALCL were reported for two patients from the same study site in the Postapproval Continued Access Study (PACAS). Both patients were diagnosed after study completion (Final Report at five years of follow-up), at the 7-10 year postoperative time-frame. Both patients have had no further treatment and remain disease free. Sientra reported both cases to FDA in MDR reports. In addition, Sientra instructed the surgeon to report both cases to the PROFILE registry, and it is Sientra's understanding that this was completed. Breast implant manufacturers do not have access to the PROFILE registry database.

Four (including the two PACAS cases mentioned above) of the 497 unique MDRs identified by FDA involve Sientra Implants. However, two of the four patients each had previous tissue expanders and breast implants from another manufacturer prior to receiving Sientra Implants. It is important to note that ALCL is not specific to breast implants; there are numerous cases of ALCL reported with the use of a wide range of medical devices (e.g., tibial implants, dental implants, gluteal implants, chemotherapy ports, hip prostheses, and gastric bands). Multiple literature reports[27],[28],[29],[30],[31],[32],[33] of ALCL underscore the fact that while BIA-ALCL it is an important consideration in breast implant surgery, ALCL also occurs with other medical devices,

[27] Tibial Implant ALCL, Palraj, B., Paturi, A., Stone, R. G., Alvarez, H., Sebenik, M., Perez, M. T., & Bush, L. M. (2010). Soft tissue anaplastic large T-cell lymphoma associated with a metallic orthopedic implant: case report and review of the current literature. *The Journal of Foot and Ankle Surgery*, *49*(6), 561-564.

[28] Dental Implant ALCL, Yoon, H. J., Choe, J. Y., & Jeon, Y. K. (2015). Mucosal CD30-positive T-cell lymphoproliferative disorder arising in the oral cavity following dental implants: report of the first case. *International journal of surgical pathology*, *23*(8), 656-661.

[29] Chest Port ALCL, Engberg, A. K., Bunick, C. G., Subtil, A., Ko, C. J., & Girardi, M. (2013). Development of a plaque infiltrated with large CD30+ T cells over a silicone-containing device in a patient with history of Sezary syndrome. *Journal of Clinical Oncology*, *31*(6), e87.

[30] Total hip arthroplasties have higher rates of lymphoma, Kellogg, B. C., Hiro, M. E., & Payne, W. G. (2014). Implant-associated anaplastic large cell lymphoma: beyond breast prostheses. *Annals of plastic surgery*, *73*(4), 461-464.

[31] Shoulder Repair, Tuck, M., Lim, J., Lucar, J., & Benator, D. (2016). Anaplastic large cell lymphoma masquerading as osteomyelitis of the shoulder: an uncommon presentation. *Case Reports*, *2016*, bcr2016217317.

[32] Lap Band ALCL, Manikkam Umakanthan, J., McBride, C. L., Greiner, T., Yuan, J., Sanmann, J., Bierman, P. J., & Bociek, R. G. (2017). Bariatric Implant–Associated Anaplastic Large-Cell Lymphoma. *Journal of oncology practice*, *13*(12), 838-839.

[33] Gluteal Implant ALCL**,** Shauly, O., Gould, D. J., Siddiqi, I., Patel, K. M., & Carey, J. (2019). The First Reported Case of Gluteal Implant-Associated Anaplastic Large Cell Lymphoma (ALCL). *Aesthetic surgery journal*.

and additionally, occurs in the general population irrespective of medical implants. The incidence of ALCL diagnosis in women is approximately 1/500,000 per year[34].

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3.3. Additional Efforts to Share and Collect BIA-ALCL Information

BIA-ALCL is a condition that Sientra takes very seriously and has spent a tremendous amount of time investigating. Sientra continues to support medical research, education, and FDA initiatives to better understand BIA-ALCL and to provide women with the highest quality and safest implant options. Some specific actions that Sientra has taken are described below.

3.3.1. Educational Materials

Sientra supported the development of a two-part educational document[35], which was disseminated to its entire sales team and all surgeon customers. In addition, the sales team was trained on the information in the documents and was instructed to distribute the educational document to any new surgeon customers. These documents were also available at Sientra's booth and distributed during the Plastic Surgery Societies Trade Shows.

