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DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

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CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

MEDICAL DEVICES ADVISORY COMMITTEE

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GENERAL AND PLASTIC SURGERY DEVICES PANEL

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March 26, 2019
8:00 a.m.

FDA White Oak Campus
Building #31, Great Room
10903 New Hampshire Avenue
Silver Spring, Maryland

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RACHEL S. BRUMMERT	Consumer Representative
NATALIE COMPAGNI PORTIS, Psy.D.	Patient Representative
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M E E T I N G

(8:00 a.m.)

DR. LEWIS: Good morning. I would like to call this meeting together. It's a meeting of the General and Plastic Surgery Devices Panel of the Medical Devices Advisory Committee.

I'm Dr. Frank Lewis, the Chair of the Panel. I'm a trauma surgeon and a general surgeon by training and a recently retired executive director of the American Board of Surgery.

I note for the record that the voting members present constitute a quorum as required by 21 C.F.R. Part 14. I would also like to add that the Panel members participating in today's meeting have all received training in FDA device law and regulations.

For today's agenda, the Panel will discuss the benefits and risks of breast implants indicated for breast augmentation and reconstruction, concerning the following topics:

- MRI screening for silent rupture of silicone gel-filled breast implants;
- The use of surgical mesh in breast procedures such as breast reconstruction and mastopexy;
- The use of real-world data and patient perspectives in regulatory decision making; and
- Best practices for informed consent discussions between patients and clinicians.

Before we begin, I would like to ask all of the Panel members and the FDA staff seated here at the table to introduce themselves. I realize we did this yesterday, but because we may have new members in the audience, we need to repeat this today. Please state your name, your area of expertise, your position, and your affiliation. And we'll begin to my right with Dr. Chevray.

DR. CHEVRAY: Good morning, my name is Pierre Chevray. I'm a plastic surgeon specializing in breast reconstruction, and I practice at the Houston Methodist Hospital in Houston, Texas, and I'm an Associate Professor of Plastic Surgery at Weill Cornell Medical College in New York.

DR. GALLAGHER: Colleen Gallagher, and I'm the Executive Director of Clinical Ethics at MD Anderson Cancer Center. I'm also the chief of the section of integrated ethics and a professor in the Department of Critical Care.

DR. ROGERS: I'm Rebecca Rogers. I'm a Professor of Obstetrics and Gynecology at Dell Medical School in Austin, Texas, and I am the Director of the Women's Health Institute and the Associate Chair for Clinical Integration Operations.

DR. BALLMAN: I'm Karla Ballman, and I'm at Weill Cornell Medicine in New York City. I am a Professor of Biostatistics and the Division Chief of Biostatistics and Epidemiology, and my expertise is in biostatistics and epidemiology.

DR. SANDLER: I'm Howard Sandler. I'm a radiation oncologist and the Chairman of the Department of Radiation Oncology at Cedars-Sinai Medical Center in Los Angeles.

(Pause.)

DR. LEWIS: Dr. Li and the microphone have a problem together, it looks like.

DR. LI: Here we go, thank you. My name is Steve Li. I have a private consulting company and laboratory, and my areas of expertise are biomaterials and bioengineering specifically related to medical implants.

MS. PAWELSKI: My name is Lynn Pawelski. I'm the Industry Representative on the Panel, and I'm the Vice President of Regulatory Affairs at Baxter Healthcare.

MS. BRUMMERT: I'm Rachel Brummert. I'm president of Patient Safety Impact in Charlotte, North Carolina, and I'm the Consumer Representative.

DR. PORTIS: Natalie Compagni Portis, and I'm the Patient Representative.

DR. ASHAR: Good morning, I'm Binita Ashar. I'm a general surgeon and the Director of the Division of Surgical Devices at FDA's Center for Devices and Radiological Health.

DR. ANDERSON: Ben Anderson, Professor of Surgery and Global Health Medicine at the University of Washington and Fred Hutchinson Cancer Research Center in Seattle. I'm a practicing breast cancer surgeon.

DR. JAFFE: I'm Elaine Jaffe. I'm Chief of Hematopathology at the National Cancer Institute. I'm a pathologist, and I specialize in lymphoma.

DR. WHITE: Jeffrey White. I'm a medical oncologist and the Director of the NCI's Office of Cancer Complementary and Alternative Medicine.

DR. LIPPMAN: I'm Marc Lippman, and I'm a Professor of Oncology and Medicine at Georgetown University here in Washington. I'm a medical oncologist, and I treat breast cancer, and do laboratory research on breast cancer.

DR. McGRATH: I'm Mary McGrath. I'm a plastic surgeon, and I'm a Professor of Surgery at the University of California, San Francisco.

MS. ENGEBRETSON: I'm Rhonda Engebretson. I'm a registered mammography technologist at the Avera Breast Center in Sioux Falls, South Dakota.

DR. BURKE: I'm Karen Burke. I'm a dermatologist at Mount Sinai Icahn School of Medicine in New York.

DR. LEITCH: I'm Marilyn Leitch. I'm a surgical oncologist at UT Southwestern in Dallas. I'm a Professor of Surgery and section chief for breast and soft tissue surgical oncology.

CDR GARCIA: Good morning, my name is Patricio Garcia. I'm the Designated Federal Officer for this meeting.

DR. LEWIS: For topics being discussed at today's meeting, we recognize that there are a variety of opinions, some of which are quite strongly held. Our goal in today's

meeting will be a fair and open discussion of these issues, and we anticipate individuals can express their views without interruption whenever they're speaking. As a reminder, individuals will be allowed to speak into the record only if they are recognized on the schedule or recognized separately by the Chairperson. We look forward to a productive meeting.

And members of the audience, if you have not already done so, please sign the attendance sheets that are located on the registration table directly outside of the meeting room.

We'll now ask Commander Patricio Garcia, the Designated Federal Officer for this Panel, to make some introductory remarks.

CDR GARCIA: Thank you, Dr. Lewis.

I will now read the FDA Conflict of Interest Disclosure Statement. FDA Conflict of Interest Disclosure Statement, General and Plastic Surgery Panel of Medical Devices Advisory Committee.

The Food and Drug Administration is convening today's meeting of the General and Plastic Surgery Panel of the Medical Devices Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the Industry Representative, all members and consultants of the Panel are special Government employees or regular Federal employees from other agencies and are subject to Federal conflict of interest laws and regulations.

The following information on the status of this Panel's compliance with Federal ethics and conflict of interest laws covered by, but not limited to, those found in 18 U.S.C. Section 208 are being provided to participants in today's meeting and to the public.

FDA has determined that members and consultants of this Panel are in compliance with Federal ethics and conflict of interest laws. Under 18 U.S.C. Section 208, Congress has

authorized FDA to grant waivers to special Government employees or regular Federal employees who have financial conflicts when it is determined that the Agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

Related to the discussion of today's meeting, members and consultants of this Panel who are special Government employees or regular Federal employees have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children and, for the purpose of 18 U.S.C. Section 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts/grants/CRADAs; teaching/speaking/writing; patents and royalties; and primary employment.

For today's agenda, the Panel will discuss and make recommendations regarding the benefits and risks of breast implants indicated for breast augmentation and reconstruction, addressing the following topics:

- MRI screening for silent rupture of silicone gel breast implants;
- The use of surgical mesh in breast procedures such as breast reconstruction and mastopexy;
- The use of real-world data and patient perspective in regulatory decision making; and
- Best practices for an informed consent discussion between patients and clinicians.

Based on the agenda for today's meeting and all financial interests reported by the Panel members and consultants, no conflict of interest waivers have been issued in accordance with 18 U.S.C. Section 208.

Lynn Pawelski is serving as the Industry Representative acting on behalf of all related industry. She is employed by Baxter Healthcare, Incorporated.

We would like to remind members and consultants that if the discussion involves any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement and their exclusion will be noted for the record.

FDA encourages all other participants to advise the Panel of any financial relationships that they might have with any firm at issue.

A copy of this statement will be available for review at the registration table during this meeting and will be included as part of the official transcript. Thank you.

For the duration of the General and Plastic Surgery Devices Panel meeting, March 26th, 2019, Dr. Lippman has been appointed to serve as a Temporary Non-Voting member and Dr. Natalie Compagni Portis has been appointed to serve as Temporary Non-Voting Patient Representative. For the record, Dr. Lippman serves as a consultant and Dr. Compagni Portis serves as a patient representative to the Oncology Drug Advisory Committee at the Center for Drug Evaluation and Research. These individuals are special Government employees who have undergone the customary conflict of interest review and have reviewed the materials to be considered at this meeting.

