General and Plastic Surgery Devices Panel of the Medical Devices Advisory Committee

Benefits and Risks of Breast Implants
March 25-26, 2019

Day 1 Summary and Overview of Day 2

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The Use of Surgical Mesh in Breast Reconstruction and Mastopexy

Clinical Overview

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Background

- Mesh manufacturers seeking marketing claims for labeling to include breast reconstruction, breast lift, or breast reduction.
  - New questions of safety and effectiveness are considered

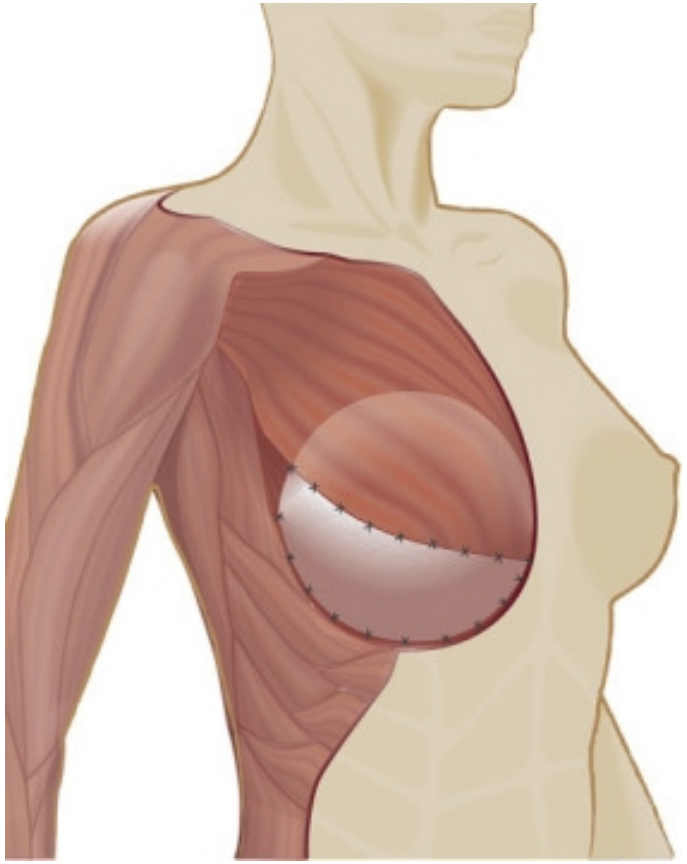
- Mesh products, particularly Acellular Dermal Matrices, are now used in the majority of all implant-based breast reconstructions
  - Discuss methods to better characterize risk/benefit profile for this use

Overview

- Clinical Overview
- Data requested
- Potential challenges

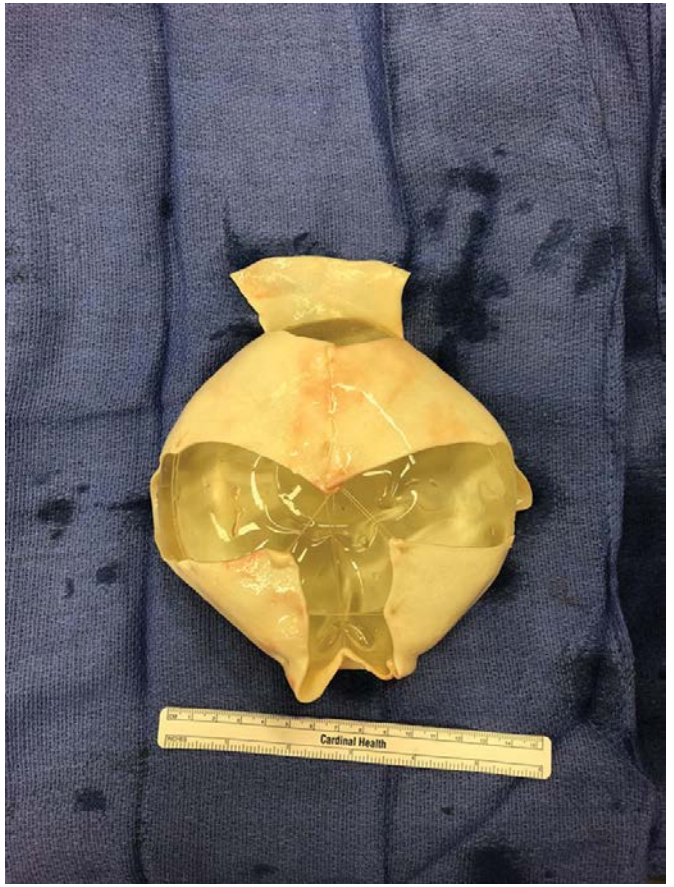
Implant Based Breast Reconstruction with Mesh

- Subpectoral/Submuscular



Plast Reconstr Surg Glob Open. 2014 Aug; 2(8): e192.

- Prepectoral



Plast Reconstr Surg Glob Open. 2018 Dec; 6(12): e2005.

Mastopexy/Reduction

- Typically performed without mesh
  - Mastopexy or breast lift
  - Breast Reduction
- The benefits/risks of implantation of surgical mesh into the breast for these procedures has not been characterized

Data Requested for Breast Indications

- Comparison to a control group that does not receive mesh
- An assessment of at least one effectiveness endpoint
- Inclusion and assessment of all relevant outcome variables
- Analysis accounting for relevant confounding variables
- Premarket follow up of at least one year, or until quiescence of inflammatory response and absorption
- Evidence of a favorable benefit/risk profile

Issues Encountered with Generating Necessary Clinical Data

- Appropriate control group
  - Comparison to a group that does not receive mesh
  - Perception of Standard of Care
  - Randomization
- Effectiveness endpoints
- Delineations between procedures or patient populations
  - Direct-to-implant vs Tissue Expander
  - Prepectoral vs Submuscular
  - Type of implant – Fill, surface, manufacturer, etc.