- The first part of the two-part education document is "Surgical Best Practices: 14-Point Plan." This was written by two Plastic Surgeon BIA-ALCL researchers and is aimed at reducing the number of bacteria present at the time of breast implant surgery, thus reducing the risk of infection. As noted in that document, "a wealth of evidence has demonstrated a link between chronic inflammation from bacterial biofilm in the pathogenesis of BIA-ALCL, especially in textured devices where the increased surface area can result in an increased amount of bacterial biofilm.[36] A meticulous procedure will help minimize the known and likely sequelae of bacterial attachment, including infection and chronic biofilm, which is implicated in the pathogenesis of both capsular contracture and BIA-ALCL."
- The second part is "Breast Implant-Associated Anaplastic Large Cell Lymphoma (BIA-ALCL) - Frequently Asked Questions" (FAQ). Sientra wrote this as a reference for plastic surgeons regarding the known information on BIA-ALCL as of 2017, to assure awareness among its sales force and customers of BIA-ALCL symptoms, diagnosis and treatment.

3.3.2. Professional Outreach

Sientra has initiated multiple outreach efforts to ensure that surgeons and Sientra's Sales Team is aware of any updates on BIA-ALCL. True to Sientra's commitment to safety and positive patient outcomes, and out of an abundance of caution, it is protocol that the entire Sientra Sales Team is trained regularly (quarterly or more) through in-person trainings, Web Ex,

[34] Altekruse SF, Kosary CL, Krapcho M, Neyman N, Aminou R, Waldron W, Ruhl J, Howlader N, Tatalovich Z, Cho H, Mariotto A, Eisner MP, Lewis DR, Cronin K, Chen HS, Feuer EJ, Stinchcomb DG, Edwards BK (eds). SEER Cancer Statistics Review, 1975-2015, National Cancer Institute. Bethesda, MD, https://seer.cancer.gov/csr/1975_2015/browse_csr.php Table 19.28, based on November 2009 SEER data submission, posted to the SEER website, 2010

[35] http://sientra.com/Content/pdfs/Sientra%2014%20Point%20Plan%20%20BIA-ALCL%20FAQ_2017.pdf

[36] Hu, H., Jacombs, A., Vickery, K., Merten, S. L., Pennington, D. G., & Deva, A. K. (2015). Chronic biofilm infection in breast implants is associated with an increased T-cell lymphocytic infiltrate: implications for breast implant-associated lymphoma. Plast Reconstr Surg, 135(2), 319-329. doi:10.1097/PRS.0000000000000886

teleconferences, and is provided with informational Frequently Asked Questions (FAQ). In fact, Dr. Mark Clemens (expert BIA-ALCL researcher) presented to and trained the entire Sientra Sales Team on BIA-ALCL at a National Sales Meeting in January 2018. In addition, Dr. Clemens presented to plastic surgeons at multiple Sientra Regional Educational Dinners (Nov. 2017, January 2018) and Web-Ex Meetings on BIA-ALCL (May 2018).

Sientra supported and distributed the joint BIA-ALCL education statement prepared by ASPS and ASAPS, with the cooperation of ISAPS, to update plastic surgeons on the known risks, symptoms. diagnosis and treatment with a treatment algorithm flow-chart. In addition, Sientra has distributed multiple surgeon education letters, as well as sponsored numerous educational videos with experts on key safety topics. In addition to BIA-ALCL, topics included: appropriate implant selection, capsular contracture, seroma testing, patient informed consent discussion, etc.

3.3.3. Sientra Support of Publications Specific to the Topic of BIA-ALCL

Sientra sponsored peer-reviewed supplements on BIA-ALCL in the *Plastic and Reconstructive Surgery Journal* (PRS) and the *Aesthetic Surgery Journal* (ASJ), both published in March 2019. Sientra also sponsored Anand Deva (expert BIA-ALCL researcher) to present at the International Beauty Through Science meeting in June 2018 and at a Sientra educational dinner on BIA-ALCL during an annual ASAPS Meeting in April 2018.

All of the activities and communications described above were driven by Sientra in order to support research, as well as increase awareness and education to plastic surgeons, their office staff and in turn, their patients.

4. SYSTEMIC SYMPTOMS REPORTED IN PATIENTS RECEIVING BREAST IMPLANTS

4.1. Sientra-specific Data (10-Year PACS)

In Sientra's completed PACS, the 10-year risks of CTD were 1.2% for the primary augmentation cohort, 1.3% for the revision augmentation cohort, 0.7% for the primary reconstruction cohort, and 3.2% for the revision reconstruction cohort. Below are more details on the CTD findings through 10 years.