The appointments were authorized by Russell Fortney, Director, Advisory Committee Oversight and Management Staff, on March 18th, 2019.

Before I turn the meeting back over to Dr. Lewis, our Chair, I would like to make a few general announcements.

Transcripts of today's meeting will be available from Free State Court Reporting.

Information on purchasing videos of today's meeting and handouts for today's presentation are available at the registration table outside the meeting room.

The FDA press contact for today's meeting is Stephanie Caccomo.

All written comments received were provided to the Panel and to the FDA review

team for their review prior to today's meeting. There is an active docket where members of the public can post written comments. The link can be found on the FDA website and registration table.

I would like to remind everyone that members of the public and the press are not permitted in the Panel area, which is the area beyond the speaker's podium. I request that reporters please wait to speak to the FDA officials until after the Panel meeting has concluded.

If you are presenting in the Open Public Hearing session and have not previously provided an electronic copy of your slide presentation to the FDA, please arrange to do so with Mr. Artair Mallett. He is at the registration table.

In order to help the transcriptionist identify who is speaking, please be sure to identify yourself each and every time you speak.

Finally, please silence your cell phones and other electronic devices at this time. Thank you.

Mr. Chair.

DR. LEWIS: Thank you, Commander Garcia.

We will begin today's meeting with introductory remarks from the FDA by Dr. Cynthia Chang, who will give a summary of the Day 1 subjects and an overview for today.

Dr. Chang.

DR. CHANG: Good morning, everyone, and welcome to the second day of our Panel meeting on the benefits and risks of breast implants. My name is Cynthia Chang, and I am the Branch Chief for the Plastic and Reconstructive Surgery Devices Branch 2.

Yesterday's discussion focused on breast implant-associated anaplastic large cell lymphoma, or BIA-ALCL, systemic symptoms reported in patients receiving breast implants,

the use of registries for breast implant surveillance, and the use of real-world data and patient perspectives in regulatory decision making.

To provide context for the deliberations, the FDA and international regulators from the European Union task force and Health Canada commented on the important clinical issues to be covered in the meeting. We then heard from Ms. Jamee Cook, who explained what she, as a patient, thinks that other patients should know about breast implants.

Next, we discussed the status of the industry sponsored breast implant studies and reports of breast implant illness, or BII, and BIA-ALCL. FDA provided an overview of the FDA-mandated post-approval studies, or PAS. The four manufacturers presented their data on their PAS studies, BII and BIA-ALCL. FDA also presented our analysis of the BII and BIA-ALCL data available to us.

During the afternoon deliberations, we heard presentations on the use of registries and other sources of data to understand BII and BIA-ALCL, including the experience from the National Breast Implant Registry, or NBIR, PROFILE, MD Anderson Cancer Center, and the National Center for Health Research. Dr. Jan Willem Cohen Tervaert provided an analysis of the autoimmune syndrome induced by adjuvants, or ASIA, and BII. We also heard from the Advisory Committee, who provided insightful comments on a diverse range of clinical and scientific issues.

I would like to highlight some of the themes that kept coming up, which may be helpful to consider when discussing the questions today.

From the many patients, we heard over and over again that the informed consent process has failed them, and they were not told of the serious risks that accompany breast implants, including the risk of BIA-ALCL and BII. They recommend that a black box warning be added to breast implant labeling and that a standardized checklist be required as part of the informed consent process.

Considering that a form or a checklist does not necessarily replace the discussion that a physician has with her patient as part of a fully informed decision, this afternoon you will be asked to discuss the role and responsibility of all stakeholders for communicating breast implant-related risks and benefits to patients.

Similarly, in yesterday's deliberations regarding registries, we heard the importance of capturing patient-reported outcomes and including patient input in the registry data, as well as the need to make the registry data available to patients, such as in periodic summary reports.

We also heard about the importance of striking the right balance between mandating data collection to achieve sufficient participation to capture operations performed by different surgeons in the same patient and the burden of entering such large volumes of data as well as the difficulty in analyzing it.

In the discussions surrounding the data available for BIA-ALCL and BII, you noted that there is a lot of missing information in the medical device reports, or MDRs, sent to the FDA, which makes it difficult to identify the specific devices and the specific device characteristics which may be associated with or causing the disease and symptoms.

For BII, the Committee indicated that many of the symptoms reported also have other reported causes, including aromatase inhibitors. You noted that there are multiple factors which could affect these symptoms, which could include genetic predisposition, implant characteristics such as silicone gel or saline filling, or shell materials. You also noted the importance of an appropriate control group to assess how the numbers reported compare to the incidence in the general population. Many of you also noted the existence of such data in prior studies, which like all studies have limitations.

In the first Panel deliberation session this morning you will be asked to continue the discussion on methods for assessing and addressing BII.

For BIA-ALCL, you discussed a variety of risk factors, noting that there is a wide range of incidences reported depending on the degree of texturing. We heard that, according to plastic surgeons, there are benefits to textured breast implants which may include stabilizing the implant within the surrounding tissue. As part of the discussion, you mentioned that instead of using textured implants, some plastic surgeons are wrapping a smooth implant in a surgical mesh. This leads us into this morning's presentations on surgical mesh.

First, the FDA will present clinical and regulatory considerations on the use of surgical mesh in breast reconstruction and mastopexy. Dr. Edwin Wilkins will follow with an overview of the data available in the Mastectomy Reconstruction Outcomes Consortium.

The Panel will then be asked to discuss the evidentiary requirements for assessing the safety and effectiveness and benefit-risk profile for the implantation of surgical mesh for these procedures.

In the afternoon, we will hear from the four breast implant manufacturers on their MRI screening data for silent rupture, as well as their perspectives on patient education and informed consent. FDA will also discuss our perspectives on these topics.

We will hear the American College of Radiology's recommendations for MRI screening for breast implant rupture, as well as from Dr. Jonathan Green from the National Institutes of Health, or NIH, on patient informed consent best practices. Representatives of plastic surgery professional societies will then discuss the importance of patient education, safety, and research.

Following the presentations, the Panel will be asked to discuss the MRI screening recommendations for silent silicone gel-filled breast implant rupture.

Finally, to tie together the theme that has been running throughout the entire meeting, the Panel will be asked to discuss the role and responsibility of all stakeholders for

communicating breast implant-related risks and benefits to patients.

We look forward to hearing your thoughts on this complex product area and what FDA should consider in the promotion and protection of patient health.

Thank you.

DR. LEWIS: Thank you, Dr. Chang.

We will next hear a presentation from Dr. Michael DeLong from the Center for Devices and Radiological Health, who will give a clinical overview of the use of surgical mesh in breast reconstruction and mastopexy.

Dr. DeLong.

DR. DeLONG: Yes. Hello, everybody, and good morning. I'm Michael DeLong, one of the medical officers in the Division of Surgical Devices. We would like to get the Panel's input on strategies to characterize the benefits and risks of mesh products being used in breast surgical procedures, including surgeries with breast implants such as prosthetic-based breast reconstruction as well as surgeries without implants, like breast lifts or breast reductions.

Recently, many mesh manufacturers have approached the Agency seeking to include breast surgical indications for marketing claims including breast reconstruction, breast lift, or breast reduction. Because these procedures can be safely performed without the use of a mesh device, new questions of safety and effectiveness are considered for the use of an additional implanted device, especially if placed in immediate proximity to a breast implant. However, despite no approvals, mesh products and particularly acellular dermal matrices are now used in the majority of breast reconstruction procedures with breast implants.

We will ask the Panel to discuss methods to better characterize the benefit-risk profile of mesh products for use in breast surgery.

I will provide a brief overview of the clinical aspects of mesh use in breast surgery,

the type of data the Center has been requesting for breast indications from manufacturers, and the potential challenges with generating these data.

There are roughly 85,000 implant-based breast reconstruction patients per year in the United States, and since the first literature description of ADM for this use in 2005, reports now estimate that the majority of breast reconstructions that involve the use of breast implants use mesh products.

The most frequently described method for using mesh is during a submuscular implant breast reconstruction, as depicted on the left side of the slide. Submuscular indicates that the implant is placed underneath the pectoralis muscle of the chest. Previously, surgeons performing a submuscular implantation would place the implant in the same location but not use mesh. Now surgeons are using mesh during these procedures, as depicted on the left side, with the mesh depicted in white.

