

# Mentor Worldwide LLC Briefing Package

Food and Drug Administration  
General and Plastic Surgery Devices Panel  
Committee Meeting

March 25-26, 2019

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## 1.0 Overview

The purpose of this briefing packet is to provide the Advisory Committee Panel with additional background information for consideration on the following FDA-identified topics prior to the March 25-26, 2019 panel meeting:

- Breast Implant Associated – Anaplastic Large Cell Lymphoma (BIA-ALCL)
- Systemic Symptoms
- Utility of MRI screening for the detection of silent rupture
- Use of registries and real-world data for post market surveillance of breast implants
- Empowering women to make informed decisions

## 2.0 Introduction

Mentor develops, manufactures, and markets innovative products for surgical and non-surgical medical procedures that allow breast surgery patients to improve their quality of life. Mentor breast implants, used for both breast reconstruction and breast augmentation purposes, are sold in more than 80 countries, are FDA-approved, CE marked in Europe, and have been chosen by millions of women around the world for over 30 years. Patient safety has been and always will be Mentor's first priority and Mentor supports the education of women and physicians who treat them in making informed choices

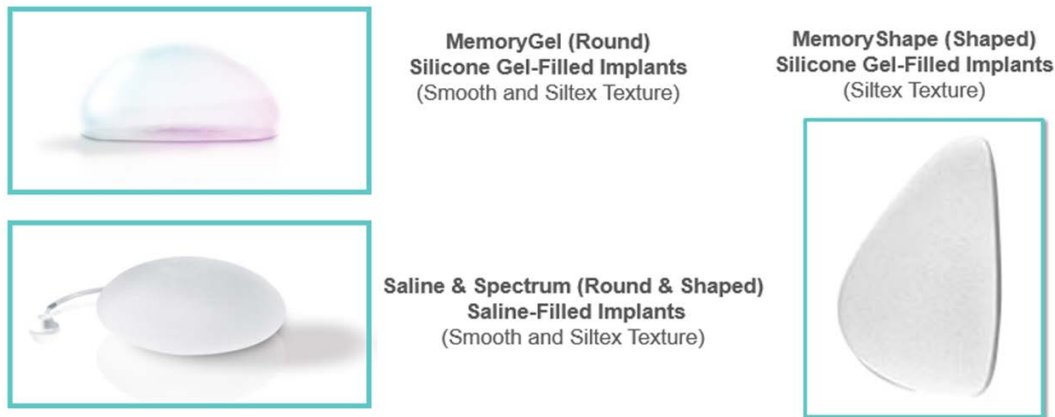
Nearly 400,000 women undergo breast implant surgeries every year in the US, with about 75% of these women choosing to augment their breasts and about 25% of these women electing to have breast reconstruction surgery.<sup>1</sup> Some women opt to have breast implant surgery to increase the breast size and, in some cases, to address post-lactational mammary involution. Other women undergo breast surgery to address congenital breast deformities, to reconstruct the breast following a mastectomy, massive weight loss or trauma or for the purposes of gender confirmation. The quality of life benefits for women with breast implants has been well documented in the literature for both breast augmentation and breast reconstruction (see Attachment 1).

## 3.0 Mentor Implants

Mentor offers a full portfolio of silicone gel-filled and saline-filled round and shaped breast implants to address the needs of the diverse population of women electing to undergo breast surgery (see Figure 1 below). Mentor's saline and MemoryGel round breast implants are provided with either a smooth or a Siltex<sup>®</sup> Texture shell, while Mentor's MemoryShape breast implants are offered exclusively with a Siltex<sup>®</sup> Texture shell. All breast implant types can be used for breast augmentation or breast reconstruction and can be placed subglandularly (below the mammary gland but above the pectoralis muscle) or submuscularly (partially or completely beneath the pectoralis muscle).

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<sup>1</sup> American Society of Plastic Surgeons (ASPS). (2018). "2017 Plastic Surgery Statistics Report." Available at: <https://www.plasticsurgery.org/documents/News/Statistics/2017/plastic-surgery-statistics-full-report-2017.pdf> Accessed: 23 February 2019.



**Figure 1:** Mentor's portfolio of breast implant products

The safety and clinical performance of Mentor's breast implants is supported by long-term clinical data. Mentor continues to enhance our understanding of the long-term safety profile of breast implants through a number of completed and on-going clinical studies. Table 1 provides an overview of the number of patients enrolled and patient-years of follow up from key MemoryGel and MemoryShape clinical studies.

<b>Table 1: Mentor Key Clinical Studies: Patients Enrolled and Observed Patient Years</b>			
<b>Study Name</b>	<b>Study Description</b>	<b>Patients Enrolled</b>	<b>Observed Patient-Years</b>
<b>MemoryGel Core</b> (start date: 2000)	A 10-year prospective clinical study designed to collect safety and effectiveness data for smooth and textured Mentor MemoryGel Breast Implants.	1,008	8,672
<b>MemoryShape Core Study</b> (start date: 2002)	A 10-year prospective clinical study to collect safety and effectiveness data for Mentor MemoryShape (formerly known as Contour Profile Gel [CPG]) Breast Implants).	955	8,010
<b>MemoryShape Continued Access</b> (start date: 2002)	A prospective study to collect continued physician experience with MemoryShape breast implants and additional safety data.	2,003	11,088
<b>MemoryGel Large Post Approval Study</b> (start date: 2006)	A post-approval study of women receiving Mentor's MemoryGel breast implants. For assessing signs and symptoms, saline breast implant participants were also enrolled.	41,452  1,039 saline control patients	255,541  6,042
<b>MemoryGel &amp; MemoryShape Combined Cohort</b> (start date: 2016)	A 10-year prospective study for the collection of additional post approval clinical data on the long-term performance of MemoryGel and MemoryShape breast implants. For assessing signs and symptoms, other aesthetic surgery implant patients were also enrolled.	<i>Planned</i> 2,518  300 other aesthetic surgery patients	On-going
<b>MemoryGel Re-Operation Phase</b> (start date: 2015)	A redesign of the MemoryGel Large Post Approval Study collecting data when the patients have secondary surgical procedures/ reoperations.	16,189	On-going

## 4.0 BIA-ALCL

Women implanted with breast implants have a risk of developing BIA-ALCL.<sup>2</sup> BIA-ALCL is not breast cancer—it is a type of non-Hodgkin’s lymphoma (cancer of the immune system), that affects lymphocytes (immune cells), typically taking between 8-10 years to develop.<sup>3</sup> BIA-ALCL is a serious condition but is highly curable if detected early. While the etiology of BIA-ALCL is still not fully understood, it is likely to be multifactorial. Factors in the development of this disease under consideration include bacterial contamination/ biofilm<sup>4</sup> (introduced at the time of surgery or a later time), particulates, chronic irritation and genetic predisposition.<sup>5,6,7</sup> A discussion focusing on the impact of implant surface texture on the development of BIA-ALCL is provided in the following section.

### 4.1 Textured implants and the development of BIA-ALCL

Recent scientific evidence demonstrates significant and clinically meaningful differences in the incidence of BIA-ALCL between different types of textured breast implants, with a consistently low number of BIA-ALCL cases reported in patients whose device history has included Mentor’s SILTEX® Texture devices. Findings have indicated that the difference in occurrence rates may be related to difference in surface area<sup>8,9</sup>. Mentor’s low surface area, SILTEX® Texture is distinct from that used by other manufacturers (see scanning electron micrograph images in Figure 2).<sup>10</sup> Mentor’s Siltex Texture is also referred to as an “imprinted textured surface” since it is created by

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<sup>2</sup> US FDA. 2019. Breast Implant-Associated Anaplastic Large Cell Lymphoma (BIA-ALCL). Available at: <https://www.fda.gov/medicaldevices/productsandmedicalprocedures/implantsandprosthetics/breastimplants/ucm239995.htm>

<sup>3</sup> Clemens, M.W., et al., How to Diagnose and Treat Breast Implant–Associated Anaplastic Large Cell Lymphoma. *Plast Reconstr Surg*. 2018;141(4):586e-599e.

<sup>4</sup> A biofilm is an “organized community of bacteria attached to a surface and enveloped within a self-produced matrix” Costerton JW, Stewart PS, Greenberg EP. Bacterial biofilms: a common cause of persistent infections. *Science* 1999;284:1318-1322; Edmiston CE, McBain AJ, Roberts C, Leaper D. Clinical and microbiological aspects of biofilm-associated surgical site infections. *Adv Exper Med Biol*. 2015;830:47-67.

<sup>5</sup> Hu H, Johani K, Almatroudi A, Vickery K, Van Natta B, Kadin ME, Brody G, Clemens M, Cheah CY, Lade S, Joshi PA, Prince HM, Deva AK. Bacterial biofilm infection detected in Breast Implant-Associated Anaplastic Large-Cell Lymphoma. *Plast Reconstr Surg*. 2016;137(6):1659-1669.