4.1.1. Connective Tissue Disease

Among 1116 primary augmentation patients, through Year 10, 11 patients have reported 12 confirmed CTDs. The diagnoses include: one patient with chronic fatigue syndrome (diagnosed 9 months post implantation); two patients with fibromyalgia (diagnosed 9 months and 5.6 years post implantation); one patient with Grave's disease (diagnosed 4.1 years post implantation); one patient with lupus (diagnosed 2.3 years post implantation); two patients with Reynaud's phenomenon (diagnosed at 9 months and 5.3 years post implantation); four cases of rheumatoid arthritis (diagnosed between 2 months and 6.1 years post implantation); and one patient with Sjögren's syndrome (diagnosed 6.8 years post implantation). The 10-year risk of a Primary Augmentation patient diagnosed with any CTD is 1.2%.

Among 363 revision-augmentation patients, through Year 10, three patients have reported confirmed CTDs. The diagnoses include: one patient with fibromyalgia (diagnosed 10 months post implantation); one patient with Grave's disease (diagnosed 8.3 years post implantation); and

one patient with scleroderma (diagnosed 9 years post implantation). The 10-year risk of a Revision Augmentation patient diagnosed with any CTD is 1.3%.

Among primary reconstruction patients through Year 10, one patient has been diagnosed with CTD, Sjögren's Syndrome (5.1 years post-implantation). Based on this, the 10-year risk among primary reconstruction patients of Sjögren's Syndrome is 0.7%.

Two of the 84 revision-reconstruction patients in the Study were diagnosed with a CTD in the 10 years after receiving implants; the diagnoses were one case of Hashimoto's Thyroiditis (1.1-year post implantation) and one case of Sjögren's Syndrome (3.7 years post-implantation). Based on this, the 10-year risk of Hashimoto's Thyroiditis is 1.4% while the risk of Sjögren's Syndrome is 1.8%, while the risk of having at least one CTD is 3.2%.

4.1.2. CTD and Neurological Signs and Symptoms

In Sientra's Study, self-reported CTD and neurological signs and symptoms were collected. Compared to before having Implants, for the primary augmentation and revision-augmentation cohorts and for the primary reconstruction and revision-reconstruction cohorts, no significant increases were found in any of the 13 CTD sign/symptom categories.

Conversely, compared to before having Implants, significant decreases were found for three of the 13 CTD sign/symptom categories for the augmentation cohorts: neurological, endocrine/exocrine and vascular. For the category of neurological, the significance is driven by the low number of post-implantation reports of migraine. For the category of endocrine/exocrine, the significance is driven by the low number of post-implantation reports of Hashimoto's thyroiditis, while for the category of vascular, the significance is driven by a decrease in telangiectasia post-implantation.

No significant decreases were found across the 13 signs/symptom categories in the primary reconstruction and revisions-reconstruction cohorts when compared to baseline, i.e., before being implanted.

The Sientra Study was not designed to evaluate cause-and-effect associations because there is no comparison group of women without implants, and because other contributing factors, such as medications and lifestyle/exercise, were not studied. Therefore, it cannot be determined whether or not these three decreases were due to the Implants.

4.2. Sientra-specific Data (US-PAS/OASIS Study)

This 10-year postapproval cohort study is designed to evaluate the long-term clinical performance of Sientra OPUS Silicone Gel Breast Implants under general conditions of use in the post-market environment. Study enrollment is complete with 5,197 Study participants and 301 control participants, and the study is in its third year of patient follow-up. Connective Tissue Disease and CTD signs and symptoms, along with neurological signs and symptoms are primary endpoints in the US-PAS that will be analyzed throughout the study. CTD signs and symptoms, and neurological signs and symptoms will be compared to the control group (patients who have undergone aesthetics procedures, e.g., rhinoplasty).

4.2.1. Connective Tissue Disease

Through two years of follow-up, study investigators have reported three CTDs (two cases of Lupus/SLE and one case of Sjögren's). Participants self-reported eight CTDs (two cases each of

Lupus/SLE, Sjögren's, and Hashimoto's, one case of Giant Cell Arteritis and a recurrence of Transverse Myelitis).