However, there are variable methods for mesh use. In the past decade, surgeons have returned to placing breast implants and tissue expanders for breast reconstruction above the pectoralis muscle. Currently, a common approach for this prepectoral reconstruction involves complete wrapping of the implant or expander with a surgical mesh product, as depicted on the right side of the slide. The mesh is then used to anchor the device on top of the patient's pectoralis muscle with sutures. The majority of surgeons performing a prepectoral breast reconstruction would only perform this procedure using mesh for various reasons.

The Panel will be asked to deliberate on whether all prepectoral and submuscular implantations should be considered comparable in terms of assessing device benefit and risk, or should each mesh, breast implant, and procedure require independent clinical data to assess benefits and risks?

Manufacturers have also been seeking to make marketing claims for use in

mastopexy and breast reduction procedures. The purpose of a mastopexy, or breast lift, is to lift a sagging breast, while the reduction lifts a breast and also removes breast tissue. Both of these procedures can be performed on patients of varying ages and typically demonstrate positive results without the use of mesh. To use mesh for these procedures, the mesh is implanted into the breast tissue using variable techniques.

Again, the Center attempts to understand the potential benefits for mesh use so that they may be quantified to characterize the benefit-risk profile for these devices. The proposed benefits have not been robustly defined, and it is unclear whether the use of mesh introduces new long-term risks such as impaired lactation or scar contracture around the mesh.

When sponsors have interacted with the Center to determine the type of clinical data that would be necessary to support a marketing application for breast surgery, the Center has been providing the following feedback. We will later ask the Panel to deliberate on the appropriateness of this list.

Because breast reconstruction or mastopexy can be performed without mesh, the Center has requested the treatment with the mesh product be compared to a control group that does receive a mesh product so that the specific benefits and risks of the mesh device can be understood.

Second, the Center has felt that at least one effectiveness outcome should be included in the characterization of mesh products for use in breast surgeries. A permanently implanted device should demonstrate some patient benefit to justify its use. The Center has previously requested the use of the BREAST-Q patient satisfaction instrument because it has been validated in these patient populations, but it is open to other proposed effectiveness endpoints suggested by sponsors as long as they are appropriate, objective, and the Center has requested that sponsors include in their

submission all relevant adverse event outcome variables to adequately characterize the safety profile of the mesh products for use in breast surgeries. These include any outcome related to the procedure, such as infection or hematoma, as well as adverse events that may arise from the combined use of two implants in close proximity, such as the capsular contracture rate or implant rupture rate.

The Center has additionally requested that submitted clinical data include all relevant confounding variables necessary to perform a robust analysis. For example, variables that may affect patient outcomes include chemotherapy history, radiation history, type of mastectomy, patient demographics and comorbidities, and implant variables like texturing, size, and manufacturer, among others.

Because these mesh devices are implanted without intention to be removed, the Center has previously requested that follow-up duration be sufficient to capture potential long-term complications. Patients should be followed until the quiescence of the inflammatory response or complete resorption of the mesh product for biodegradable products with a minimum of 1 year. Permanent mesh implants should be followed with the same timeline as other permanently implanted devices.

Of note, postmarket surveillance is likely to be required for all mesh products used in breast reconstruction as well, given that continued interaction with the permanent breast implant is possible.

Ultimately, the Center believes that a mesh product needs to demonstrate a favorable benefit-risk profile to receive approval for marketing for that indication, which is consistent with the approval process for any device.

However, certain challenges have been encountered when reviewing sponsor clinical trial proposals designed to generate appropriate data to characterize mesh products for breast procedures. One issue is identifying an appropriate control group for comparison.

As discussed previously, the Center has requested a control group that has not received a mesh product because these procedures can be performed without mesh and this comparison is necessary to characterize the benefits and risks of mesh devices specifically.

Sponsors have frequently reported difficulties finding surgeons who do not use mesh products now that the majority of implant-based breast reconstructions are performed with mesh. In particular, many surgeons will not perform prepectoral reconstruction without the use of mesh, which limits the identification of a control group for prepectoral reconstructions.

Additionally, many surgeons have preferences related to the use of these mesh devices, and randomization may not be feasible without surgeons willing to randomize their patients.

We have also encountered difficulties identifying appropriate and objective effectiveness endpoints to characterize device benefits. The Center has expressed a preference that sponsors use the BREAST-Q patient satisfaction instrument because the other potential benefits of mesh use do not necessarily have validated instruments for assessment.

Finally, we have not clearly identified how to separate procedure or patient populations as separate indications. For example, does a favorable benefit-risk profile for two-stage submuscular reconstruction with an eventual smooth round saline implant support use in direct-to-implant prepectoral reconstruction with a textured shaped silicone implant?

We will ask the Panel to deliberate on the level and type of evidence that should be required to support a marketing application for mesh use in breast reconstruction or other breast procedures. We will ask the Panel how to delineate between different procedures and which methods for use should be considered separate indications.

Thank you. We will now have Joe Nielsen come up and talk about the regulatory issues related to mesh use.

Thank you.

DR. LEWIS: Dr. Nielsen.

DR. NIELSEN: Good morning, everyone. My name is Joe Nielsen, and I'm a biologist in the Division of Surgical Devices --

DR. LEWIS: Could you stand a little closer to the microphone, please?

DR. NIELSEN: Sure. Sorry. Good morning, everyone. My name is Joe Nielsen, and I'm a biologist in the Division of Surgical Devices at FDA, and I'll be presenting a brief overview of the regulation of surgical mesh used for breast surgery.

So, there are three categories of surgical mesh that are being used in breast surgery: synthetic meshes made from polymeric materials, acellular dermal matrices, or ADMs, derived from animal sources such as porcine or bovine and/or ADMs derived from human cadavers.

Human-derived ADMs used for breast reconstruction procedures is considered a non-homologous use and therefore does not meet the criteria for regulation solely under 21 C.F.R. Part 1271, which covers human cell tissue and cellular products.

Manufacturers of surgical meshes used for breast surgery indications are encouraged to contact CDRH with questions regarding marketing authorization.

Surgical meshes are classified by 21 C.F.R. 878.3300. This regulation defines the intended use of a surgical mesh as the reinforcement of soft tissue or bone where weakness exists. Surgical meshes in this regulation are most commonly indicated to repair abdominal wall hernias.

FDA has reclassified surgical mesh indicated for transvaginal repair of pelvic organ prolapse into Class III. So, FDA has not cleared or approved any surgical mesh specifically

indicated for use in breast surgical procedures, and we believe that both preclinical and clinical testing are needed to adequately evaluate the safety, effectiveness, and benefit-risk profile of surgical mesh used for breast surgery.

CDRH has determined that a specific breast surgery indication for surgical mesh is a new intended use. To make this determination, we relied on FDA's general to specific guidance document. Intended use is defined as the general purpose or function of a medical device while the indications for use is defined as the disease or condition the device will treat, prevent, or cure.

A change from a general to a specific indication for use is defined in FDA's guidance as any proposed increase in the level of specificity. In the case of breast-specific indications, the level of specificity is increased by the identification of the breast cancer patient population and the indication's effect on the clinical outcomes, in this case, aesthetic outcomes.

Once an increase in specificity is identified, the seven decision-making considerations outlined in the guidance are used to evaluate whether a specific indication changes the intended use of the medical device.

For breast surgery specific indications, we have determined that new risks such as potential effects on capsular contracture, implant rupture, implant malposition, reconstructive failure, and impact on imaging and lactation, as well as the significant public health impact to the breast cancer patient population, the lack of a sufficient knowledge base, and different clinical endpoints, taken together, constitute a new intended use for a surgical mesh. Therefore, premarket approval is required to provide a reasonable assurance of safety and effectiveness and an acceptable benefit-risk profile for breast-specific indications.

And so, finally, manufacturers who are seeking breast surgery indications are

encouraged to contact CDRH with questions regarding marketing authorization, and patients and providers are encouraged to talk about the benefits and risks of surgical mesh in their breast surgery.

DR. LEWIS: Thank you.

We will now hear from Dr. Edwin Wilkins from the University of Michigan. Dr. Wilkins, please come to the podium and begin.

DR. WILKINS: Thank you, Dr. Lewis.

Good morning, everyone. I've been asked to discuss this morning findings from the Michigan -- excuse me, the Mastectomy Reconstruction Outcomes Consortium study specifically as they apply to the use of acellular dermal matrix. First of all, I have no conflicts to disclose.