Panel Questions

Please discuss the following:

- Level of clinical evidence that should be required for a marketing application
- Clinical trial designs that would be acceptable to characterize these indications
- Whether different specific surgical uses may be considered separate and require independent clinical evidence and marketing applications.

The Regulation of Surgical Mesh for Breast Indications

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Regulation of Surgical Mesh for Breast Indications

- Types of surgical meshes
  - Synthetic: polymeric
  - Animal-derived acellular dermal matrices (ADMs): porcine, bovine
  - Human-derived acellular dermal matrices (ADMs): human cadaveric
- Synthetic and animal derived surgical meshes are regulated by CDRH
- Human-derived ADMs for breast reconstruction procedures where the dermis is used in the recipient to form an extension of the submuscular pocket for placement of a breast implant is considered non-homologous use
  - Does not meet criteria for regulation solely under 21 CFR Part 1271
- Manufactures of surgical meshes used for breast surgery indications should contact CDRH with questions regarding marketing authorization

Regulation of Surgical Mesh for Breast Indications

- 21 CFR 878.3300: Surgical meshes are intended to be implanted to reinforce soft tissue or bone where weakness exists
- FDA has reclassified surgical mesh used for transvaginal repair of pelvic organ prolapse into class III
- FDA has not cleared or approved any surgical mesh specifically indicated for use in breast surgery
- Clinical evaluation needed to evaluate the safety, effectiveness and benefit-risk profile of surgical mesh used for breast surgery

Regulation of Surgical Mesh for Breast Indications

- Specific breast indications are a new intended use for a surgical mesh.
- Premarket approval (PMA) required to demonstrate a reasonable assurance of safety and effectiveness and an acceptable benefit/risk profile

Levels of Specificity

- ✓ Identification of a particular disease entity or target population – breast cancer patient population
- ✓ Identification of an effect on clinical outcome – improvement of aesthetic outcomes

Decision-Making Considerations

- ✓ Potential new risks: capsular contracture, implant rupture, implant malposition, reconstructive failure, impact on imaging and lactation not seen hernia repair
- ✓ Public health impact: breast cancer patient population versus hernia patient population
- ✓ Knowledge base: inability to rely on existing data to evaluate benefits and risks of mesh use in breast surgery
- ✓ Different clinical endpoints: aesthetic, e.g. PROs, and functional endpoints, versus functional endpoints, e.g. hernia repair/recurrence

Regulation of Surgical Mesh for Breast Indications

- Manufactures of surgical meshes used for breast surgery indications should contact CDRH with questions regarding marketing authorization

- Patients and providers are encouraged to talk about the use of surgical mesh and the benefits and risks of surgical mesh in their breast surgery


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Panel Deliberations – Question 5

5. The use of an implanted surgical mesh in breast surgery has potential risks, including: infection, seroma, capsular contracture, explantation, reconstructive failure, implant rupture, alteration of breast physiology and interference with imaging. Some surgeons, however, will not perform pre-pectoral (above the pectoralis muscle) placement of a breast implant without the use of surgical mesh. FDA has not evaluated the safety and effectiveness, and the benefits and risks, of surgical mesh in any breast surgery and has not cleared or approved any surgical mesh for use in breast surgery/reconstruction.

   a. FDA has advised manufacturers seeking to justify claims of mesh use with breast implants to achieve reconstruction that the data provided should include the following (i-ii below). Please discuss if this is appropriate or if there are additional considerations.

      i. A comparison of patients treated with the subject device to a breast reconstruction control group that does not receive mesh.
      ii. Inclusion and evaluation of relevant adverse events for both the treatment and control arms.

Panel Deliberations – Question 5 cont.

5a. FDA has advised manufacturers that the data provided should include the following (iii-vii below). Please discuss if this is appropriate or if there are additional considerations.

iii. Assessment of the effectiveness of the surgical mesh device for breast reconstruction compared to the no-mesh control in at least one effectiveness outcome assessing patient benefit. The outcome measure chosen should be clinically relevant and unbiased .

iv. Pre-specified statistical analysis accounting for reasonably obtainable relevant confounding variables including: radiation, chemotherapy, patient demographics and medical history, type of reconstruction, type of mastectomy, type of breast implant, etc. This analysis would also potentially allow identification of specific patient populations or methods for use that result in a favorable benefit-risk profile.

v. An analysis comparing treatment and control on both a per-breast and per-patient basis, where feasible and appropriate.

vi. Premarket clinical follow-up to a minimum of 12 months post-implantation. If time to mesh resorption or time to quiescence of the inflammatory response of the tissue surrounding the mesh exceeds 12 months, then longer duration follow-up may be necessary.

vii. Evidence of a favorable benefit-risk profile for breast reconstruction with the subject device compared to breast reconstruction without the use of mesh.

Panel Deliberations - Question 5 cont.

5b. Considering the number of combinations of different surgical mesh, breast implant, surgical reconstruction procedures (e.g., prepectoral, submuscular, direct to implant, tissue expander to implant) possible, please discuss the extent to which each combination should be studied separately. Should all prepectoral and submuscular implantation, or direct-to-implant and tissue expander-to-implant reconstructions, be considered comparable in terms of assessing device benefit/risk, or should each mesh/breast implant/procedure require independent clinical data to assess benefits and risks? For prepectoral breast reconstruction specifically, current clinical practice is to generally use mesh with a breast implant; this makes it challenging to have a prepectoral implantation control arm without mesh. For prepectoral breast reconstruction with mesh, could the control arm be subpectoral implantation without mesh?

5c. Given that implantation of mesh for breast reconstruction involves the implantation of 2 devices i.e., surgical mesh and breast implant, please discuss if it is possible to consider benefit versus risk for the mesh and breast implant separately or if a single benefit risk assessment should be made for the combination of the mesh and breast implant together as a unit.