<sup>6</sup> Clemens MW, Nava MB, Rocco N, Miranda RN. Understanding rare adverse sequelae of breast implants: anaplastic large-cell lymphoma, late seromas, and double capsules. *Gland Surg*. 2017;6(2):169-184.

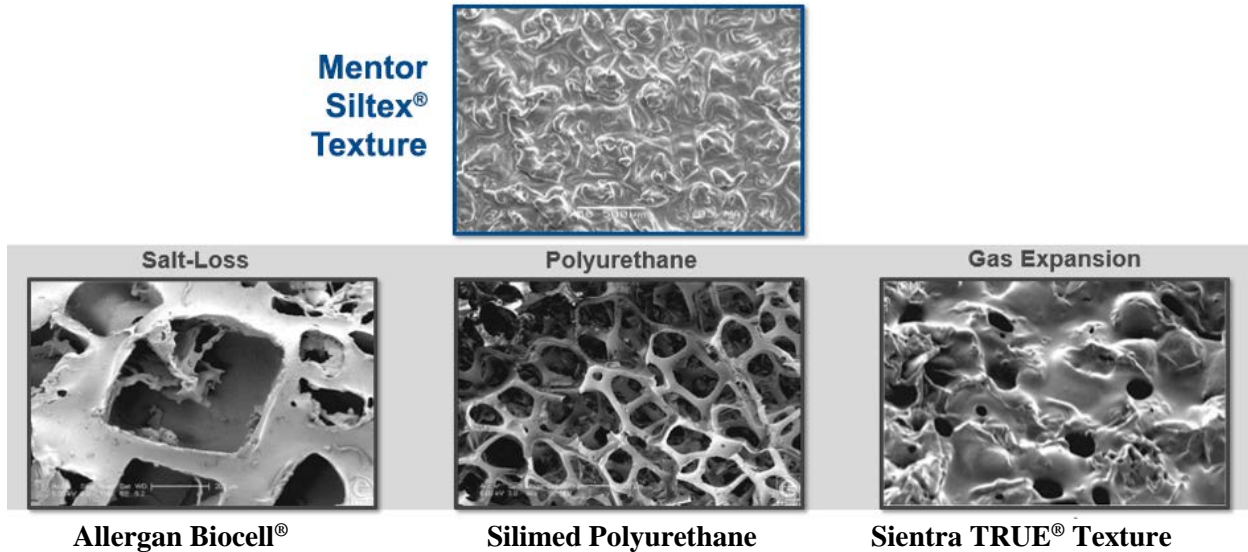
<sup>7</sup> Webb LH, Aime VL, Do A, Mossman K, Mahabir RC. Textured breast implants: A closer look at the surface debris under the microscope. *Plast Surg (Oakv)*. 2017;25(3):179-183.

<sup>8</sup> Loch-Wilkinson, A., et al., Breast implant associated Anaplastic Large Cell Lymphoma in Australia and New Zealand - high surface area textured implants are associated with increased risk. *Plast Reconstr Surg*. 2017;140(4):645-654.

<sup>9</sup> Magnusson M, Beath K, Cooter R, Locke M, Prince HM, Elder E, Deva AK. Special Update: The epidemiology of Breast Implant Associated Large Cell Lymphoma in Australia and New Zealand confirms the highest risk for grade 4 surface breast implants. *Plast Reconstr Surg*. 2019 Feb 13. doi: 10.1097/PRS.0000000000005500. [advanced online article].

<sup>10</sup> Mentor Siltex® breast implants were sent to an independent laboratory, Eurofins, for testing average surface roughness based on guidance provided in ISO14607:2018. The measurements of 30 µm to 35 µm average surface roughness place the Siltex® Texture implants in the ISO *microtexture* (10µm - 50µm) category.

pressing foam into the silicone shell before it is fully cured. When the foam is removed, a negative imprint of the foam's surface remains on the surface of the implant (some refer to this process as "negative imprint stamping").



**Figure 2:** Scanning electron micrographs of breast implant surfaces<sup>11</sup> Scale bars are as indicated.

Table 2 shows the results from multiple published BIA-ALCL studies conducted in several different countries. The number of BIA-ALCL cases reported in patients with Mentor implants is low in comparison to the total number of cases identified. It is important to note that the low number of BIA-ALCL cases is not a function of low sales volume as Mentor has maintained for years either higher or roughly equal breast implant market share with the next leading manufacturer worldwide.

<sup>11</sup> Barr S, Hill E, Bayat A. Current implant surface technology: an examination of their nanostructure and their influence on fibroblast alignment and biocompatibility. *Eplasty* 2009;9:e22; Calobrace MB, Schwartz MR, Zeidler KR, Pittman TA, Cohen R, Stevens WG. Long-Term Safety of Textured and Smooth Breast Implants. *Aesthet Surg J*. 2017;38(1):38-48.



**Table 2. Low Representation of Mentor Devices in Published BIA-ALCL Reports**

Author	Implants Included	Total # BIA- ALCL Cases	BIA-ALCL Cases in Patients Whose Device History Included Mentor Implants
Brody et al. 2015 <sup>12</sup> (multiple countries)	Allergan, Inamed, McGhan, CUI, Nagor, PIP, Silimed, Sientra, Polytech, Mentor	173	3 Mentor Only Cases (1.7%) 3 Mentor + Another Manufacturer (1.7%)
Gidengil et al. 2015 <sup>13</sup> (multiple countries)	Allergan, Inamed, McGhan, CUI, Nagor, Silimed, Sientra, Polytech, Mentor	54	0 Mentor cases (0%)
Doren et al. 2017 <sup>14</sup> (US)	Allergan, Mentor	100	5 Mentor Only Cases (5%) 3 Mentor + Another Manufacturer (3%)
Johnson et al. 2017 <sup>15</sup> (UK)	McGhan, Allergan, Polytech, Nagor, PIP, Mentor, Inamed	23	0 Mentor Only Cases (0%) 2 Mentor + Another Manufacturer (8.7%)
De Boer et al. 2018 <sup>16</sup> (Netherlands)	Allergan, Inamed, McGhan, Nagor, EuroSilicone, PIP, Mentor, Sebbin	32	1 Mentor + Another Manufacturer (3.1%)
Magnusson et al. 2019 <sup>17</sup> (Australia/ New Zealand)	Allergan, Mentor, Polyurethane (Silimed), Nagor, PIP, Polytech, Surgitek	110	1 Mentor Only Case (0.9%) 9* Mentor + Another Manufacturer (8.2%)

\* Includes 3 cases with Mentor smooth implant in patients who also had other textured implant of another manufacturer [there are currently no confirmed cases of BIA-ALCL in patients whose implant history included only smooth implants]

Note: The Brody, Gidengil and Doren study populations likely include some degree of overlap.

<sup>12</sup> Brody GS, Deapen D, Taylor CR, Pinter-Brown L, House-Lightner SR, Andersen JS, Carlson G, Lechner MG, Epstein AL. Anaplastic large cell lymphoma occurring in women with breast implants: analysis of 173 cases. *Plast Reconstr Surg.* 2015;135(3):695-705.