As Dr. DeLong has articulated, the use of ADM, or acellular dermal matrix, in mastectomy reconstruction has become quite common for implant-based procedures. Although hard statistics are hard to come by, it appears that approximately 75 to 80% of these cases now use ADM. The rationale for using these materials include superior aesthetic outcomes as well as superior expansion dynamics, although these have not been well demonstrated.

Although there are previous studies assessing the use of this material, they've had some significant limitations, including retrospective designs, single center/single surgeon populations, small patient numbers, and often the absence of control groups. Most importantly, most of these studies have focused on clinical outcomes, i.e., complications, but not patient-reported outcomes. So, in essence, we've evaluated these materials from the surgeon's standpoint but not from the patient's point of view.

So, let me give a brief background on the Mastectomy Reconstruction Outcomes Consortium, or MROC, study because it's good to know where our data came from. The

study ran from 2012 to 2017. It involved 11 leading U.S. and Canadian centers in post-mastectomy breast reconstruction and a total of 58 plastic surgeons.

The specific aims of the overall study were to compare long-term outcomes for commonly used options for breast reconstruction and to evaluate both complications and patient-reported outcomes (PROs).

We used a prospective cohort design with pre/post measures. The project was funded by the NCI in 2011. Patients were recruited from 2012 to 2015. Data collection concluded a little over a year ago.

We studied first-time reconstructions only, not revisions, due to the potential of confounding with the latter group. We looked at immediate or delayed procedures and mastectomies for either cancer treatment or prophylaxis. And you can see the list of procedure types that we included in the evaluations. Today we're going to focus on, obviously, the expander/implant group.

Our measures included complications as well as a long list of patient-reported outcomes including psychosocial, physical, sexual well-being, perhaps most importantly patient satisfaction, anxiety, depression, body image, pain, and fatigue.

Our data sources were electronic medical records at the various institutions as well as a patient survey panel including a number of previously validated survey instruments. Most notably, we used the BREAST-Q, which as I think you heard previously is a condition-specific survey instrument for breast reconstruction patients that assesses health-related quality of life. A number of these other instruments you're probably familiar with as well. EORTC, for example, is a condition-specific QOL measure for breast cancer patients. The PROMIS 29 is one of the NCI's own instruments. We also had two pain measures plus two well-established measures of depression and anxiety.

The BREAST-Q, and I think you heard some about this yesterday, I expect, covers

seven domains assessing a number of things including satisfaction, psychosocial, and physical well-being. The Satisfaction with Breast Subscale is fairly comprehensive, and it covers a number of different points including size, shape, and symmetry, natural appearance, texture, as well as how well the reconstruction functions in bras and clothing. And as we'll see later, the specificity of these questionnaire items is important as we start interpreting the satisfaction scores.

So, we did EMR reviews annually, including preoperatively. We did the patient survey panels pre-reconstruction as well as 1 week, 3 months, 1 year, and 2 years post. The pre-reconstruction assessments were important because baselines were an important covariate in our analyses. Not surprisingly, where you end up at 2 years partly depends on where you started before reconstruction with a number of these measures.

So, we enrolled at a total of over 4400 patients. Over 1300 were withdrawn, mainly because they ended up not having reconstruction. So, we ended up with just over 3100 active participants. Reflecting current trends in breast reconstruction, over 90% of our procedures were immediate; that is, they were initiated at the time of the mastectomy.

So, we've run a number of analyses and published them over the past 5 years, including overall complications, PRO results, effects of radiation, and a number of other clinical covariates, as you can see. But, again, the one we're going to focus on today is risks and benefits of ADM.

So that's sort of some background on MROC and where the data came from.

So, this is a paper we published about a year and a half ago in the journal *Plastic and Reconstructive Surgery,* in which we looked at the use of ADM in immediate two-staged breast reconstruction, implant based. The objective of this analysis was to assess the effects of ADM on both complication rates and PROs in these procedures.

So, we started with all patients undergoing immediate two-stage implant-based

reconstruction following mastectomy for either cancer treatment or prophylaxis. We had 2 years of follow-up on the patients included, and we had two cohorts, ADM or non-ADM.

We included a number of independent variables in our analysis besides ADM, including demographics, indication for mastectomy and mastectomy type, age, BMI, smoking status, nodal management, i.e., sentinel node or axillary lymph node dissection, radiation and chemotherapy, because we expected that those would impact outcomes as well, which in fact, many of them did.

So, complications we tabulated in a number of different ways. First of all, total complications, that is any or all; major complications defined as complications of sufficient magnitude that they required re-hospitalization or reoperation; failure, meaning a complication of sufficient severity to require removal of the device; and finally, infection as defined by CDC criteria.

We looked at time to expander/implant exchange because one of the rationales for using ADM is that some practitioners feel that the expansions can be carried out sooner and quicker and hopefully translating into an exchange, the second stage occurring at an earlier date. Admittedly, that was a proxy measure.

The PROs we focused on here were satisfaction with breast, as well as physical, sexual, and psychosocial well-being, as well as postop pain because the thought was that with ADM, the expansions would be less onerous for the patient and result in lower pain levels, less muscle dissection at the initial operation.

So, for our analyses we carried out bivariate and mixed effects regression for complications in each of the PRO subscales. Our response rate at 2 years was not great, it was 60%, and so to hopefully deal with response bias, we also did multiple imputations with chained equations, actually created 10 models, and then ran the regressions for each of those imputed models and then essentially combined them using Rubin's rule.

I apologize for talking about statistics this early in the morning.

So, total patients in the analysis, close to 1,300, pretty evenly split between ADM and no ADM. In the initial bivariate analyses, we saw significant cohort differences for mastectomy indications, mastectomy type, lymph node management, radiation, and chemotherapy.

So, these are the unadjusted complications rates for the various categories. I don't see a pointer here, and I apologize. Total complications rates, the top line and then major complications, infection and failure, and as you can see, the ADM category, ADM cohort, had higher rates of all of the above. However, statistical significance was not achieved in any of these categories, although for major complications we did approach statistical significance at p 0.052.

So, we then fit the regression models and controlled for all of the previously described clinical variables and demographic variables. We also adjusted for site and surgeon because in many -- well, in probably all cases, those have some effects as well. Not too differently from the bivariate analyses, the only statistically significant difference, and actually it's marginal at 0.052, was for major complications where ADM patients were 43% more likely to experience a major complication. The odds ratios for wound infection and failure are sort of in the same ballpark, but because there were fewer of those cases, we did not reach statistical significance for either of those. That may or may not represent a Type II statistical error.

We also got to wondering, since complication rates may vary by brand, we had four manufacturers' types with significant numbers of patients. And so, we also looked at each of these compared to no ADM, and it turns out that for two of the brands there were statistically significant differences. For Brand B, higher risk or significantly higher risk of major complication. For Brand C, significantly higher risks of all complications, major

complications, and reconstructive failure with fairly significant odds ratios up to three to four times the no ADM group. And I apologize for that slide; it's a little intense.

For PROs, patient-reported outcomes, interestingly, we found no significant differences between the ADM and the no ADM group for satisfaction with breasts as well as psychosocial and sexual well-being nor for physical well-being or postoperative pain. And, again, we've controlled for the list of clinical and demographic covariates that you see there and adjusted for site and surgeon.

So, we also asked the question did ADM brand make a difference in PROs because some of the brands had lower complication rates, some higher complication rates. So, for the lower complication brands, would we be able to see a PRO benefit compared with no ADM? But, in fact, we found no statistically significant differences for any of the PRO measures when comparing each ADM brand individually with the non-ADM group.

And so, the next question we've asked more recently is if, in fact, overall, we saw no PRO benefit, are there patient subgroups who, in fact, may benefit from the use of ADM, because this has been postulated in the literature.

And so, what we did was go back and do subgroup analyses looking at interactions between each of the clinical variables and ADM use and looking at their effects on complications and PROs, and this included the same list of covariates that we've been talking about. And, once again, no subgroups were identified in which ADM was associated with better outcomes compared with non-ADM cases.

What we did see, though, and this was sort of an incidental finding, was that BMI essentially had no effect on overall complication rate in the non-ADM group, which you see here in blue. However, in the ADM group, as BMI went up in the higher categories, the risk of complication did go up, and so we saw that effect, the BMI effect, with ADM patients but not with the non-ADM cohort.

And, finally, did ADM shorten the time to exchange, because that's one of the reasons, one rationale, again, that have been used for employing ADM, and in fact, there was a 0.2-month difference, like a 6-day difference between the non-ADM and the ADM cohorts. This was not statistically significant. So, ADM did not impact the time to exchange.