Panel Deliberations - Question 5 cont.

5d. Please discuss how benefits, should be assessed with respect to risks. As you consider this issue please comment on the appropriate duration of time for patient follow-up, both in premarket and in postmarket studies, to characterize benefit/risk and safety/effectiveness over time.

5c. Please discuss whether a registry for characterizing benefit/risk for breast implant reconstruction involving mesh may be necessary and, if so, how it should be structured and potentially interface with existing breast implant registries.

The History of Silent Rupture Screening and Informed Consent for Breast Implants

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Breast Implant History

- After Congress established the Center for Devices in 1976, breast implants were placed into Class II by the original classification panels and reviewed through the premarket notification [510(k)] process. Thus, approval of silicone gel-filled implants was not required. It was only necessary to establish substantial equivalence to an existing device. Labeling for silicone gel-filled breast implants did not include informed consent or a recommendation for MRI screening.
- In 1988, due to emerging safety concerns, the FDA re-classified breast implants to class III, requiring premarket approval. However, silicone gel-filled breast implants continued to be reviewed through the 510(k) process until the FDA issued a final rule calling for submission of premarket approval applications (PMAs) in April 1991.

Breast Implant History

- In January 1992, FDA announced a voluntary moratorium on silicone gel-filled breast implants, requesting that manufacturers stop supplying them and surgeons stop implanting them, while the FDA reviewed new safety and effectiveness information.
- In April 1992, FDA concluded that none of the PMAs submitted for silicone gel-filled breast implants contained sufficient data to support approval. Thus, in the US, silicone gel-filled breast implants were only available to women for reconstruction procedures through entry into a clinical study. However, saline-filled breast implants remained available for augmentation and reconstruction during this time via 510(k) review.
- In May 2000, the FDA approved the first PMAs for saline-filled breast implants for augmentation in women age 18 and older and for reconstruction in women of any age. While patient labeling was included, there was no requirement for informed consent.

Breast Implant History

- In October 2003 and April 2005, respectively, an FDA Advisory Panel recommended approval with conditions of Allergan's and Mentor's silicone gel-filled breast implant PMAs. Among the conditions of approval for the approval of the PMAs, the panel recommended that FDA require labeling recommendations for MRI screening and patient informed consent documents.
- In November 2006, acting on the previous recommendations of the panel, FDA approved Allergan and Mentor's PMAs for silicone gel-filled breast implants. This was the first time silicone gel-filled breast implants were available for augmentation, in addition to reconstruction and revision, since the moratorium was established in 1992. The device labeling included a recommendation that a patient undergo an MRI at 3 years and then every two years thereafter and included informed consent documentation that the patient could sign once they had discussed all the potential risks of breast implants with their plastic surgeon.


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FDA Presentations on Patient Education & Informed Consent and Core Study MRI Data

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U.S. Food and Drug Administration

Approved Silicone Filled Gel Breast Implants (Core Studies)

Device	PMA #	Approval Date
Allergan Natrelle	P020056	11/17/2006
Allergan Natrelle 410	P040046	02/20/2013
Mentor MemoryGel	P030053	11/17/2006
Mentor MemoryShape	P060028	06/14/2013
Sientra	P070004	03/09/2012

Patient Education/Informed Consent

- Patient Labeling
- Physician Labeling
- FDA website

Breast Implants and Labeling

https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/BreastImplants/ucm063743.htm

Risks of Breast Implants

https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics

Breast Implant Complications

https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/BreastImplants/ucm259296.htm

BIA-ALCL

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

Breast Implants: Other Resources

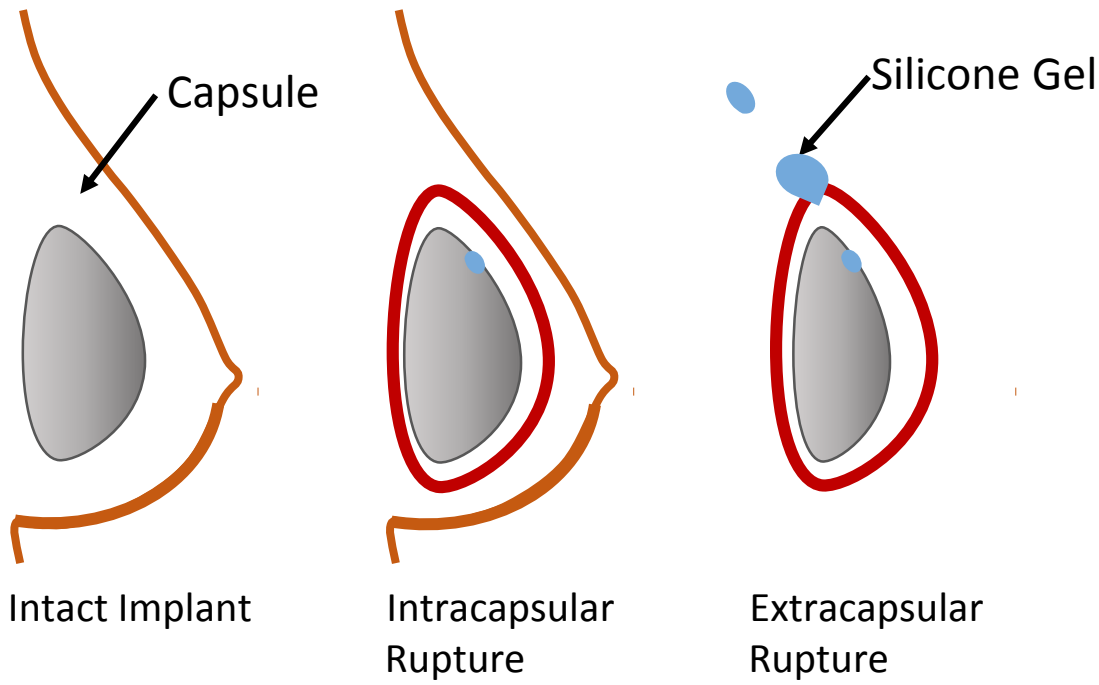
https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/BreastImplants/ucm063878.htm

Breast Implant Rupture

- Rupture is a tear or hole in the outer shell of the breast implant

- Silicone gel filled breast implants
  - Intracapsular rupture
  - Extracapsular rupture

- Silent rupture
  - Absence of noticeable changes
  - MRI detection



Labeling Recommendation Since November 17, 2006

Physician Labeling:

The first MRI should be performed at 3 years postoperatively, then every 2 years thereafter.