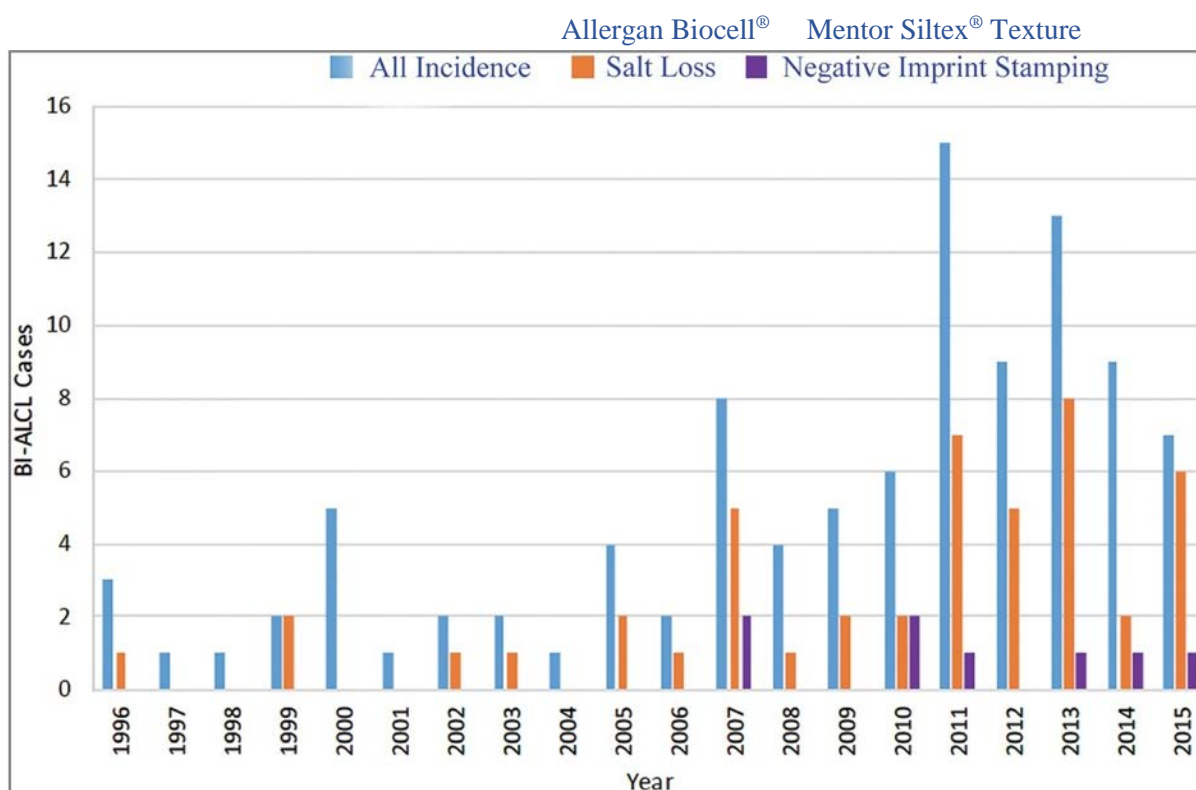
<sup>13</sup> Gidengil CA, Predmore Z, Mattke S, van Busum K, Kim B. Breast implant-associated anaplastic large cell lymphoma: a systematic review. *Plast Reconstr Surg.* 2015;135(3):713-720.

<sup>14</sup> Doren EL, Miranda RN, Selber JC, et al. (2017). U.S. Epidemiology of Breast Implant-Associated Anaplastic Large Cell Lymphoma. *Plast Reconstr Surg.* 139(5):1042-1050.

<sup>15</sup> Johnson L, O'Donoghue JM, McLean N, Turton P, Khan AA, Turner SD, Lennard A, Collis N, Butterworth M, Gui G, Bristol J, Hurren J, Smith S, Grover K, Spyrou G, Krupa K, Azmy IA, Young IE, Staiano JJ, Khalil H, MacNeill FA. Breast implant associated anaplastic large cell lymphoma: The UK experience. Recommendations on its management and implications for informed consent. *Eur J Surg Oncol.* 2017;43(8):1393-1401.



Doren et al (2017) conducted a retrospective review of BIA-ALCL in the US from 1996 through 2015, based on literature and institutional database review, along with texture breast implant sales from implant manufacturers' annualized data.<sup>18</sup> The results demonstrated that the overall incidence among patients with salt-loss textured implants (Allergan's Biocell textured implants) was 1.87 per 1 million person-years. In contrast, the overall incidence rate of BIA-ALCL among patients with imprinted textured implants (Mentor's SILTEX<sup>®</sup> Texture implants) was 0.33 per 1 million person-years. Compared with Allergan's Biocell salt-loss textured implants, Mentor's imprinted textured implants were associated with a significantly lower incidence rate ( $p < 0.001$ ) [see Figure 3].



**Figure 3:** Number of US BIA-ALCL cases by year and implant manufacturer (Doren et al 2017). Mentor's Siltex<sup>®</sup> Texture implants are identified as "Negative Imprint Stamping" (cases reflected in the purple bars); Allergan Biocell textured implants are identified as salt loss (cases reflected in the orange bars). The total number of cases are represented by the blue bars.

<sup>16</sup> de Boer M, van Leeuwen FE, Hauptmann M, Overbeek LIH, de Boer JP, Hijmering NJ, Sernee A, Klazen CAH, Lobbes MBI, van der Hulst RRWJ, Rakhorst HA, de Jong D. Breast implants and the risk of Anaplastic Large-Cell Lymphoma in the breast. *JAMA Oncol.* 2018;4(3):335-341.

<sup>17</sup> Magnusson M, Beath K, Cooter R, Locke M, Prince HM, Elder E, Deva AK. Special Update: The epidemiology of Breast Implant Associated Large Cell Lymphoma in Australia and New Zealand confirms the highest risk for grade 4 surface breast implants. *Plast Reconstr Surg.* 2019 Feb 13. doi: 10.1097/PRS.0000000000005500; with further details provided in Loch-Wilkinson et al., *Plast Reconstr Surg.* 2017;140(4):645-654.

<sup>18</sup> Doren EL., Miranda RN., Selber JC., et al. (2017). U.S. Epidemiology of Breast Implant-Associated Anaplastic Large Cell Lymphoma. *Plast Reconstr Surg.* 139(5):1042-1050.

One of the most detailed published studies of BIA-ALCL occurrence rates was based on the number of BIA-ALCL cases (81 cases) diagnosed in Australia and New Zealand between 2007 and March 2018.<sup>19,20</sup> Sales data from the three leading breast implant manufacturers (Mentor, Allergan and Silimed) dating back to 1999 (eight years prior to the first occurrence of BIA-ALCL in this region) were secured to estimate implant-specific risk.

The results demonstrated that high surface area Silimed Polyurethane (PU) and Allergan Biocell<sup>®</sup> salt-loss textured implants were associated with a significantly increased risk of developing BIA-ALCL as compared to that for the low surface area Mentor Siltex<sup>®</sup> Texture implants. The authors suggest that the higher surface area implants provide a greater opportunity for bacterial growth that, once reaching a threshold level, cause an ongoing immune activation that leads to the development of the lymphoma. Incidence rates for this study are summarized in Table 3.

**Table 3:** Risk of developing BIA-ALCL per implant surface type

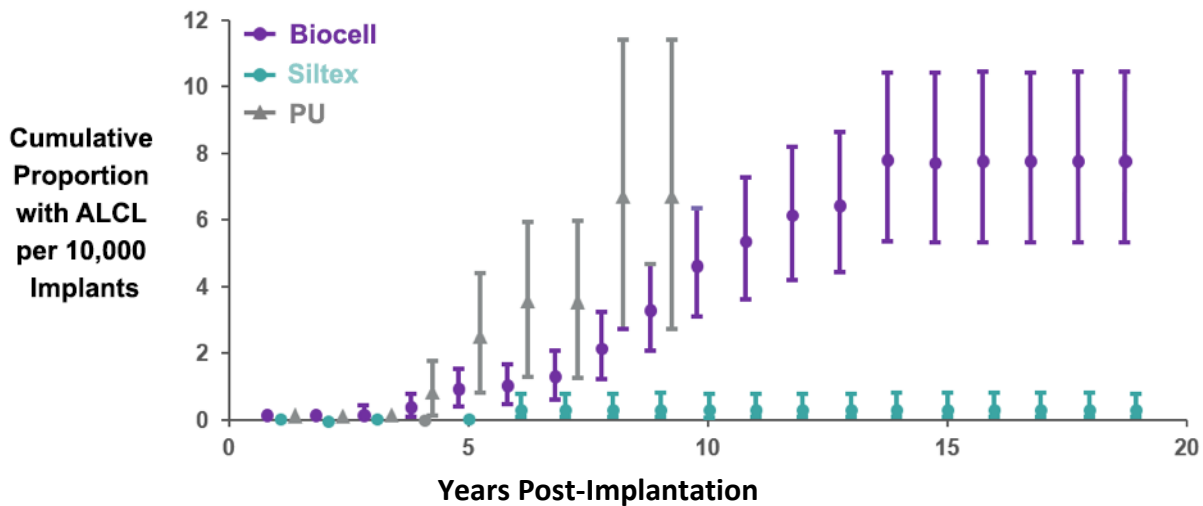
<b>Manufacturer / Texture</b>	<b>BIA-ALCL Incidence</b>
Silimed / Polyurethane	1 case per 2,832 implants (CI 1,582 - 5,673)
Allergan / Biocell <sup>®</sup>	1 case per 3,345 implants (CI 2,475 - 4,642)
Mentor / SILTEX <sup>®</sup> Texture	1 case per 86,029 implants (CI 15,440 - 1,301,759)

CI = confidence interval

Figure 4 below presents the cumulative proportion of patients with BIA-ALCL per 10,000 implants by implant texture. These results also demonstrate clinically meaningful differences in the rates of BIA-ALCL over time among implant textures.

<sup>19</sup> Loch-Wilkinson, A., et al., Breast implant associated Anaplastic Large Cell Lymphoma in Australia and New Zealand - high surface area textured implants are associated with increased risk. *Plast Reconstr Surg.* 2017;140(4):645-654.