4.2.2. CTD and Neurological Signs and Symptoms

Participant self-reported CTD signs and symptoms and neurological signs and symptoms two years post-implantation were compared to those self-reported by control participants. Based on propensity regression analyses, the risk of signs and symptoms was not statistically significantly different between implanted participants and controls (i.e., the 95% CIs of the estimated ratios included zero). The overall Relative Risk (RR) for CTD signs and symptoms is RR=1.14; 95% CI [0.85, 1.52], and for neurological signs and symptoms, RR=1.04; 95% CI [0.80, 1.37].

4.3. Systematic Evidence Review

Prior reports and evidence reviews, including a 1998 National Science Panel Report[37], a 1999 Institute of Medicine report (IOM)[38], and a 2011 FDA 2011 *FDA Update on the Safety of Silicone Gel-Filled Breast Implants,* concluded that there was no evidence that silicone gel breast implants cause systemic health effects, such as connective tissue disease.

As part of the development of the National Breast Implant Registry (NBIR), an updated systematic evidence review of long-term health outcomes and silicone gel breast implants was conducted by Ethan Balk, et al[39]. This independent review was funded by the ASPS PSF and breast implant manufacturers. The review not only included published literature, but also included clinical trial data from silicone gel breast implant manufacturers. Sientra participated as a member of the Advisory Panel to provide background information to the research team, along with representatives from other breast implant manufacturers, ASPS PSF, FDA, and women's health research advocates.

The conclusions from this updated evidence review essentially corroborated the previous systematic reviews conducted over the past 20 years. As a result of this confirmatory evidence review, FDA terminated the Sientra PACCS, stating the following regarding the Systematic Review Report:

- *Please be advised that the systematic literature review conducted by Tufts University showed insufficient evidence of association between silicone gel-filled breast implants and lymphoma, brain cancer, cervical cancer, rare connective tissue diseases (CTDs), or rare neurological events. As a result of this recent data review, the FDA concluded that using case-control studies to study these rare events would not provide additional value. Please be advised that the FDA is no longer requiring silicone gel breast implant manufacturers to conduct case-control studies to study*

[37] Diamond, B. A., Hulka, B. S., Kerkvliet, N. I., & Tugwell, P. (1998). 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 multidistrict litigation. US District Court for the Northern District of Alabama, Birmingham, AL*, *17*.

[38] Institute of Medicine 1999. Safety of Silicone Breast Implants: Washington, DC: The National Academies Press. https://doi.org/10.17226/9602.

[39] Balk, E. M., Earley, A., Avendano, E. A., & Raman, G. (2016). Long-term health outcomes in women with silicone gel breast implants: a systematic review. *Annals of internal medicine*, 164(3), 164-175.

lymphoma, brain cancer, cervical cancer, rare connective tissue diseases (CTDs), or rare neurological events

- *Please be advised that the Tufts Evidence Review found evidence of a potential association between silicone gel-filled breast implants and lung cancer, rheumatoid arthritis and suicide. These less rare endpoints will be evaluated by your cohort study "US Post- Approval Study (US-PAS)".*

5. MAGNETIC RESONANCE IMAGING (MRI) SCREENING FOR SILENT RUPTURE OF SILICONE GEL-FILLED BREAST IMPLANTS

MRI evaluations to screen for silent rupture were required in the Investigation Device Exemption (IDE) clinical trials conducted to support PMA approval and are recommended as periodic screening postapproval. Regarding that, Sientra's current physician labeling states:

> *Rupture of a silicone gel breast implant may be silent/asymptomatic (i.e., there are no symptoms experienced by the patient and no physical signs of changes with the implant), rather than symptomatic. You should advise your patient to undergo regular MRIs to screen for silent rupture even if she experiences no problems. The first MRI should be performed at 3 years postoperatively, then every 2 years, thereafter. The importance of these MRI evaluations should be emphasized. If rupture is noted on MRI, then you should advise your patient to have her Implant removed. You should provide her with a list of MRI facilities in her area that have at least a 1.5 Tesla magnet, a dedicated breast coil, and a radiologist experienced with reading breast implant MRIs to diagnose a silent rupture. Diagnostic procedures will add to the cost of having implants, and patients should be aware or advised that these costs may exceed the cost of their initial surgery over their lifetime and that their insurance carrier may not cover these costs.*

While MRIs are effective in detecting silent rupture, it is unclear what the optimum time period or intervals are for undergoing screening MRI for silent rupture. It is doubtful for various reasons, including, but not limited to heath care coverage, as well as logistics, that women follow the recommendation to receive MRIs every 2 years for the duration they have the implants. There is also some belief that other imaging technologies may be just as effective as MRIs at detecting silent rupture, while being less obtrusive.