So, we found the use of ADM in immediate expander reconstruction was associated with a marginally higher overall complication rate but had no significant effects on PROs compared with the non-ADM cases. Brand differences were observed for complications, but not for PROs. And, finally, ADM, as I mentioned a moment ago, had no significant effect on time to exchange.

So, important to mention the limitations: Our study was not an RCT, so there is always the possibility of selection bias in surgeons. It was an observational and not an interventional study, meaning that we studied what the surgeons were already doing, and it may be that there was a bias in selection for ADM versus not using it. The interesting thing about that is when we looked at each surgeon's practice patterns, we found the majority of surgeons used ADM either all the time or almost all the time or didn't use it much or at all. People tended to fall into those two camps. There was a smaller group in the middle that appeared to be using it more discriminately. So, it makes one wonder about the selection bias issue.

There's always the possibility of confounding by variables known or unknown that we did not control for.

The other thing to mention here is that these products continue to evolve, so not all the products that we studied in 2012 to 2015 -- that's when the patients were entered into the study -- not all of those are still being used. And so, when we assess these, it's a moving target. If you wanted us to study the products that are in use today, we would have results for you with a study like this in 2023 or 2024, at which point the products probably have

evolved further. So, it's really hard to study with a longitudinal design what's currently in use.

Our analyses did not evaluate direct-to-implant, or DTI, reconstructions because we had only a handful of those cases where ADM was not used. We also did not even collect the data point for prepectoral placement because in 2012 and 2015 between those dates there were very few of those cases. It was not widely practiced as it is now. So, again, we get into the moving target issue.

So, the things we wonder about. Why do plastic surgeons perceive aesthetically superior results with ADM in immediate expander reconstruction while patients don't? At least in our study.

Are the PRO measures sufficiently sensitive? Well, the reason I went into the BREAST-Q satisfaction subscale in depth is those are pretty sensitive questions. So, the BREAST-Q is designed to pick up subtle differences in breast reconstruction, particularly in satisfaction, and we have seen these with other comparisons but not with ADM.

Are we, as plastic surgeons, more critical of results? Probably. But then again, if we can see a difference and the patients can't, it does beg the question why are we using the material?

Now, since ADM offers clear technical advantages in direct-to-implant and prepectoral reconstructions, you know, are there PRO benefits for these procedures? That is yet to be determined. That is entirely possible.

So, we'd like to thank -- I would like to thank the NCI for its generous support and, most importantly, the patients and surgeons of MROC. And I appreciate the opportunity to present our data. Thank you.

DR. LEWIS: Thank you, Dr. Wilkins

I'd now like to ask all of the presenters from this morning to take their positions up

here by the podium. We have an opportunity for clarifying questions from the Panel. And we'll begin with Dr. Ballman.

DR. BALLMAN: So, I have some questions for Dr. Wilkins. I'm sorry to drag you through statistics so early in the morning, but it cannot be avoided. So, first of all, can you tell me what the study was powered on, what particular endpoint?

DR. WILKINS: It was powered on the number of patients we anticipated having at the end of the study and looking for intermediate effects.

DR. BALLMAN: So, there was no primary outcome that you were trying to detect a difference upon a priori?

DR. WILKINS: No.

DR. BALLMAN: Okay. Also, I mean, we realize that no statistical difference doesn't mean no difference, right? And, you know, those p-values for the complication rates, you know, there's no magic threshold and, you know, most of them were not in favor of using a mesh. It looked like, you know, in general, there was a higher complication rate. And this study is not assessing for other outcomes such as BII?

DR. WILKINS: It did not, no.

DR. BALLMAN: And so even if there's longer-term follow-up, there will be no sort of information available on BII?

DR. WILKINS: Well, the study is now concluded, so unfortunately not.

DR. BALLMAN: Okay, okay. And, you know, it does appear there -- I mean, it is interesting, and I do believe that surgeons probably have a favorite technique, but it still is interesting, there obviously is selection bias because the baseline characteristics did not look the same. So, another question is, were more sophisticated statistical techniques such as propensity score analyses or inverse probability weighting used when doing the analyses?

DR. WILKINS: We did not.

DR. BALLMAN: Okay, thank you.

DR. LEWIS: Dr. Wilkins, I have a couple of questions. Did I understand correctly that the assignment of patients to one or the other group, to the acellular group or not, was basically dictated by the surgeon's preference and not by any randomization?

DR. WILKINS: That is correct; it was strictly an observational study.

DR. LEWIS: And in your data was there any clinical indication, any clinical parameter which appeared to correlate with the use of ADM, or was it essentially a random choice by the surgeon?

DR. WILKINS: We did not detect any particular variable that drove the choice. It really was surgeon preference.

DR. LEWIS: And, lastly, you didn't report any sort of technical indicators relative to the procedure that might be -- that the matrix might provide a benefit for, for example, a shorter operation or easier placement or any other technical factors intraoperatively. Were you aware of any of those, or do you have any data related to time of operation, etc.?

DR. WILKINS: We did not look at OR time. As far as ease of placement and intraoperative factors, we did not look at those because we don't really know how to measure them. It's hard to measure what's going on in the surgeon's brain as far as whether he or she decides to use ADM. Ease of placement, I suspect if you ask 10 surgeons, you'd probably get 10 different answers.

DR. LEWIS: Dr. McGrath.

DR. McGRATH: There would, in fact, be some differences in the way that the surgeons mobilize the pectoral muscle, divided it and so forth, between the two groups. Was there any way that you could detect that or spell that out, because in the cases presumably with the ADM, they probably would not have cut off or opened up or divided

the pectoralis muscle as much or differently, but could you sort that out in this study?

DR. WILKINS: Again, there's not a good quantitative way to measure that. It's sort of like the problem we used to have with defining types of free TRAMs, you know, Type 1, Type 2, Type 3, how much muscle did you preserve, how much you didn't because, you know, one person's mobilization of the entire lower border of the pec may not be the same as another's. It's a qualitative call that's very difficult to measure, and to be honest, if I can't measure it objectively, I don't collect that data point. But it's a good point to make.

DR. LEWIS: Dr. White.

DR. WHITE: Yes. What was the median follow-up for patients?

DR. WILKINS: It was a standard follow-up of 2 years. It was a prospective study.

DR. WHITE: So, the intent of the study is to look for sort of short-term adverse effects --

DR. WILKINS: Yes.

DR. WHITE: Would the use of the mesh, is the goal -- is it generally accepted that the goal of this use is for -- what is the goal of the use of mesh?

DR. WILKINS: I hesitate to speak on behalf of all plastic surgeons, but the things that we talk about the most are easier, quicker expansion, better lower pole projection, things like that. Less postop pain.

DR. WHITE: So, there's no intent to fix -- to prevent sort of movement of the device or to decrease -- to prevent movement?

DR. WILKINS: Yeah, I think that's part of it, too. It depends on the surgeon, but certainly keeping the expander or -- I don't want to really talk too much about direct-to-implant since that was not in the study, but the idea of keeping the device centered and keep it from sliding to the side, lateralizing into the rest of the mastectomy is also, I think, a consideration for many surgeons. Particularly if they're going to a smooth tissue expander

which does adhere to the surrounding tissue, keeping it in the proper position and preventing displacement, I suspect, would be an important point for some surgeons.

DR. LEWIS: Dr. Chevray.

DR. CHEVRAY: I have a comment based on Dr. White's question and then a question. I think what you're asking -- well, this study was designed when prepectoral breast reconstruction was not nearly as common as it is now. So, the concept that you would wrap an implant in a mesh, you know, prepectoral reconstruction, one of the reasons for that is to place the implant and keep it placed where you want it. And probably the second most important reason is to prevent or minimize capsular contracture. Those two reasons are less important when you're putting the implant underneath the pectoralis major muscle, which is the only technique that was studied in Dr. Wilkins's study because of the time that the study was designed.

So when you're placing a tissue expander or an implant deep to or below the pectoralis major muscle, the main reasons for the mesh were, or are, to allow the lower pole of the breast to be expanded greater than the upper pole, so it's a cosmetic or an aesthetic reason and you get a better breast reconstruction, and also it was thought that you could expand more quickly and therefore get to the second surgery where you're exchanging the tissue expander with an implant more quickly. I think those were probably the two most important reasons for using mesh when you put the implant or tissue expander below the muscle, which is to get a better cosmetic result by allowing greater lower breast expansion.

DR. WILKINS: Yeah, and bear in mind that the pectoralis does not cover the entire implant in the absence of ADM, and so there is still a bare area, if you will, on the lower pole which the ADM is used to cover in these particular cases. And so, I think displacement is still somewhat of an issue even with placement subpectorally.