<sup>20</sup> Magnusson M, Beath K, Cooter R, Locke M, Prince HM, Elder E, Deva AK. Special Update: The epidemiology of Breast Implant Associated Large Cell Lymphoma in Australia and New Zealand confirms the highest risk for grade 4 surface breast implants. *Plast Reconstr Surg.* 2019 Feb 13. doi: 10.1097/PRS.0000000000005500. [advanced online article].



**Figure 4:** Cumulative proportion with BIA-ALCL per 10,000 implants. Allergan Biocell® textured implants are identified in purple. Silimed Polyurethane (PU) implants are identified in grey. Mentor Siltex® Texture implants are identified in turquoise.

The Australia/ New Zealand authors identified the limitations in their study including the small number of cases for Siltex® and polyurethane resulting in wide confidence intervals. In addition, the authors state other limitations include: “*limited information on deaths by other causes, short-duration follow-up in some cases, reliance on the accuracy of sales data supplied by manufacturers, cluster patterns of incidence skewing the distribution, and the possibility that there are other unidentified cases of breast implant–associated ALCL through missed clinical and/or pathologic diagnosis.*”

All types of textured breast implants have at least some reported cases of BIA-ALCL, but the more than an order of magnitude (greater than 10-fold) difference in the incidence of BIA-ALCL (Biocell® vs. Mentor SILTEX® Texture) is a clinically meaningful difference that is likely not able to be accounted for by inclusion of additional covariates and represents a true difference between textures.

The high BIA-ALCL incidence rate for salt-loss textured implants from the Australia / New Zealand series were confirmed in a recent, prospective, clinical data set of 17,656 patients from the United States receiving Allergan’s Biocell salt loss textured breast implants. Updated findings by Dixon & Clemens (2018),<sup>21</sup> of the original report by McGuire et al. (2017), now indicate an incidence of 1 in 4,424 salt-loss implants or 1 in 2,207 patients (95% CI 1: 1,120 to 1: 5,112).

<sup>21</sup> Dixon JM, Clemens M. Breast implants and anaplastic large cell lymphoma. *BMJ*. 2018;363:k5054

#### 4.1 Risk Benefit Profile for Mentor Siltex® Texture Breast Implants

Like all medical procedures, it's important that patients fully understand and carefully weigh all risks with the potential benefits. The rare risk of BIA-ALCL with Mentor Siltex® Texture breast implants is detailed above, which is just one of several potential risks associated with breast implant surgery. There are also a number of clinical benefits of Mentor's Siltex® Texture breast implants, based on long term clinical data, which are important to note:

- Lower capsular contracture rates and associated reoperations with the use of Mentor's Siltex Texture breast implants compared to Mentor smooth implants in augmentation patients; and
- Lower asymmetry rates and associated reoperations with the use of Mentor's Siltex Texture breast implants compared to Mentor smooth implants in reconstruction patients.

Based on the lower occurrence of these complications and the subsequent reoperations/ inherent risks in these patients, Mentor SILTEX® Texture breast implants provide significant risk reduction benefits. These data, when taken together with Mentor's rare occurrence/risk of BIA-ALCL, result in a favorable risk benefit assessment for the use of Mentor SILTEX® Texture devices in both augmentation and reconstructive breast surgery.

Detailed results documenting the specific clinical benefits of Mentor's Siltex® Texture breast implants are provided in Attachment 2.

#### 5.0 Systemic Symptoms

Some women with breast implants have reported a range of systemic symptoms. These may present differently in different patients. These symptoms should continue to be examined.

As many of these same symptoms are experienced by women in the general population, determining the underlying cause is challenging. To better understand the potential etiology of such systemic symptoms, Mentor reviewed data obtained from our clinical studies that included long-term collection of these symptoms.

As described in further detail below, our initial analyses of systemic symptoms indicate that risk of symptoms being experienced by patients did not increase with longer device exposure times, as one might expect to happen if the implants were associated with the symptoms.

##### 5.1. Study Findings on Systemic Symptoms

Patients in the MemoryGel and MemoryShape Core Studies, and the MemoryGel Large Post Approval Study, were asked to complete an annual questionnaire, which included a number of potential rheumatologic or neurologic symptoms. These symptoms were collected for patients at

baseline and post-implantation at each annual visit throughout the study. The core studies provided the most extensive follow-up on patients for the evaluation of these symptoms and those results are presented in this section (as has been noted previously by FDA, interpretation of the MemoryGel Large Post Approval Study results is limited by low follow up rates).

Ten-year Kaplan-Meier cumulative incidence rates for newly-reported symptoms were reviewed for each of the four breast-implant patient subgroups (primary augmentation, revision augmentation, primary reconstruction, and revision reconstruction) and for the overall population (all subgroups combined) (Table 4). Note that these symptoms are reported more frequently with the reconstruction patients compared to augmentation patients, as would be expected due to differences in age, general health status, and treatments commonly received by post-mastectomy breast reconstruction patients.

**Table 4:** MemoryGel Core and MemoryShape Core Study Kaplan-Meier Estimated Cumulative Incidence Rates at 10 Years for Newly Reported Symptoms

	<b>MemoryGel Core Study</b>				
<b>Finding/ Symptom</b>	<b>Primary Augmentation</b>	<b>Revision Augmentation</b>	<b>Primary Reconstruction</b>	<b>Revision Reconstruction</b>	<b>Overall</b>
Fatigue	5.5%	8.3%	7.5%	10.9%	6.7%
Insomnia	4.2%	6.3%	4.7%	9.2%	4.9%
Dryness of eyes/nose	2.3%	3.0%	2.9%	4.1%	2.7%
Joint pain	8.9%	12.8%	18.5%	24.3%	12.6%
Frequent muscle pain	3.0%	2.4%	5.3%	5.3%	3.6%
Dryness of mouth	0.8%	1.5%	2.5%	1.7%	1.3%
Unusual hair loss	1.9%	7.1%	4.1%	1.7%	3.1%
	<b>MemoryShape Core Study</b>				
Fatigue	3.5%	3.8%	4.9%	8.5%	4.2%
Insomnia	2.3%	4.4%	4.0%	4.3%	3.0%
Dryness of eyes/nose	2.2%	3.6%	2.9%	3.6%	2.6%
Joint pain	4.9%	8.3%	12.9%	17.4%	7.7%
Frequent muscle pain	1.6%	1.8%	1.7%	4.8%	1.8%
Dryness of mouth	0.9%	1.8%	1.3%	4.6%	1.3%
Unusual hair loss	1.4%	1.7%	0.7%	10.0%	1.7%

For the 10-year MemoryGel Core and MemoryShape Core studies, the data were also examined to investigate whether rates of reporting new systemic symptoms increased over 10 years with longer exposure to the implanted device. One might expect that if the implant were causing these systemic symptoms, that longer exposure to the device would lead to an increase in the rate of reported symptoms.