Patient Labeling:

You should have your first MRI at 3 years after your initial implant surgery and then every 2 years thereafter.

Data Source - Core Studies

- MRI and Non-MRI cohorts included for assessment of rupture rate
  - Augmentation
  - Revision Augmentation
  - Reconstruction
  - Revision Reconstruction

CORE STUDIES

	Allergan Natrelle	Allergan Natrelle 410	Mentor MemoryGel	Mentor MemoryShape	Sientra Round	Sientra Shaped
Patients	715	941	1008	955	1574	221
MRI Cohort	264	306	420	419	491	82
Follow up	10 years	10 years	10 years	10 years	10 years	
Study Compliance Rate at Year 10	62- 73 %	55-81 %	57-73 %	60-74 %	58 – 67 %	
MRI Schedule (years)	1, 3, 5, 7, 9	1, 3, 5, 7, 10	1, 2, 4, 6, 8, 10	1, 2, 4, 6, 8, 10	3, 4, 6, 8, 10	
MRI Compliance rate at Year 9 or 10 % Expected MRI Cohort Patient level	75-100%	48-85%	46-68%	42-57%	67-80%	

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% Silent rupture in MRI Cohort (Out of All Unconfirmed and Confirmed ruptures)	93% (Implant Level)	95% (Implant Level)	97% (Patient level)	88% (Patient Level)	100%	100%
% Silent rupture in non-MRI Cohort (Out of All Unconfirmed and Confirmed ruptures)	82% (Implant Level)	91% (Implant Level)	96% (Patient level)	83% (Patient Level)	100%	

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% Silent rupture in non-MRI Cohort (Out of All Unconfirmed and Confirmed ruptures)	82% (Implant Level)	91% (Implant Level)	96% (Patient level)	83% (Patient Level)	100%	
% Intracapsular Rupture of Explanted Ruptured Devices (Implant Level)	100%	73%				
% Extracapsular Rupture of Explanted Ruptured Devices (Implant Level)	7%	4%				

CORE STUDIES

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% Silent rupture in non-MRI Cohort (Out of All Unconfirmed and Confirmed ruptures)	82% (Implant Level)	91% (Implant Level)	96% (Patient level)	83% (Patient Level)	100%	
% Intracapsular Rupture of Explanted Ruptured Devices (Implant Level)	100%	73%				
% Extracapsular Rupture of Explanted Ruptured Devices (Implant Level)	7%	4%				
% Intracapsular Rupture of Silent Ruptures (Patient Level)			85% (100% First Detected by MRI)	67% (100% First Detected by MRI)		
% Extracapsular Rupture of Silent Ruptures (Patient Level)			3% (100% First Detected by MRI)	13% (100% First Detected by MRI)		