DR. CHEVRAY: And some surgeons who do not use ADM would raise the serratus muscle to try and cover the lower part of the implant or just your expander that's not covered by the pectoralis major muscle.

DR. WILKINS: Um-hum.

DR. CHEVRAY: Okay, my question for Dr. Wilkins was I imagine that of the 58 surgeons involved with the study, different surgeons were associated with use or not use of ADM so that if the surgeons were a variable, that would be associated with use of ADM or not. So, you had Surgeon A who used ADM most all the time and Surgeon B who did not use ADM most of the time, they were different surgeons, maybe even at different centers across the country or in Canada and the U.S., but still in the end, there was no detectable difference in the patient's perception of the end result of their reconstruction.

DR. WILKINS: That's correct. Now, we did, as I mentioned, adjust for surgeon and site but still, the surgeon's an important variable in the process. One of the reasons we wanted multiple centers and as many plastic surgeons as we could get was to try to minimize surgeon effect compared to, you know, previous studies with, you know, one or two or three surgeons where it's virtually impossible to separate the surgeon effect from the effect of other surgical variables.

DR. LEWIS: Dr. Wilkins, a follow-up on Dr. Chevray's question, just clarifying. What was the proportion of subpectoral versus prepectoral placement of patients who had ADM and patients who did not have ADM?

DR. WILKINS: We did not record prepectoral placement because it was --

DR. LEWIS: You had no prepectoral patients?

DR. WILKINS: I don't know for sure, but back in those years it was rare enough where we didn't even consider it as a variable.

DR. LEWIS: So, we cannot infer anything from this study about prepectoral

placement, which as he noted has become more common?

DR. WILKINS: That is correct.

DR. LEWIS: Thank you.

Yes, Dr. Anderson.

DR. ANDERSON: This is a question for Dr. Nielsen. In your overview of the regulatory issues, as I understood you, there are three groups: there is the synthetics, the animal dermal matrix, and the human dermal. And then you showed us a regulation, and you were indicating that there was something different about the humans, in comparison to the other two, that related to this. I didn't follow. What does that have to do with us and is there something different that we would respond about the first two versus the third?

DR. NIELSEN: So, I'm not sure it really has any impact on you as a user of it, but it does have a regulatory impact on the regulation of it. And so, the distinction that we're making is the source of it. So the human derived has to go through a series of questions that are defined in 1271 to determine whether or not they're regulated solely under C.F.R. 1271, and that's a different regulatory oversight that that particular type of ADM is covered by if it meets those criteria, and what we're saying, though, what I was trying to convey is that because we've determined that it's a non-homologous use for a dermal-derived tissue, that it doesn't solely meet the requirements of 1271 and therefore requires additional regulatory oversight.

DR. ANDERSON: So, for the Panel's perspective, the human material has to go through additional processes, but in terms of our talking about its use and issues and problems, that does not -- that doesn't make any difference to us, that's strictly an FDA thing, is that it?

DR. NIELSEN: It's a regulatory distinction that we're making.

DR. ASHAR: I'd like to help us out. So, for the Panel's purposes, we were considering

whether it's animal derived, human derived, or synthetic to be comparable and to understand what the level of evidence is regardless of its source. You could go back and try to say oh, okay, this one category should be treated differently than another, but the Agency is not doing that.

DR. ANDERSON: Thank you.

DR. BURKE: But when you have a porcine dermal mesh, you would have to do allergy testing, I would think. And then given everything we learned yesterday about textures and non-textures, I would think the synthetic things might be very variable and that the textures of all three of these are different, and certainly, if you have an animal substance, you'd have to do allergy testing in the patient, I would think, before you could implant something.

DR. NIELSEN: I mean, I think that's -- the message that we're trying to deliver is that we don't understand all of the differences and what impact those differences may have on the performance of the different types of categories of mesh.

DR. ROGERS: I have a question for Dr. Wilkins. In terms of the meshes used, you had a variety of the brands, were they cadaveric, were they animal derived, were they synthetic, or was it just a wide variety? Because I think that has, you know, at least in pelvic reconstructive surgery, made a tremendous difference.

DR. WILKINS: Um-hum. I think three were human derived and one was porcine. I'd have to go back and confirm that, but that is my recollection.

DR. ROGERS: And no synthetics?

DR. WILKINS: No, ma'am. I take that back. To be truly accurate, there were a handful of other types, but not of sufficient numbers to analyze. I think there were a few synthetics.

DR. ROGERS: One other question. So, it seems there's been a massive shift in terms

of practice from not using meshes to using meshes, and historically, this was just because people thought they were going to get better outcomes. Is that what, just from your perspective, what prompted the shift?

DR. WILKINS: Yeah. Obviously, I don't have any hard data on those trends, but my impression is that yes, I think, as I mentioned, surgeons felt like they were getting better results with the meshes, things like, as we mentioned, improve the lower pole projection, for example. So that is my impression, but that is not evidence based.

DR. LEWIS: Dr. Leitch.

DR. LEITCH: I have several questions. So, you're saying the brands were all human derived, the three?

DR. WILKINS: Of A, B, C, D, I believe one was porcine and the rest human derived.

DR. LEITCH: Because since there was some difference in the complications, that would be interesting to know. And then for the patients who did not get the ADM, did they all get additional muscle coverage with the serratus elevation?

DR. WILKINS: We did not record that data point.

DR. LEITCH: Okay. And I may have missed it, the implant type that was used most commonly, textured versus smooth?

DR. WILKINS: We had large numbers of both. I cannot quote the percentages off the top of my head.

DR. LEITCH: Again, some of the thoughts here are the use of it being to permit motion of the implant if it were smooth.

DR. WILKINS: Yeah, that would've been an interesting covariate to include. We have not done that yet.

DR. LEWIS: Dr. Sandler.

DR. SANDLER: Dr. Wilkins, just to kind of leap to conclusions, you presented a

nonrandomized trial, but it seemed to me as if your conclusion was that the ADM did not improve patient outcomes and may have had slightly more complications. So, has that changed practice? Is this is a practice changing study? For example, did you formally use ADM and now stopped? We heard yesterday that ADM is very, very expensive, and in a value-based world, in the absence of strong evidence that it improves outcomes, I would think that there would be some momentum to try to reduce the cost of the procedures by not using unnecessary devices.

DR. WILKINS: It's a good point, and I am very much an advocate of evidence-based medicine. Now that we have these results, I need to rethink what I do because I still, at least up until the present time, use ADM and I'm one of those people that -- again, anecdotally, just based on my own experience, that I really do feel I get better results. And, you know, I date back to 1989 and the pre-ADM days and, you know, I'm sure I do some other things differently, too, but my results now and since I started using ADM 10 years ago, I think, are better. But, again, that's the surgeon's point of view, and I'm pretty sure that's not the point of view that counts. If the patients can't see it or feel it, why am I doing it? And so, there's a contradiction there, and I fully acknowledge that.

DR. LEWIS: Dr. Li.

DR. LI: I presume that the FDA is talking about possible approval of synthetics as a device for this. Does the FDA envision that there would be some kind of guidance document over properties that one might have or one might need for the surgical mesh, because I'm not actually sure how I would set up such a guidance document. Yesterday we spent the day talking about silicone, which has been around for 40 years, and we're still fussing over its materials of construction and its texture and how it adheres bacteria, some of the things that polypropylene that are used for mesh are actually better environments for bacteria than silicone, yet it's being used as a mesh. So, I'm not sure what the FDA is

envisioning when they say we'd like to have some way to approve a synthetic for surgical mesh. How do you envision that would look?

DR. NIELSEN: We do have a surgical mesh guidance, and it is in the process of being updated, but I think, you know, the message that we're delivering here today is that with that new intended use determination, that that requires a premarket approval. And so, we would be basing the approval of that particular product on its own individual dataset that evaluates its safety and its effectiveness and its benefit-risk profile.

DR. LI: That makes sense. The only thing, I have to say I was a little -- I'm a little bit -- I'm not sure what's the right word, I'm not really sure I want to use the word fearful, but yesterday we talked about the ALCL which takes years to show up. So, if you have your typical 1- to 2-year postmarket surveillance and you have the same thing that happens in a mesh that happens to a few of these breast implants, you're not going to catch it. So it's already kind of a complicated milieu that we don't completely understand, so I'm just concerned that, you know, we can set up things that pass 2 years, which silicone breast implants do, but yet we run into these longer-range problems, and now after Dr. Wilkins' presentation, we seem to be wanting to introduce a new medical device that doesn't really seem to have an obvious benefit. So, it seems like the risk-benefit is off.