Whether or not to remove a ruptured implant if asymptomatic is not clear-cut. FDA requires the physician labeling to include language that the physician is to advise the patient to have her implant removed if rupture is noted on MRI. Sientra's physician labeling specifically states the following:

> *"If rupture is noted on MRI, then you should advise your patient to have her Implant removed. You should provide her with a list of MRI facilities in her area that have at least a 1.5 Tesla magnet, a dedicated breast coil, and a radiologist experienced with reading breast implant MRIs to diagnose a silent rupture."*

Sientra's physician labeling goes on to state:

> ***Additional Information on the Consequences of Rupture from Literature:***
>
> *Studies of Danish women evaluated with MRI involving a variety of manufacturers and implant models showed that about three-fourths of implant ruptures are intracapsular and the remaining one-fourth is extracapsular.*[40] *Additional studies of Danish women indicate that over a 2-year period, about 10% of the implants with intracapsular rupture progressed to extracapsular rupture as detected by MRI.*[41] *Approximately half of the women whose ruptures had progressed from intracapsular to extracapsular reported that they experienced trauma to the affected breast during this time period or had undergone mammography. In the other half, no cause was given. In the women with extracapsular rupture, after 2 years, the amount of silicone seepage outside the scar tissue capsule increased for about 14% of these women. This type of information pertains to a variety of silicone implants from a variety of manufacturers and implant models, and is not specific to Sientra's OPUS Silicone Gel Breast Implants.*

Ultimately, whether or not to proceed with removing an asymptomatic rupture found on MRI, is a decision that must remain between the patient and her physician, as there are many factors that weigh into assessing the risks of either decision.

6. THE USE OF SURGICAL MESH IN BREAST PROCEDURES, SUCH AS BREAST RECONSTRUCTION AND MASTOPEXY

Currently, there are no surgical meshes for breast use that have been granted marketing clearance or approval. In fact, FDA has recently taken the position that mesh used for breast procedures is a new intended use and, thus, not eligible for the 510(k) route. FDA took a conservative stance regarding breast surgical mesh without clearly establishing the type and extent of data to support approval.

The use of surgical mesh in breast procedures impacts not only the breast implant industry, but also the surgical mesh industry. Use of surgical mesh not specifically indicated for use in breast procedures continues, which supports a clinical need in real-world practice.

Sientra's post-approval studies described above did not include the use of surgical mesh with their breast implants. However, the National Breast Implant Registry is collecting data on the use of surgical mesh and should provide a wealth of data in the future on real-world use.

Moving forward, Sientra recommends that FDA have an open forum with all key stakeholders to discuss not only its concerns (regulatory and scientific), but also to discuss the type and extent of data (nonclinical and clinical) that would be appropriate for mesh for breast use, with and without breast implants. An outcome of this process would be the eventual release of a guidance document.

[40] Hölmich, L. R. *et al.* Untreated silicone breast implant rupture. *Plast Reconstr Surg* 114, 204-214; discussion 215-216 (2004).
[41] Hölmich, L. R. *et al.* Self-reported diseases and symptoms by rupture status among unselected Danish women with cosmetic silicone breast implants. *Plast Reconstr Surg* 111, 723-732; discussion 733-734 (2003).

7. THE USE OF REGISTRIES FOR BREAST IMPLANT SURVEILLANCE

7.1.1. Benefits of Registries

Sientra fully supports the use of registries to collect safety and/or effectiveness data on breast implants. Registry data can be used to:

- Form the infrastructure to conduct post-approval studies
- Support expanded indications of marketed devices
- Support premarket clearance or approval of modified devices
- Support reclassification petitions
- Design more clinically relevant preapproval clinical trials

Registries should theoretically lead to better utilization of resources and share burden across more than one stakeholder.