CORE STUDIES

	Allergan Natrelle	Allergan Natrelle 410	Mentor MemoryGel	Mentor MemoryShape	Sientra Round	Sientra Shaped
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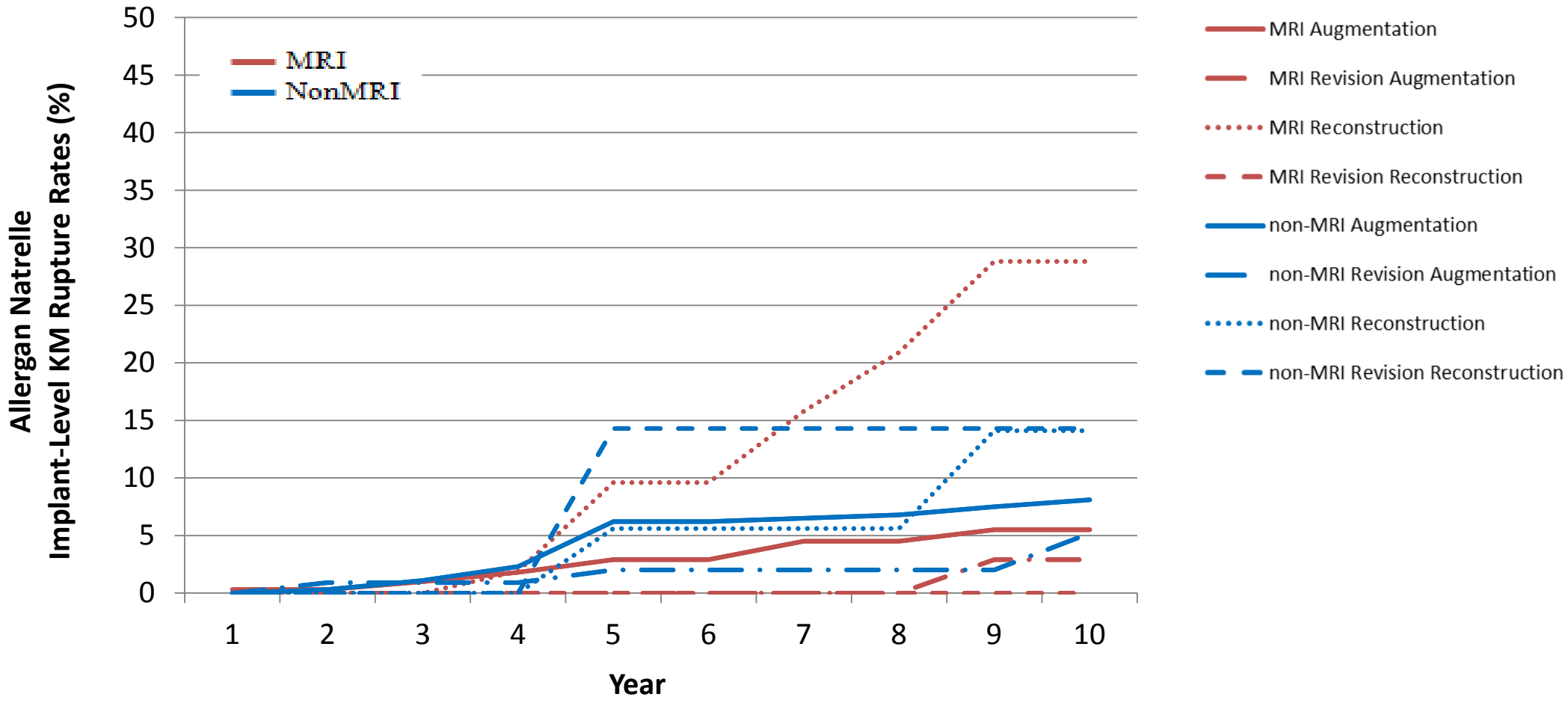
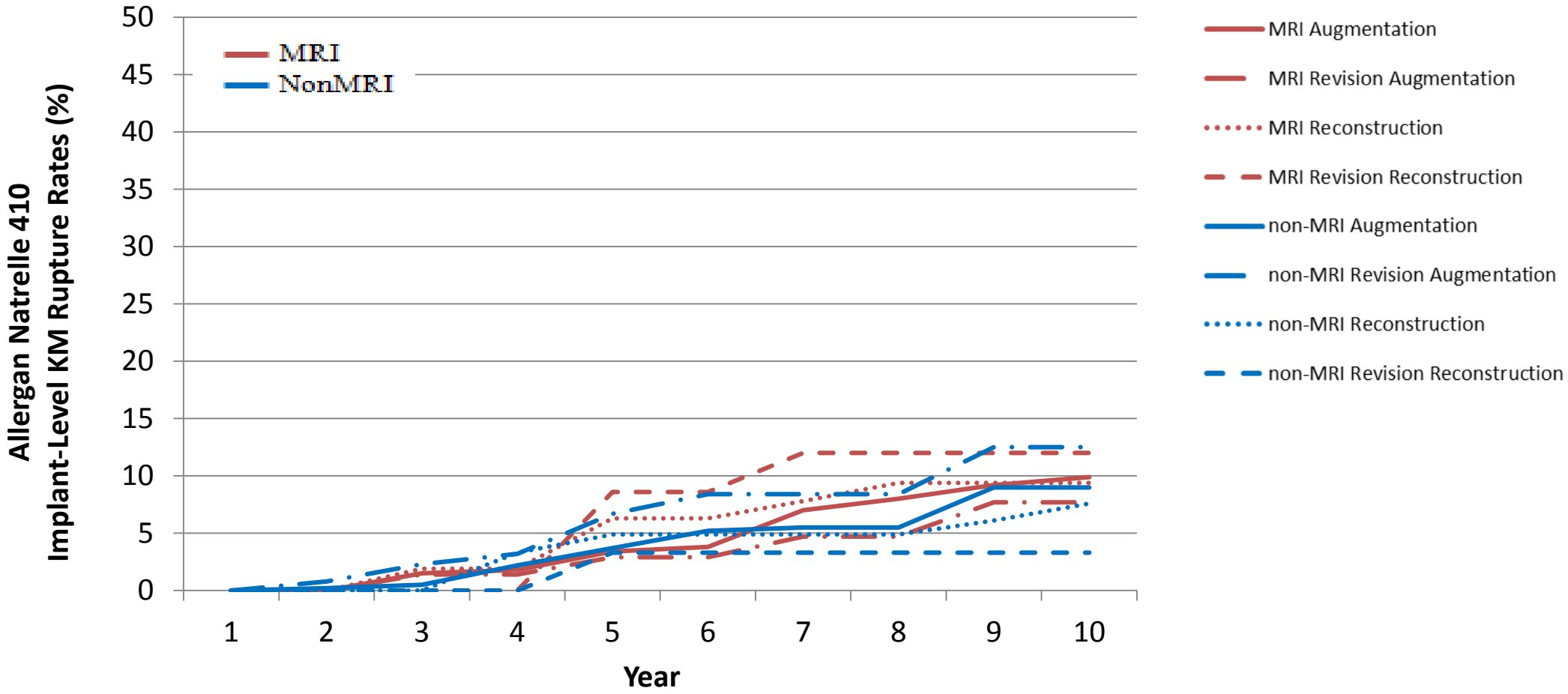
% Silent rupture in non-MRI Cohort (Out of All Unconfirmed and Confirmed ruptures)	82% (Implant Level)	91% (Implant Level)	96% (Patient level)	83% (Patient Level)	100%	
% Intracapsular Rupture of Explanted Ruptured Devices (Implant Level)	100%	73%				
% Extracapsular Rupture of Explanted Ruptured Devices (Implant Level)	7%	4%				
% Intracapsular Rupture of Silent Ruptures (Patient Level)			85% (100% First Detected by MRI)	67% (100% First Detected by MRI)		
% Extracapsular Rupture of Silent Ruptures (Patient Level)			3% (100% First Detected by MRI)	13% (100% First Detected by MRI)		
% Intracapsular Rupture of Explanted Silent Confirmed Ruptures					96%-100% (40-100% First Detected by MRI)	100% (Unknown)
% Extracapsular Rupture of Explanted Silent Confirmed Ruptures					4 % (100% First Detected by MRI)	Unknown