DR. ASHAR: Okay, if I could comment. I think the reason why we're here is because we're looking at this Panel for guidance on how to understand the benefit-risk profile of these devices despite the fact they're commonly being used today. So, it's a challenging circumstance for us when sponsors come to us and say I can't perform a clinical trial because I can't get a control arm, because everybody's doing this, you know, why don't you just go ahead and approve this. And so, when we are struck with a problem of how to establish benefit-risk, that's why we're here asking you for advice.

DR. LI: Well, I think it's almost -- at the moment, seems to be an impossible problem

because if the problems are out 5, 7, 8 years and we have no way to diagnose or predict them on Day 1, it seems to me there ought to be a clear warning, a very clear warning, on the device, at best, that we don't really have any idea what this will do in the long term, especially if you're going to include resorbable devices. You're putting the mesh in because you're trying to stop motion, so motion is going on, so there's going to be wear. So, I don't mean to make the problem harder than it already is, but all these things, in fact, will go on, and they all have been hypothesized as pathways to bad clinical outcomes, and we have no real way of assessing those. So that's really more of a comment than a question.

DR. LEWIS: I have a question for either Dr. DeLong or Dr. Nielsen. One of the issues in trying to evaluate this question is whether this material has been used in other anatomic sites over time and whether the FDA has any prior evidence for use in other sites. Most of the meshes which have been approved that are normally used in hernias, in fact, are totally different from acellular matrices; they're really synthetic meshes. So, are there any situations where acellular matrices, either porcine or human, have been previously evaluated for any clinical indication?

DR. DeLONG: So many of these manufacturers and their products are cleared through the 510(k) process because of the different intended use for their original -- their original intended use, and so that includes things like abdominal wall repair. However, the 510(k) process doesn't necessarily always include longitudinal follow-up. So, they have been cleared and they are used, but I don't know that we have robust data on their long-term adverse event profile. And so, you know, those may appear in MDRs, but like we talked about yesterday, the MDR reporting can be variable, and it's difficult to use a system like the MDR to effectively capture incidence rates of long-term complications, if that makes sense. So, in essence, no, I don't believe we have that data.

DR. LEWIS: Okay, we only have time for two more questions basically.

Dr. Burke.

DR. BURKE: I just wonder how long these have been used for pelvic-based repair or abdominal wall repair. I mean, how long have -- first of all, I think that you have three very different kinds of material, and I think that's really crucial to know what it is.

And then my second question is do they -- I mean, have we -- and how long has it been ever tried for breasts? I mean, have we seen if there are more seromas or fewer with the breast implant with the mesh?

DR. DeLONG: So many of the mesh products are actually pre-amendment devices that predated the 1976 amendment, and so they were already on the market when the Center was established, and so there is a long history of mesh use. There's a variety of mesh products. Some of them have, you know, reached the market more recently. In terms of this specific use in breasts, you know, the literature report that we're most familiar with that first describes use in breast reconstruction is 2005, but uses in mastopexy, reduction, or now prepectoral breast reconstruction are more recent, likely, I would say, the last decade, that time range.

DR. LEWIS: Dr. Rogers.

DR. ROGERS: I have a question about -- and we have extensive experience of using mesh in the pelvic floor reconstruction and many misadventures there and the type of mesh matters quite a bit. I have a question about the consent. Since you're putting in two implants and one is mesh and the other is the implant, the breast implant, do you consent separately for that, or do you just consider the second implant part of the whole procedure, because it's a very different device, so we're talking about two devices. So, I'm just curious about patient information about that because, certainly for pelvic reconstructive surgery, a lot of discussion goes into the use of a graft, and here we're using a mesh and a device, so I'm just curious about how that works. I don't know, Dr. Wilkins, if you could comment or --

I know that's not part of your study. I'm just curious about it.

DR. WILKINS: It's not. I can only answer for our center, but certainly the use of ADM is part of the patient information process. We do not separately permit for it nor do we permit for, for example, what type of implant we're going to use. We obtain a surgical permit which describes tissue expander placement at the time of mastectomy, but we actually have a 20-page brochure which we give patients. Of course, there's no way of telling whether they read it or not, but it describes different implant types, it describes the use of ADM. But the whole information-giving process is -- it's a bit of a black box because how much information do you give people, how do you give it, how do you know that they got it, how do you know that you have informed consent? And so, one of the things we're looking at as a follow-up to MROC is now that we have all these data, how do we convey that to the people who need it most and that's the patients who are considering these operations. It's a whole other research project.

DR. LEWIS: I thank all of the panelists for their excellent presentations this morning and responding to the questions.

We are now going to move ahead to the Open Public Hearing. We'll proceed with the first portion of the hearing starting now, and we'll have the second portion this afternoon. For the record, all the Panel members have been provided with written comments prior to this meeting for their evaluation. During the Open Public Hearing, public attendees may address the Panel to present any data, information, or views relevant to the meeting agenda.

Commander Garcia will now read the Open Public Hearing disclosure process statement.

CDR GARCIA: Thank you, Dr. Lewis.

Both the Food and Drug Administration and the public believe in a transparent

process for information gathering and decision making. To ensure such transparency at the Open Public Hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentation. For this reason, FDA encourages you, the Open Public Hearing speaker, at the beginning of your written or oral statement, to advise the Committee of any financial relationship that you may have with any company or group that may be affected by the topic of this meeting. For example, this financial information may include a company's or a group's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you, at the beginning of your statement, to advise the Committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

Dr. Lewis.

DR. LEWIS: The FDA and the Panel place great importance on the Open Public Hearing process. The insights and comments provided can help the Agency and this Panel in their consideration of the issues we're dealing with this morning. We recognize that there are a variety of opinions, but one of the goals is for the Open Public Hearing to be conducted in a fair and open way where every participant is listened to carefully and treated with dignity, courtesy, and respect. We thank you in advance for your cooperation in staying within the timelines.

As yesterday, each registered speaker will be given 3 minutes to address the Panel, and we have 21 presenters to be accommodated within 60 minutes, so it's essential that you stay within the 3-minute limit in order to be fair to people who are toward the end of the list so that they have adequate time to present their point of view as well. We therefore ask that each presenter speak clearly to allow the transcriptionist to provide an accurate description and to stay within their time limits, and if you go substantially over

your 3 minutes, we may turn off the microphone.

I'll now ask that Speaker 1 step up to the podium, and that person is Dr. Marisa Lawrence.

DR. LAWRENCE: Good morning. I'm Dr. Marisa Lawrence, and I have no financial disclosures. I'm a board-certified plastic surgeon who's used breast implants in patient care for the past 25 years. I'm a member of both the Aesthetic Society and the ASPS. In the past 2 years I've evaluated over 200 women for systemic symptoms they believe to be related to their breast implants. My slides? My slides are not -- okay.

Although there's not sufficient evidence to show an association between breast implants and connective tissue disorders at this time, these women are requesting implant removal for what is referred to as breast implant illness. Currently, there's no diagnostic testing for this illness. To better understand their concerns, I began to collect data from my patients as I spoke with them, reviewed their medical histories, and performed their surgeries. I created pre- and postoperative questionnaires to track symptoms and medical eval and conditions. My study is ongoing with patients being added on a daily basis. Although far from complete, I wanted to share some of the information I have obtained so far.

The study currently includes 100 women ages 28 to 77 with implants placed between 1983 and 2018. Slightly more than half of the patients began to experience symptoms within 1 year of implant placement. An additional 34% began having symptoms between 1 and 5 years of placement. Most patients had no abnormality in serologic or other diagnostic studies. However, 13 of the 100 patients did develop a confirmed autoimmune disease after their implants were placed. Breast implant illness does not appear to be isolated to one type of implant. Patients reported symptoms with textured and smooth surfaces as well as silicone and saline filled.

Data collection is still ongoing, but based on 38 post-explantation questionnaires completed 6 to 12 weeks after surgery, 31 patients had partial resolution of their symptoms, 5 patients experienced no change, and 2 patients had complete symptom resolution. Slide 9 was supposed to show the patient-reported symptoms that demonstrated the most improvement following implant removal. There were five of them.