- Registry scope and integration
  - Relationship to company-sponsored post-approval studies
  - How current and future post-approval studies will be integrated into device registries
  - Links to other registries - domestic and/or international
  - Link to disease-specific registries
  - Link to claims databases or other datasets
  - Device scope (e.g., one type or combine types into one registry)
- Development and implementation
  - Best strategies to incentivize physicians and patients to participate
  - Depth of data collection for newly created registries (e.g., phased approach or immediately comprehensive)

7.1.2. The National Breast Implant Registry (NBIR)

The National Breast Implant Registry (NBIR) was implemented in October 2018 to strengthen the postmarket surveillance infrastructure for breast implants. It was developed by a Steering Committee that includes representatives from the ASPS Plastic Surgery Foundation, FDA, breast implant industry and patient advocacy. The same Steering Committee is responsible for managing the Registry. Breast implant industry is currently funding the NBIR along with PSF. An additional intent of the NBIR is to serve a dual purpose of Device Tracking to reduce the burden of multiple data collection efforts for surgeons and their staff. Unique Device Identification (UDI) information, which has a myriad of benefits for numerous stakeholders, is also being captured for each breast implant entered into the NBIR.

The collective data amassed will facilitate trending that can be used to improve the safety of breast implants and breast implant procedures. The NBIR collects prospective data on patient demographics, risk factors, comorbidities, implant-specific information, procedural information, and complication/adverse event data related to breast implants for U.S. patients.

7.1.3. The Aesthetic Neural Network (ANN)

In addition to supporting the NBIR, Sientra also supports the Aesthetic Neural Network (ANN), an ASAPS data collection platform provided by the Aesthetic Surgery Education and Research Foundation (ASERF). ANN and ANN version 2 are designed to automatically and retrospectively extract operative information from a surgeon's electronic medical records, and then compile the data so that he or she can study previous outcomes and review factors such as complications and longevity of results. The ANN will help surgeons achieve better outcomes for their patients.

Following our commitment to BIA-ALCL physician education and patient safety, Sientra has funded ANN version 2, which includes a data collection feature to collect safety outcome data, including data related to the BIA-ALCL.

8. THE USE OF REAL-WORLD DATA AND PATIENT PERSPECTIVES IN REGULATORY DECISION-MAKING

Is real-world practice driving data collection or is data collection driving "real-world" practice?

Registries can play a larger role in the Total Product Life Cycle (TPLC), leading to a more efficient preapproval process. Collaboration is key (with FDA, other manufacturers, professional societies and other key stakeholders).

Section 7 above briefly describes the National Breast Implant Registry, which was implemented in October 2018. Sientra is one of the industry representatives that serves an active role on the Steering Committee. This registry should provide useful, real-world information that can be shared with physicians and patients. This registry should allow for an improved informed consent process for patients.

In August 2012, Sientra was invited to participate in a CDRH workshop. Sientra's presentation (Innovative Approaches to Evaluate Rare Outcomes in PAS) outlined the complexity of designing effective post-approval studies.

In September 2012, Sientra was invited to participate in a second CDRH workshop. The key points from Sientra's presentation (Using Registries for TPLC Evidence Appraisal of Medical Devices: An Industry Perspective) are outlined above.

9. BEST PRACTICES FOR INFORMED CONSENT

The public information on breast implants is overwhelming in quantity and detail compared to many medical devices. Being able to make a true informed consent decision regarding whether or not to receive breast implants involves many factors and responsible parties. Sientra wants women to feel confident in FDA-approved Sientra Breast Implants and in their decision to have breast augmentation or reconstructive surgery.

The patient labeling is the key source of information for the informed consent process. The development of the patient labeling is a joint effort between FDA and industry, with FDA having the final say before PMA approval is granted. Then, a Focus Group study is required as a condition of PMA approval to assure that the patient labeling is informative and readable to the lay audience. So how does this effort translate to a potential breast implant patient being able to make an informed consent? It doesn't. Instead, it just serves as the foundation for informed consent.

Industry makes the labeling readily available to potential patients. Sientra, for example, makes its patient labeling available to potential patients on its website. However, achieving true informed consent involves additional layers. The easiest approach is simply to provide the documents to the patients and have them read the information on their own. However, based on the complexity and mere volume of information, this is most likely not a sufficient approach for most patients.