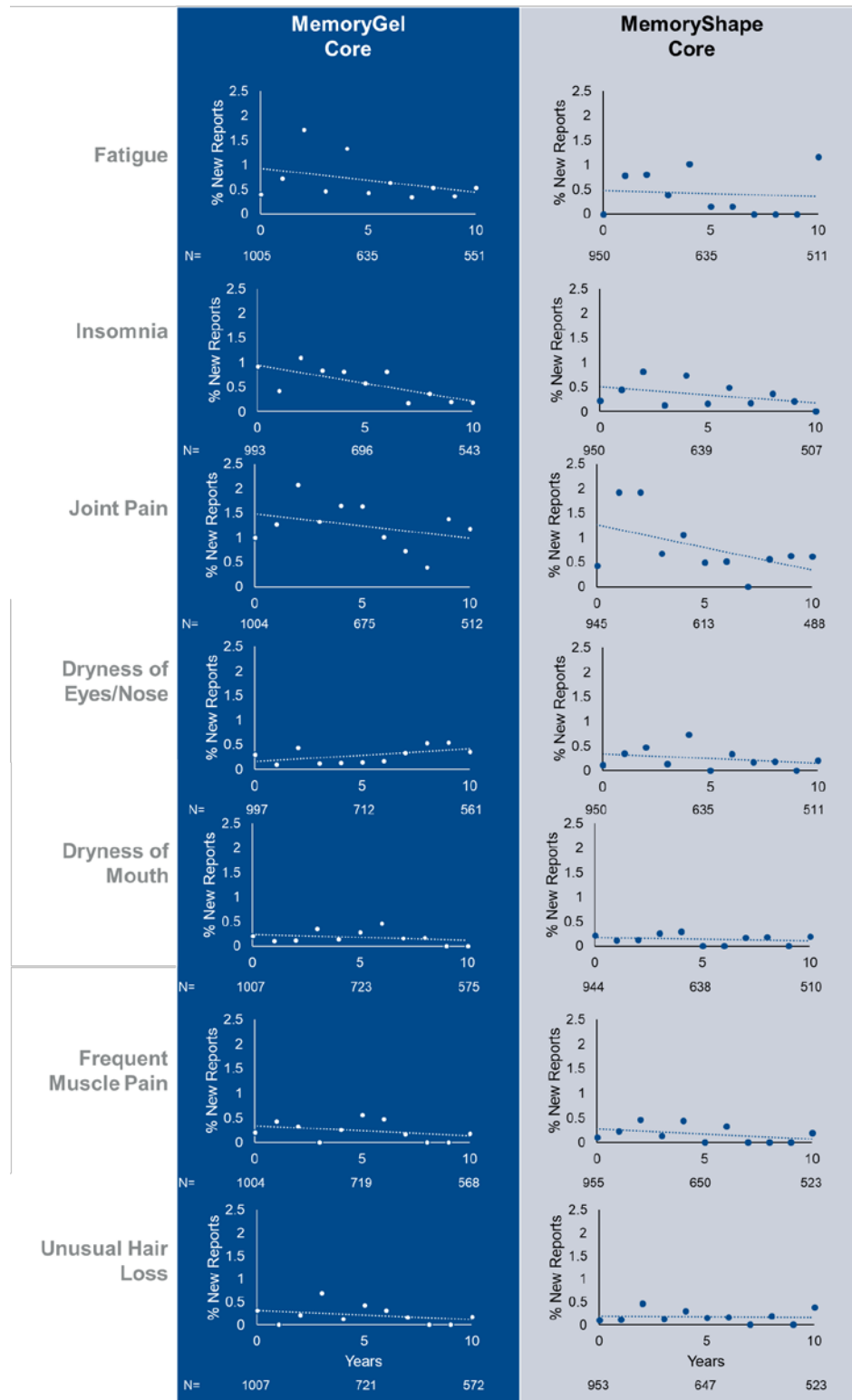
Per FDA's Guidance document on *Saline, Silicone Gel, and Alternative Breast Implants* (2006), Generalized Estimating Equations (GEE) analyses, adjusting for the effect of current age (in complete years at the time of the visit; a time-varying covariate), were performed to look at the incidence of symptoms commonly associated with rheumatologic/neurologic disorders, comparing baseline to the 1 through 10-year results. This model accounts for repeated measures within subjects and tests for whether there is an increase in the rate of reported symptoms over time after

breast implantation. It should be noted that the GEE analysis was able to be performed only when at least one patient experienced the complication at baseline and at least one patient experienced the complication during Years 1-10.

For the symptoms where the GEE age-adjusted analysis could be performed (62% of symptoms across both studies in the overall set of patients), no statistically significant increases in rates after implantation were identified, indicating that symptom reports did not increase as exposure time increased. For those symptoms where the GEE analysis could not be performed due to the few occurrences either at baseline or post implantation, the rates were reviewed to identify any symptoms with potentially increasing rates with longer exposure. This review did not identify any consistent increasing trends in reported rates over time for any symptom. Reported rates ranged between 0.0% and 1.02% and were randomly distributed across the study visits (i.e. years post implantation).

Figure 5 presents scatterplots over time with a linear trend for the percentage of patients reporting new symptoms at baseline and at each annual visit for the two core studies. As can be seen for a variety of commonly discussed symptoms, including fatigue, insomnia and joint pain, there does not appear to be an increase in the percentage of patients experiencing these symptoms over time, aligning with the conclusions of the GEE analysis.





**Figure 5:** Reported Incidence of Newly Reported Symptoms by Year

## 6.0 Rare Disorders

Some publications have suggested that there may be an increase in the occurrence of rare harms in women with silicone breast implants. In all of Mentor's clinical studies, data are collected on medical history at baseline and at each visit. Patients are asked if they have been diagnosed with new disorders. Mentor examined patient self-reported connective tissue disease (CTD) including Rheumatoid Arthritis (RA), Sjogren's Syndrome, scleroderma, Systemic Lupus Erythematosus (SLE), fibromyalgia and other CTD, as well as patient reports of melanoma and stillbirths.

### 6.1. Connective Tissue Disease (CTD)

The Memory Gel Large Post-Approval Study included CTD reported by study patients. The most significant limitation in interpreting such findings, however, is the self-reported nature of these data. Self-reported CTD among breast implant patients has been previously demonstrated to significantly overestimate the actual rate of CTD present. Karlson and colleagues (1999), in a comparison of self-reported diagnosis of CTD with medical records in female health professionals within the Harvard Women's Health Cohort Study, found only 22.7% of self-reported CTD among women with breast implants was valid upon medical record review.<sup>22</sup> Therefore, the current cases reported in the Memory Gel Large Post-Approval Study may represent a significant overestimate of the actual rate.

New cases of RA were reported to be higher in patients with MemoryGel breast implants participating in the Large Post Approval Study as compared to women in a published study who underwent other types of plastic surgery (unadjusted Relative Risk [RR] = 1.56).<sup>23</sup> In addition to the issue of self-reporting, however, 24.9% of the patients with implants reporting new diagnosis of RA also reported having a family history of RA, which is a recognized high-risk factor for this disease. In fact, patients with a family history of RA have about a 40% chance of developing RA.<sup>24</sup> The higher rates of new cases of RA in breast implant patients may be at least partially explained by the high family history rates.

Similarly, for both Sjogren's Syndrome and scleroderma, MemoryGel patients in the MemoryGel Large Post Approval Study were estimated to have a higher risk (unadjusted relative risk of 6.71 and 3.31, respectively) compared to rates in the published literature for patients having other types of plastic surgery.<sup>25</sup> It should be noted, however, that for Sjogren's Syndrome and scleroderma, the absolute numbers of new diagnoses that also reported a family history during the MemoryGel Large Post Approval Study (4 for Sjogren's Syndrome and 3 for scleroderma) were too low to make definitive conclusions about the impact of family history. Unfortunately, the family history

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<sup>22</sup> Karlson EW, Lee IM, Cook NR, Manson JE, Buring JE, Hennekens CH. 1999. Comparison of self-reported diagnosis of connective tissue disease with medical records in female health professionals: the Women's Health Cohort Study. *Am J Epidemiol.* 150(6):652-660.

<sup>23</sup> Brinton LA, Buckley LM, Dvorkina O, Lubin JH, Colton T, Murray MC, Hoover R. Risk of connective tissue disorders among breast implant patients. *Am J Epidemiol.* 2004;160(7):619-627.

<sup>24</sup> Frisell T, Saevarsdottir S, Askling J. Family history of rheumatoid arthritis: An old concept with new developments. *Nat Rev Rheumatol.* 2016 Jun;12(6):335-343.

<sup>25</sup> Brinton LA, Buckley LM, Dvorkina O, Lubin JH, Colton T, Murray MC, Hoover R. Risk of connective tissue disorders among breast implant patients. *Am J Epidemiol.* 2004;160(7):619-627.

rates for these diseases are not available in the published literature for the comparison group of patients having other plastic surgery.

Table 5 summarizes the family history data from the MemoryGel Large Post Approval Study discussed above. The table states the reported rates of family history of RA, Sjogren's Syndrome and scleroderma for patients who reported that they themselves had a new diagnosis of the disease ("diagnosed") and patients who did not report a new diagnosis of the disease ("not diagnosed").

<b>Table 5: Prevalence of Family History Reported throughout the MemoryGel Large Post Approval Study for Identified Diagnoses</b>						
	<b>Rheumatoid Arthritis</b>		<b>Sjogren's Disease</b>		<b>Scleroderma</b>	
	Diagnosed (N=349)	Not Diagnosed (N=40,655)	Diagnosed (N=62)	Not Diagnosed (N=41,322)	Diagnosed (N=46)	Not Diagnosed (N=41,363)
Number (%) With Family History of Given Condition	87 (24.9%)	3546 (8.7%)	4 (6.5%)	175 (0.4%)	3 (6.5%)	163 (0.4%)

These data show that the family history rates of autoimmune diseases reported by breast implant patients later developing an autoimmune disease during the clinical study are higher than those who were not diagnosed. In addition, data from the literature indicate that the risk of developing a given autoimmune disease is related to family history of any autoimmune disease, not just the disease the patient may have.<sup>26</sup> These data indicate why interpreting clinical data from breast implant studies can be difficult, as family history may be a critical factor in interpreting disease incidence rates post implant.

With regard to other rare harms, the rate of newly diagnosed SLE, fibromyalgia, and other connective tissue disorders were not significantly increased in patients participating in the MemoryGel Large Post Approval Study compared to rates reported for women having other types of plastic surgery.