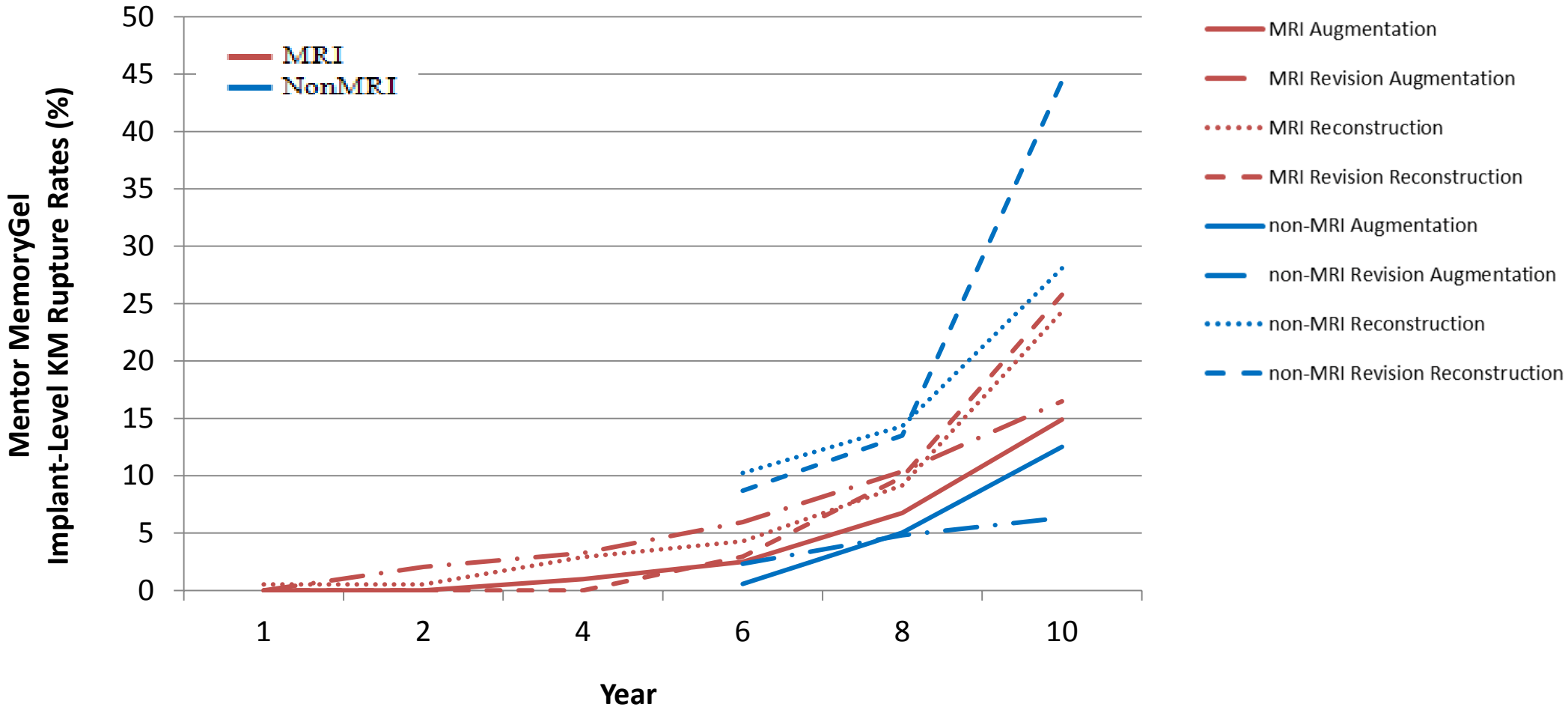
Allergan Natrelle Implant-Level KM Rupture Rates (%)