It is common knowledge that many patients and patient advocacy groups do not believe that they are really being informed of the risks. More specifics are necessary to address this challenge, whether this comes from the advocacy groups, directly from patients, or from physicians. The range of issues is too broad otherwise. For example:

- Is the patient labeling too lengthy, too difficult to understand, or not structured in an optimum manner? How does one balance a comprehensive sharing of information without overwhelming the patient?
- Are patients always given access to the patient labeling prior to signing the informed consent document?
- Do patients feel rushed to make a decision, whether self-imposed or based on discussion with their healthcare provider?
- How does the fact that there are several healthcare providers involved in their care at different and overlapping times impact their ability to have consistent information?
- What oversight, if any, is there on the content of the informed consent document for breast implants? Is the information in the individual informed consent documents consistent with the labeling? Do all relevant healthcare providers refer to the patient labeling and stress the importance of reading it PRIOR to making a decision?
- Are patients given adequate time to read the patient labeling before signing the informed consent document?
- Are patients offered an opportunity to go through the patient labeling and informed consent with a knowledgeable healthcare provider and ask questions? In turn, are any questions asked of patients to assure they understood the content?
- Do patients know how to search for a physician with the necessary experience with breast implants?
- Is there somebody in the process who is dismissive about the risks?
- The surgeon counseling and patient consent process between each patient and her surgeon is invaluable.

Sientra's U.S. PAS collected Participant feedback on the Informed Decision Process that occurred preoperatively. Through 3 years, 97% of participants felt the educational brochure (labeling) helped them understand the risks and benefits of breast implantation. Similarly, 97% of participants felt that the educational brochure, in addition to discussions with their surgeons, provided the information needed to make an informed decision. Participants were also asked to identify the areas of the brochure they wish had more information, (i.e., looking back to the time the Participants decided to have breast implant surgery). Through 3 years, the top three areas included: implant longevity, reoperations and other potential complications. Table 18 presents the metrics for Participant feedback.

Table 18 Informed Decision Evaluation through Year 3 (Participant-Reported)

US-PAS All Gel Participants		
	Participants	
	n	*%(N = 4,050)**
Patient felt that the educational brochure:		
Helped her understand the risks and benefits	3,912	96.6%
Provided the information needed (and discussions with her surgeon) to make an informed decision	3,929	97.2%
Wished the brochure had more information	766	18.9%
Wished the brochure had more information in these areas:	*n*	*%(N = 766)*
Breast examination techniques	139	18.1%
Implant longevity, i.e., implants are not permanent devices	216	28.2%
MRI screening recommendation	94	12.3%
Mammography	154	20.1%
Managing postoperative expectations	156	20.4%
Possible effects on breast-feeding	126	16.4%
Reoperations	199	26.0%
Rupture	91	11.9%
The breast augmentation or reconstruction procedure	72	9.4%
Other potential complications	168	21.9%

10. CONCLUSIONS AND BENEFIT/RISK DISCUSSION

As demonstrated in this Briefing Document, patient safety and product quality is Sientra's highest priority. And because of this commitment, we are:

- Exclusively dedicated to providing Sientra Implants only to board-certified and board-eligible plastic surgeons, who are the most highly trained and skilled surgeons to provide patients with the best outcomes.
- Devoted to providing transparent data and collaborating with experts, societies and the FDA to further research, as well as promote awareness, education and best-practices for breast implants.

- Driven to assure continued evolution in safe implant options and to provide patient educational materials aimed at increasing patients' awareness and understanding of the benefits and risks of breast implants, as well as encouraging conversations with their healthcare providers.
- Offering the most complete warranty program in the industry, which provides an industry-first 20-year coverage

Deciding to have breast implant surgery is a very personal choice, and we want women to feel confident in FDA-approved Sientra Breast Implants and their decision to have breast augmentation or reconstructive surgery. At Sientra, we are guided by the science behind our products, and the science demonstrates the long-term safety and effectiveness of our Implants for use under general conditions in the postmarket environment. The final, 10-year results of the PACS Study demonstrate that Sientra's Implants continue to be safe and effective for their intended use, and importantly, patients continue to report high satisfaction with their Breast Implants throughout 10-years of follow-up.

Even with our strong Breast Implant safety profile, Sientra recognizes the value that breast implant registries contribute to the growing body of knowledge regarding breast implant surgery. Sientra also embraces the responsibility manufacturers have to ensure the continuing safety of their implants and enduring positive outcomes for patients. To that end, Sientra actively supports the NBIR and the ANN project. Furthermore, Sientra invests in multiple philanthropic programs to support patients experiencing breast cancer.

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