In the two, 10-year core studies (MemoryGel Core and MemoryShape Core), there were very few incidences of RA, Sjogren's Syndrome and scleroderma reported. There were 3 new diagnoses of RA in the MemoryGel Core study with a cumulative incidence rate of 0.44% at 10 years and 5 new diagnoses of RA in the MemoryShape Core study with a cumulative incidence rate of 0.61% at 10 years. For Sjogren's Syndrome, MemoryGel Core had 3 reported cases (0.44% at 10 years) and MemoryShape Core had 2 reported cases (0.25% at 10 years). For Scleroderma, MemoryGel Core had 1 reported case (0.13% at 10 years) and MemoryShape Core had no reported cases. Inclusive of all rheumatic diseases, there were a total of 23 new diagnoses in the MemoryGel Core study (2.62% at 10 years) and 18 new diagnoses (2.35% at 10 years).

<sup>26</sup> Tincani A, Andreoli L, Cavazzana I, et al. Novel aspects of Sjögren's syndrome in 2012. *BMC Med.* 2013; 11:93.

## 6.2. Stillbirths

Data from the long-term Mentor studies were evaluated regarding stillbirth rates. In MemoryGel Large Post Approval Study, the reported rate for stillbirths was higher for patients in the study prior to receiving implants (6.0%; 5,238 out of 86,732) as compared to the rate following implantation (2.7%; 85 out of 3,133). In both cases, stillbirth rates were higher than the national average of 0.46%. These analyses point out the criticality of having thorough pre-implant patient history to be able to appropriately interpret post-implant data. Regarding the core studies, there was 1 report of stillbirth in 291 pregnancies (0.3%) the MemoryGel Core Study; no specific data on stillbirth was collected in the MemoryShape Core Study.

## 6.3 Melanomas

MemoryGel patients had a significantly increased rate of melanoma compared to incidence rates from the SEER 9 registry (7.8 per 10,000-person years, Standardized Morbidity Ratio of 4.0). Nearly all the 65 reported cases of melanoma in the MemoryGel Large Post Approval Study were reported by patients in the augmentation cohorts (62/65). Given the clearly demonstrated link between sun exposure and melanoma, the statistically significant increase is understandable in light of the increased sun exposure likely experienced by many breast augmentation patients. Furthermore, if the implants were directly associated with increased risk for melanoma, one would have expected to see increased melanoma rates in the reconstruction implant patients as well.

## 6.4 Summary of Rare Disorders

Some rare diseases including CTD and other rare harms were reported to occur at higher rates in patients participating in Mentor's clinical studies discussed above than in referenced comparator populations. However, these data require careful interpretation as self-reported CTDs are likely to be an overestimate of actual occurrence. When analyzing post-implant data, it is also critical to consider the patients' medical history (including family history) and lifestyle as pre-implant risk factors may significantly impact post-implant disease rates. As with any studies of this type, it is important to ensure that any comparator groups have similar baseline risk factors.

## 7.0 MRI Screening

Patients with silicone implants are currently advised to undergo MRI to screen for silent rupture (asymptomatic and no physical signs of changes to the implant) even if the patient is not experiencing any problems. As per FDA's guidance document on breast implants, MRIs are recommended starting at 3-year post-operatively than every 2 years after.

To assess the utility of MRI screening for implant rupture, Mentor analyzed data from our clinical studies. Patients participating in the core studies were instructed to receive MRI screenings according to Mentor's FDA-approved protocol. Core study findings demonstrated that MRI screening accurately identified ruptures. However, even in this situation where there was no cost to the patient, compliance was low (55% at 6 years, 50% at 8 years, and 45% at 10-years post-implantation). In the case of post market studies, e.g. the MemoryGel Large Post Approval Study,

in which such costs were the responsibility of the patient, compliance was notably lower (compliance rates were consistently 5% annually). Patients provide many explanations as to why they do not undergo MRI screening, including a previous negative experience and claustrophobia. However, an important factor is likely cost when the patient is responsible for repeated MRI screening fees. More current estimates of compliance rates, when the patient is covering the cost of the MRI screening fees, are currently being studied in Mentor's Combined Cohort study.

Consistent with published literature<sup>27</sup>, the vast majority of ruptures detected by MRI are experienced after 6 years post-implantation. This has led some to suggest that the recommendation to start screening at 3 years may not be supported by clinical data available, and that a different screening timeline might be of value and potentially increase patient compliance.<sup>28</sup>

Technologies other than MRI are currently being investigated to evaluate their effectiveness for detection of silent ruptures, including High Resolution Ultrasound, for which promising findings have been reported.<sup>29</sup> While awaiting full validation of High Resolution Ultrasound screening, MRI remains the gold standard for detection of silent rupture. Evidence-based refinement of current screening timelines may be of benefit, particularly considering financial and emotional challenges experienced by patients. Therefore, we encourage exploration of validated, innovative, cost-saving solutions to identify silent rupture.

## 8.0 Registries & Real-World Data for Enhanced Surveillance of Breast Implants

Mentor has collaborated with the Plastic Surgery Foundation (PSF), FDA and other manufacturers to facilitate the development of the National Breast Implant Registry (NBIR). The purpose of the NBIR is to strengthen post-market surveillance of current and future breast implants in the US. Data from the NBIR will supplement long-term clinical data collected through on-going post approval studies such as Mentor's Combined Cohort Study and Mentor's MemoryGel Reoperation Phase Study. Real-world data collected via the NBIR is expected to allow surgeons, researchers and manufacturers to identify trends and other information that may lead to a better understanding of the safety profile of breast implants.

Experience has shown that loss to follow-up, when attempting to collect detailed information on a regular basis, is high. As a result, recently launched registries, like the NBIR, have chosen a streamlined approach to data collection with a modest amount of baseline data collected at enrollment into the registry, but without collecting extensive data on potential confounding factors. This approach is well-suited for collecting follow-up data at the time a woman needs a reoperation (for any reason), or if a device is recalled. However, this approach does not generate enough data to conduct proper epidemiologic studies. As an alternative to asking participants to complete

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<sup>27</sup> Hölmich LR, Friis S, Fryzek JP, Vejborg IM, Conrad C, Sletting S, Kjøller K, McLaughlin JK, Olsen JH. Incidence of silicone breast implant rupture. *Arch Surg*. 2003 Jul;138(7):801-806.

<sup>28</sup> McCarthy CM, Pusic AL, Kerrigan CL. Silicone breast implants and magnetic resonance imaging screening for rupture: do U.S. Food and Drug Administration recommendations reflect an evidence-based practice approach to patient care? *Plast Reconstr Surg*. 2008;121(4):1127-1134.

<sup>29</sup> Bengtson BP, Eaves FF 3rd. High-resolution ultrasound in the detection of silicone gel breast implant shell failure: background, in vitro studies, and early clinical results. *Aesthet Surg J*. 2012;32(2):157-74.



lengthy questionnaires, it might be possible for independent researchers to link registry data, with consent from participants, to their electronic health records or other sources of data (e.g., health insurance claims). This would allow independent researchers to identify appropriate comparison groups, identified in the same electronic databases, and to obtain access to appropriate data that will provide sufficient depth and breadth to conduct valid studies. All of this could be possible without the need for repeated contact with participants following the initial consent. However, it will be essential to protect patient privacy and data when implementing any of these recommendations.

There are multiple breast implant registries currently being implemented around the world. Coordination of these registries on a global basis would provide larger sample sizes to address questions about uncommon diseases (e.g., scleroderma, neurologic diseases). To allow for a comparison of results across data sources from the various registries, certain elements would need to be standardized. To accomplish this goal, the first need is for a common data structure across registries, with common definitions for a modestly sized set of core common data elements. Under a model known as a distributed data network, which is the approach used by the FDA Sentinel Network<sup>30</sup>, there would be no need to aggregate data from multiple registries in a single database. The common data structure allows a single statistical analysis program to be written and sent to each participating registry, which would run the analysis and return results to a coordinating center, which then combines results using statistical methods for meta-analysis. This structure avoids the logistical issues associated with sharing large amounts of data and avoids concerns about privacy, since no data are shared across registries.

## 9.0 Empowering Informed Patient Choices

Mentor takes seriously our responsibility to communicate the risks associated with breast implants to surgeons and their patients. Mentor continually provides surgeons and patients with transparent and balanced information so they can evaluate the benefits and risks associated with breast implants together in a well-informed manner, prior to making decisions.

There are inherent risks associated with breast implants and Mentor warns of such known risks in its Product Insert Data Sheets (PIDS) and patient education brochures. Mentor instructs surgeons to provide the FDA-required patient education brochure to their augmentation and reconstruction patients while the patient is still deciding whether to have their breast implant surgery. Mentor recommends patients read the material and then wait 1 to 2 weeks before deciding to proceed with surgery. The patient education brochures include an “Acknowledgement of Informed Decision” section at the end where patients can acknowledge, with their signatures, that they have read and understood the information provided about the benefits and risks of our breast implants.