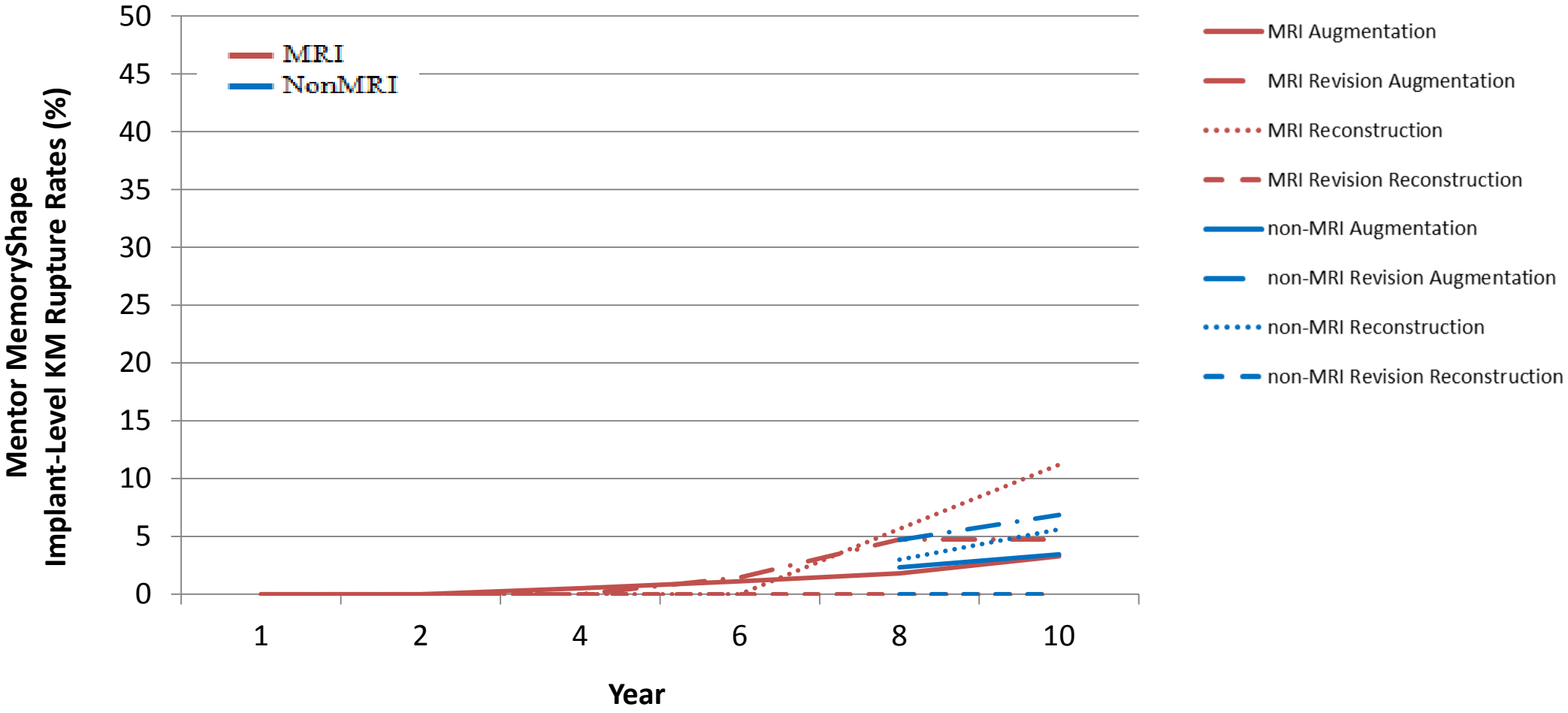
Allergan Natrelle 410 Implant-Level KM Rupture Rates (%)



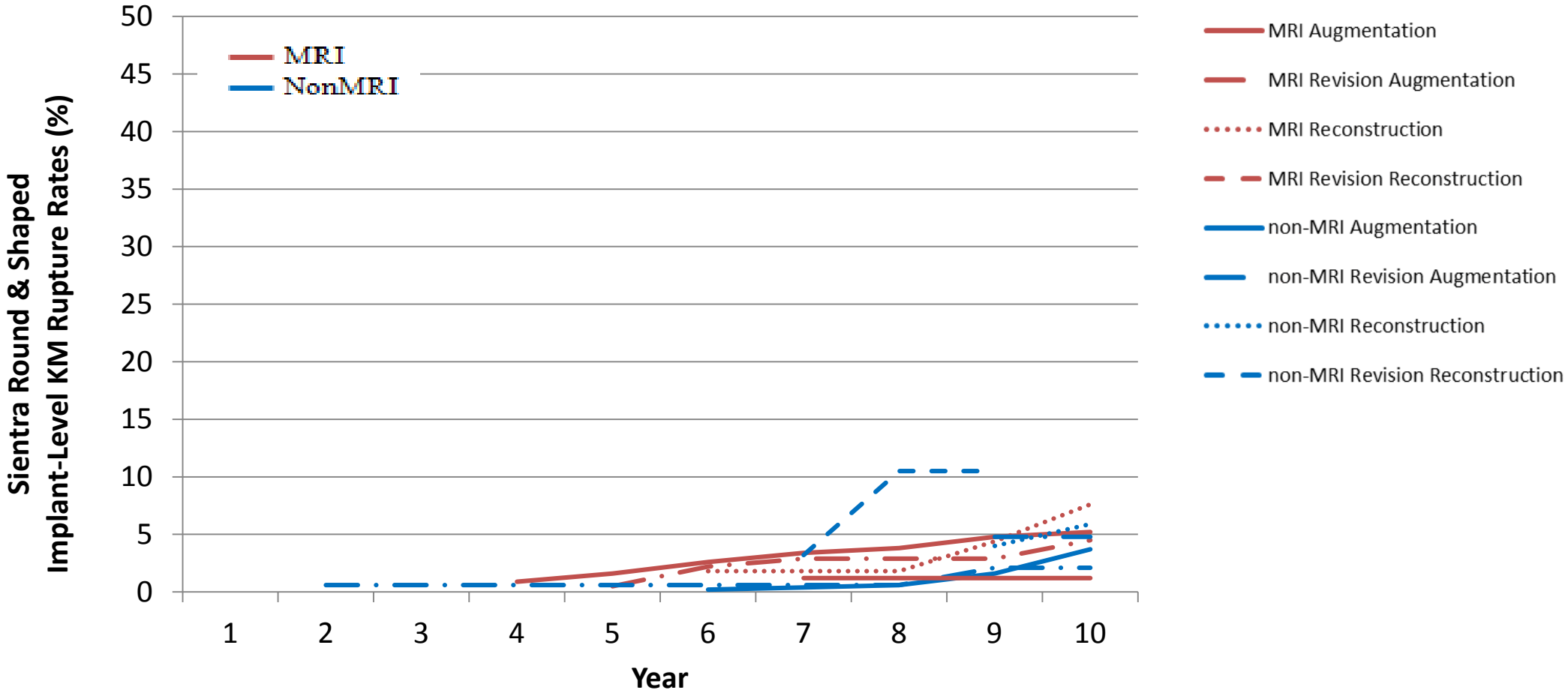
Mentor MemoryGel Implant-Level KM Rupture Rates (%)