In addition to the required labeling and patient education brochures, Mentor has generated updated, concise, and easy-to-read material for both surgeons and patients highlighting breast implant considerations and risks such as BIA-ALCL. For the patient, Mentor created a 2-page Risk Information Booklet that surgeons can use when discussing breast implant risks with their patients, including the latest information about more common complications and BIA-ALCL. For the

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<sup>30</sup> <https://www.fda.gov/safety/fdasentinelinitiative/ucm2007250.htm>

surgeon, Mentor continues to update an Evidence Based Perspectives sharing the latest published data.

As new information is learned about breast implants, Mentor updates its corporate website, patient website, surgeon portal and other social media outlets in a timely fashion. Finally, Mentor continuously supports direct education and dialogue with surgeon customers via webinars, meetings, and sponsorships of society conferences where the latest data are shared with the plastic surgery community at large. Mentor also ensures continuous education for its field representatives, who serve as front line communicators with surgeons who use Mentor's products.

## 10.0 Summary

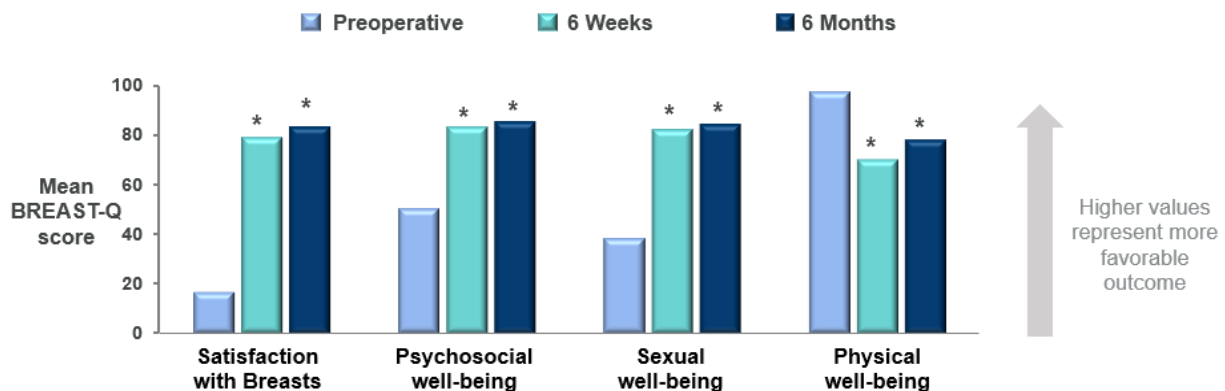
Mentor works with FDA and professional societies to provide surgeons and patients with transparent and balanced information so that they can evaluate the benefits and risks associated with breast implants prior to making decisions. Mentor breast implants are supported by long term clinical data and are safe and effective for use in augmentation and reconstruction patients. Both Mentor's smooth and Siltex<sup>®</sup> Texture breast implants have a favorable benefit-risk profile that make them viable options for women electing to have breast surgery to improve their well-being and quality of life. Mentor supports the continued assessment of possible risks through the collection of long-term safety data via post market surveillance efforts, collaborative and independent research, ongoing clinical studies and support of breast implant registries.

Mentor looks forward to partnering with the plastic surgery community and FDA to identify additional ways we can continue to monitor breast implant safety and educate patients and their physicians about the benefits and risks associated with breast implants.



## Attachment 1: Quality of Life Benefits

A prospective study of 611 women receiving Mentor breast implants for bilateral submuscular augmentation employed the validated BREAST-Q patient-reported outcome measure to evaluate patients preoperatively, at 6 weeks, and at 6 months postoperatively.<sup>31</sup> A higher score on the BREAST-Q represents a more favorable quality of life outcome. As shown in Figure A-1, the results of this study demonstrated high patient satisfaction and statistically significant improvements in psychosocial and sexual well-being at both 6 weeks and 6 months post-surgery. As noted by the study authors, submuscular augmentations, as compared to subglandular placement, are associated with a delay in recovery of physical functioning, which likely accounts for the initial decrease and returning over time of physical functioning.



\*P<0.01 vs. preoperative score, t-test

**Figure A-1.** Quality of Life benefits of breast augmentation with Mentor breast implants

Similarly, for women who undergo mastectomy (unilateral or bilateral), breast reconstruction offers improved psychosocial (anxiety, depression, and self-esteem) and satisfaction outcomes.<sup>32,33,34</sup> Women have reported that breast reconstruction with mammary implants has been an aid in their recovery from breast cancer and has reduced emotional stress by helping to return their bodies to a more natural appearance, as opposed to not having reconstructive surgery or wearing an external prosthesis.

<sup>31</sup> Alderman AK, Bauer J, Fardo D, Abrahamse P, Pusic A. Understanding the effect of breast augmentation on quality of life: prospective analysis using the BREAST-Q. *Plast Reconstr Surg*. 2014;133(4):787-795.

<sup>32</sup> Elder EE, Brandberg Y, Bjorklund T, et al. Quality of life and patient satisfaction in breast cancer patients after immediate breast reconstruction: a prospective study. *Breast* 2005;14: 201-208.

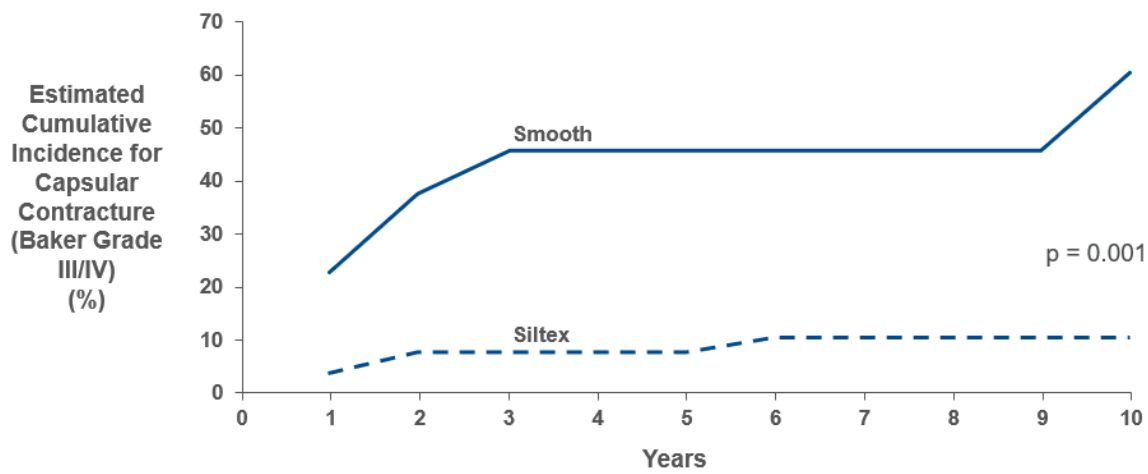
<sup>33</sup> Platt J, Baxter N, Zhong T. Breast reconstruction after mastectomy for breast cancer. *Canadian Medical Association Journal* 2011;183(18): 2109-2116.

<sup>34</sup> Al-Ghazal SK, Fallowfield L, Blamey RW. Comparison of psychological aspects and patient satisfaction following breast conserving surgery, simple mastectomy and breast reconstruction. *European Journal of Cancer* 2000;36(15): 1938-1943.

## Attachment 2: Specific Clinical Benefits of Mentor Siltex Texture Breast Implants

### Reduction in Capsular Contracture / Reoperation Rates

Long-term clinical data support lower capsular contracture rates with the use of Mentor's SILTEX® Texture breast implants compared to Mentor smooth implants in augmentation patients. This finding was demonstrated in a long-term (10 year), Level I evidence, double-blind, randomized, controlled clinical study conducted in the UK by Collis and colleagues (2000).<sup>35</sup> In this study, 53 patients were randomized to receive either subglandular Mentor MemoryGel smooth (n=26) or SILTEX® Texture (n=27) silicone breast implants. The patients were evaluated by a surgeon blinded to the type of implant. The study demonstrated a significantly lower capsular contracture incidence among patients with SILTEX® implants at both 3- and 10-years post-implantation ( $p=0.001$ ) [see Figure A-3].



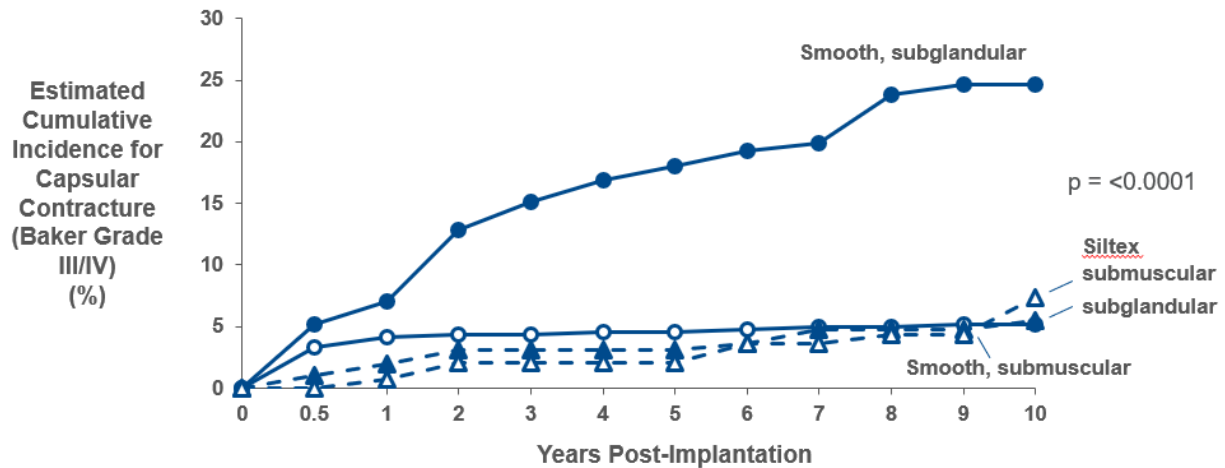
MemoryGel smooth (n=26); MemoryGel SILTEX® Texture (n=27)

**Figure A-3.** Development of capsular contracture: Kaplan Meier Analysis (UK study)

A lower capsular contracture rate with Mentor's SILTEX® Texture implants was also demonstrated among the primary augmentation patients participating in Mentor's prospective, multicenter, long-term (10 year) MemoryGel Core Study conducted in the US. In this study, patients received Mentor MemoryGel® smooth (N=786) or SILTEX® Texture (N=344) silicone breast implants implanted in either of two locations, subglandularly or submuscularly. The Kaplan-Meier estimated cumulative risk of capsular contracture (Baker III/IV) through 10 years in primary augmentation patients in Mentor's MemoryGel® Breast Implants Core Study is presented in Figure A-4. The data are presented separately by surface (smooth vs. SILTEX® Texture) and device placement (subglandular vs. submuscular/subpectoral). The findings

<sup>35</sup> Collis N, Coleman D, Foo IT, Sharpe DT. Ten-year review of a prospective randomized controlled trial of textured versus smooth subglandular silicone gel breast implants. *Plast Reconstr Surg*. 2000;106(4):786-791.

demonstrate a statistically-significant 5-fold reduction in capsular contracture in patients with Mentor SILTEX® Textured vs. smooth implants placed in the subglandular plane.

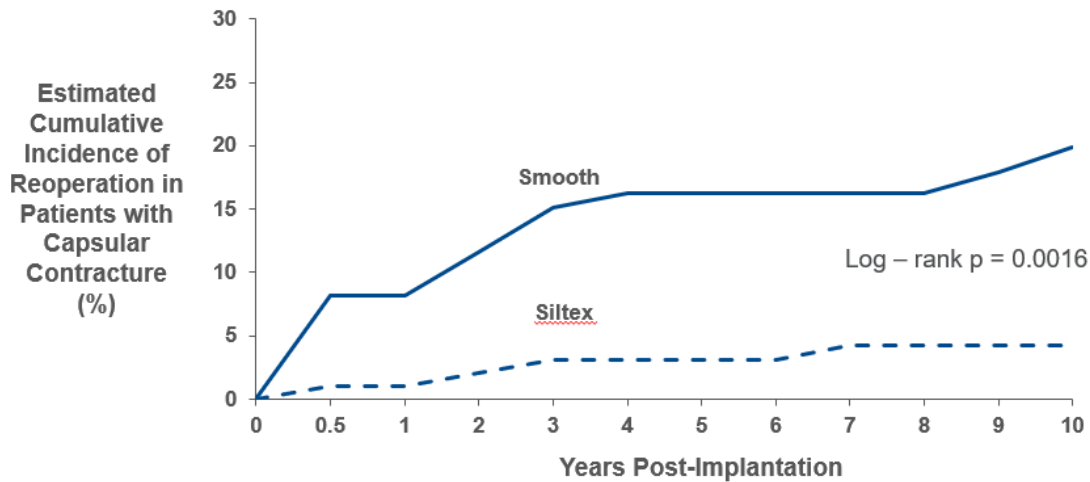


**Figure A-4:** Kaplan-Meier estimated cumulative risk of capsular contracture (Baker III/IV) through 10 years in primary augmentation patients in Mentor's MemoryGel® Breast Implants Core Study

It might be suggested that simply using submuscular placement might be the solution to reducing the incidence of capsular contracture without the need for texture. It is important, however, to note that following the trend of increasing prepectoral placement in breast reconstruction,<sup>36</sup> there is an emerging resurgence in the use of subglandular placement for breast augmentation, in part owing to reduced pain that has been associated with such device placement. Thus, textured implants continue to be a relevant risk mitigating factor for capsular contracture.

In the MemoryGel® Core Study cited above, the most frequent reason for reoperation in primary augmentation patients was capsular contracture (Baker III/IV). A comparison of the estimated cumulative incidence of reoperation through 10-years for patients with capsular contracture (III/IV) between those with subglandular textured versus subglandular smooth devices demonstrated a statistically significantly lower incidence rate for such reoperation for patients with the SILTEX® Texture vs. smooth devices (2.02% [95% C.I. 0.51-7.84] versus 19.84% [95% C.I. 0.51-7.84]). These reoperation results are presented in Figure A-5.

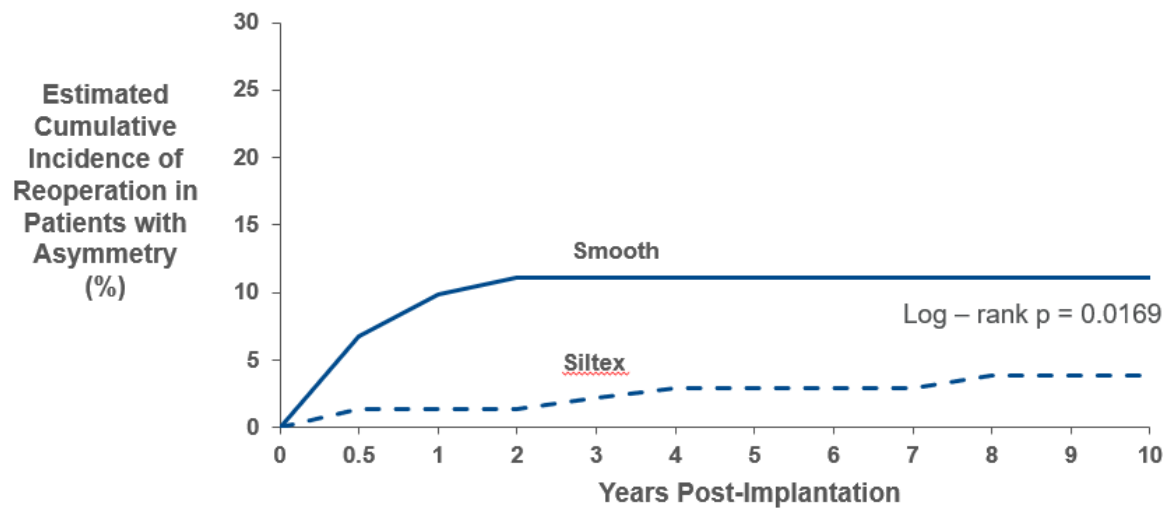
<sup>36</sup> Glasberg SB. The economics of prepectoral breast reconstruction. *Plast Reconstr Surg.* 2017;140(6S):49S-52S.



**Figure A-5:** Kaplan-Meier estimated cumulative risk of capsular contracture (Baker III/IV) with reoperation through 10 years in primary augmentation patients in Mentor’s MemoryGel® Breast Implants Core Study

#### Reduction in Asymmetry / Reoperation Rates

In the same MemoryGel® Core Study, the most frequent reason for reoperation in primary reconstruction patients was asymmetry. A comparison of the estimated cumulative incidence of reoperation through 10-years for patients with asymmetry between those with SILTEX® Texture versus smooth devices demonstrated a statistically significantly lower incidence of reoperation for the textured devices (3.88% [95% C.I. 1.63-9.13] versus 11.1% [95% C.I. 6.29-19.2]). These results are presented in Figure A-6.



**Figure A-6:** Kaplan-Meier estimated cumulative risk of asymmetry through 10 years in primary reconstruction patients in Mentor’s MemoryGel® Breast Implants Core Study































































