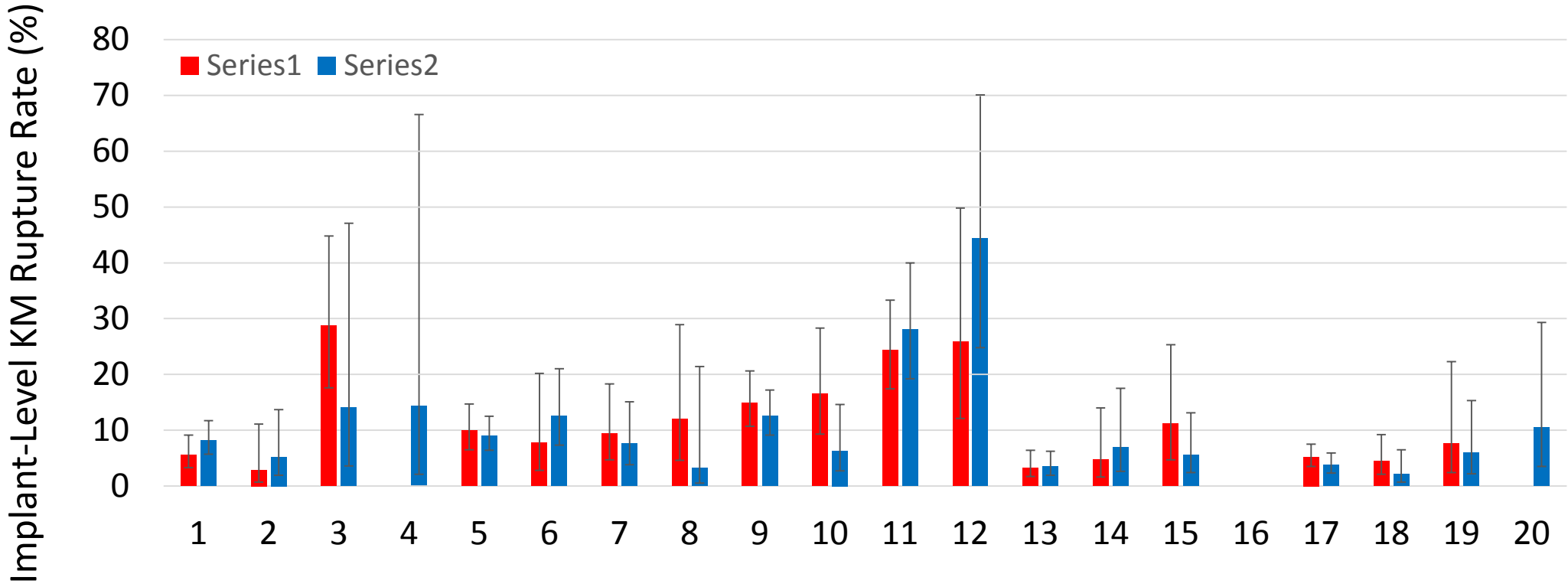
Mentor MemoryShape Implant-Level KM Rupture Rates (%)



Sientra Round and Shaped Implant-Level KM Rupture Rates (%)



Implant Level 10-year KM Rupture Rates with Confidence Intervals



Conclusions

- Rupture is one of the most reported device problems for breast implants
- Data limitations restrict statistically robust interpretations of rupture information presented in interim and final Core study reports
- Rupture rates increase the longer implants are in place. Overall, rupture rates generally are less than 5% before Year 4 and then increases around 4-6 years post-implantation. After Year 6, the rupture rates continue to increase at variable rates
- The majority of rupture events in the Core studies were silent and intracapsular in nature regardless of cohort
- In general, there does not appear to be a difference in 10-year rupture rates between MRI and Non-MRI cohorts in the Core studies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Panel Deliberations – Question 6

6. The FDA currently recommends that patients have their silicone gel implants evaluated for silent rupture by MRI, beginning at 3 years post implantation and every 2 years after that. American College of Radiology currently recommends the following: *For asymptomatic women (any age) with silicone implants, no imaging is recommended for implant evaluation*. Issues related to health insurance reimbursement have been reported, and data from implant manufacturer studies indicates low compliance with this recommendation. Please discuss the following:

   a. Should the FDA continue to recommend MRI screening for silent rupture of silicone gel-filled breast implants?
   b. If FDA should continue to recommend MRI screening, what level of evidence for clinical benefit would be required to support screening?
   c. What is the clinical benefit of continued screening, and what is the risk of not screening?
   d. Are there alternative screening methods that should be used?

Panel Deliberations – Question 7

7. Choosing to obtain a breast implant, whether for augmentation or reconstruction, is a deeply personal choice and should be discussed between a patient and their provider in a transparent and balanced way with clear information about the benefits and risks of breast implants and the procedure. Please discuss the following issues related to communication of risks associated with breast implants:

    a. What additional steps can FDA take to ensure that patients are better informed about the risks of breast implants?
    b. Please discuss what additional steps providers and patients can take to ensure that patients are better informed about the risks of breast implants both at the time of breast implant surgery and longitudinally.
    c. Breast implant patient labeling contains information on the risks and benefits of breast implants, results from clinical studies, a checklist of pertinent information and additional resources. Please discuss how to inform patients on how to best request and review breast implant patient labeling before surgery.

Panel Deliberations – Question 7 cont.

7. Please discuss the following issues related to communication of risks associated with breast implants:
   d. Please discuss what BIA-ALCL information should be communicated to patients who are considering breast implants and are concerned about the risk of developing BIA-ALCL.
   e. Please discuss what information about possible systemic symptoms should be communicated to patients considering breast implants and to patients that have breast implants.
   f. Are there opportunities to leverage existing social media platforms and other technologies to communicate benefit and risks associated with breast implants when deciding to obtain breast implants, and to stay informed on breast implant safety after receiving breast implants?
   g. In closing, please comment on whether there are additional actions, not otherwise raised over the course of these two days, that the FDA should consider taking.

Panel Deliberations – Question 8

8. In closing, please comment on whether there are additional actions, not otherwise raised over the course of these two days, that the FDA should consider taking.