As a patient advocate, I want to provide all of my patients with accurate and up-to-date data while discussing treatment options. My study, while small and not yet complete, suggests that there is no direct relationship between breast implant illness and implant type. Some patients have improvement in symptoms after implant removal, but explantation does not guarantee resolution of illness. Long-term follow-up, genetic testing, DNA sequencing to identify the capsular microbiome, pathologic and histologic examination of capsule tissue, and toxicology evaluation of implant-based substances are all needed to better evaluate our patients.

Thank you for your time.

(Applause.)

DR. LEWIS: Thank you.

Dr. Danielle LeBlanc.

MS. DYKEMAN: My name is Sue Dykeman, and I'm presenting Dr. LeBlanc's testimony as she had a family emergency.

"I am a board-certified plastic surgeon in practice for 14 years. I endorse the safety of breast implants and the importance of providing accurate information to patients. Informed consent detailing the risks of implants, including capsular contracture and rupture, the rare risks of ALCL and the potential risk of BII, is essential for patients contemplating implants. I use a layered approach to education and informed consent including brochures, consent forms, and verbal information. I submit implant data to the

manufacturer for every patient and participate in the NBIR. I follow my patients annually and offer free lifetime evaluations to my cosmetic implant patients. I explain the recommendation for MRI surveillance, though most of my patients refuse due to the high cost and their lack of concern. Implementation of high-resolution ultrasound would be a welcome option for my patients.

"I have used numerous textured breast implants in my career and have diagnosed and treated one referred case of BIA-ALCL. She recovered well and opted to have new implants inserted. I have not had any cases of ALCL in my personal patient population but have initiated several workups for presenting symptoms. I began limiting my use of textured implants in 2017, with the exception of textured tissue expanders. My patients are included in the decision-making process for textured implants when they may offer an aesthetic advantage.

"I have seen an increase in questions about BII in consultations requesting implant removal in the last 2 years. Post-explantation, certain patients report some improvement in their symptoms, though the majority have reported no change but express relief at having their implants removed.

"I routinely use acellular dermal matrix in my reconstructions but have limited experience with mesh. I believe more studies are required for the combination of mesh and acellular dermal matrix in reconstruction.

"I rely heavily on current data and education provided by the Aesthetic Society and ASPS to educate and counsel my patients. I also listen to my patients who gather information and questions from social media and patient advocacy groups.

"I believe that the benefits of breast implants outweigh the risks for a majority of my patients. I also believe that more detailed data is needed for ALCL and BII. I look forward to hearing the conclusions of this Panel as it works with patient advocacy groups, the

Aesthetic Society, and ASPS.

"Thank you for your time."

DR. LEWIS: Thank you, Dr. LeBlanc.

Ms. Kyndra Lee.

MS. LEE: Good morning. My name is Kyndra Lee, and I'm an independent aesthetic practice and software consultant. For this past year I've been working closely with the technology development firm Anzu and the Aesthetic Society on implementing and enhancing the Aesthetic Neural Network, better known as ANN.

As you heard yesterday, ANN is a technology platform that allows for HIPAA-compliant data collection. This data can be collected either passively from the physician's practice management system or actively by a physician inputting data quickly and easily on a platform available on their smartphone. Our goal through the continued development and enhancement of ANN is to provide simple, accurate, and readily available technology that will help solve the overwhelming problem of harnessing breast implant data.

Unlike other countries where successful breast implant registries have been deployed, the United States is burdened with the task of collecting literally a million times more data than these other countries. This issue was touched on yesterday during the Panel discussions when concerns arose about the ability to create a registry that could capture the 1,800 breast implant procedures happening in the U.S. every single day. There's also a need to collect this data without unduly overburdening the physicians and the patients whose participation is required to collect the needed data. ANN has the ability to collect this data without creating laborious data entry protocols for physicians. By creating an interface with a practice management system, ANN captures a certain level of data without requiring a single click or keystroke. At present, ANN is passively collecting and properly classifying data on more than 1100 aesthetic procedures per day. This data

can easily be queried and retrieved.

During yesterday's session, the Panel also addressed the need to attain and analyze retrospective breast implant data. In any physician office where the ANN practice management interface is deployed, we can passively extract retrospective patient and procedure data looking all the way back to the year 2000. This retrospective data could provide insight into the questions and concerns that have been raised over the past 2 days.

At present, ANN houses data on 3.6 million aesthetic procedures, and we are continuing our effort to increase the volume of data available to all plastic surgeons and their patients. Together with NBIR, we should begin to have robust data that will allow physicians to identify, communicate, and act on breast implant device safety concerns.

Thank you for your time

DR. LEWIS: Thank you.

Ms. Lisa Sowder.

DR. SOWDER: Good morning. I'm Dr. Lisa Lynn Sowder, a plastic surgeon in private practice for 28 years in Seattle. I'm a clinical instructor at the University of Washington. I've traveled here at my own expense. I appreciate the opportunity to speak about breast implant illness and explant surgery.

Breast implant illness crossed my radar screen about 5 years ago. Prior to then, I was very busy removing old, nasty implants and capsules from women with pain, capsular contracture and rupture and also because gravity, weight gain, and aging had rendered their implanted breasts no longer attractive. I call this graduation from breast implants, and these patients are thrilled to be implant free. I still see a lot of these ladies, but now I am seeing more and more women who feel their breast implants are destroying their health. Half of them have saline implants and many have clean, intact, and aesthetically pleasing implants. They present with a constellation of dozens of symptoms and sometimes

blame their implants for disorders with clear and established etiologies. Examples from two recent patients include plantar fasciitis and glaucoma.

All of my breast implant illness patients are connected on social media, and they all suffer from anxiety and worry about what they have read about implants, commonly referred to on social media as toxic bags of death. I have come to wonder if some of these patients are worried sick and suffer from a social contagion caught from social media. We have turned away from our patients and they from us. Patients have turned to social media where they find overwhelmingly negative and alarmist posts about breast implants and sometimes some very bad advice. Many of these social media sites block or exile those who question the validity of their claims. I would implore the BII community to open your sites to conflicting opinions just as this hearing has. The truth about breast implants is probably more complicated than any of us imagine. We should work to find it together.

And I would implore plastic surgeons, when asked to remove implants for any reason, to do so. You don't have to embrace BII to do a good explant and capsulectomy. My BII patients are so relieved to be free of the object of their dread, their breast implants, many are less concerned about their post-explant appearance than I am, and most of them feel better after explant, sometimes right in my recovery room. Is this real or the placebo effect? Either way, I'll take it.

I've never been a big fan of breast implants. I recognize the problems with breast implants and the suffering in this room, and I support the implant registries, and I would ask why did it take us so long to create these registries?

Thank you so much.

DR. LEWIS: Ms. Julie Lykins.

MS. LYKINS: Good morning, my name is Julie Lykins, and I am from California. In 1990, after nursing two kids, I decided to get McGhan, now Allergan Biocell textured

silicone implants. I was happy and fairly healthy for the first 20 years, except for allergies, sinus infections, joint pain, hot flashes, and night sweats. Like most women, I was never advised to replace my implants. I don't know how to change the slide. Oops, I went too far. Oh, well.

According to a survey from over 1,000 women that I conducted in the support groups, only 13% were aware that they were supposed to get an MRI every 2 years, but the bigger problem is that most doctors are not educated on what the symptoms of a ruptured implant are. My ruptures were not silent. I had symptoms of a rupture that are listed on the FDA website, including pain, tenderness, tingling, numbness, burning, and change in breast shape. My doctors never ordered an MRI of my breasts. I suspected ruptures, but they were undetected by mammograms, ultrasounds, MRIs, over 15 medical professionals including four plastic surgeons.

For 5½ years I suffered and was at the doctors several times per week, including visits to urgent care, the emergency room, and even hospitalized. I was tested for many autoimmune diseases, heart attack, and stroke. I am thankful for Nicole Daruda's group and website, healingbreastimplantillness.com, where I finally learned what was wrong with me.

Silicone injections to the breast are illegal, so how can it be safe to have any silicone in our bodies? Upon explanting 3 years ago, I learned that my implants had been ruptured for over 10 years due to shell failure. I'm now approximately 85% better, but I'm still experiencing symptoms of BIA-ALCL such as weight loss, swollen lymph nodes, rashes, fatigue, pain, and night sweats. Or could these symptoms be from silicone that has migrated throughout my body? My textured implants caused severe Stage IV capsular contracture calcification and double capsules. None of my inner capsules were tested for CD30. Therefore, I do not feel I have been properly tested for BIA-ALCL. How many

thousands of other women have not been properly tested?

This is called rare, but it is not being tested for, it's underdiagnosed, and it's underreported. The FDA needs to immediately ban and recall textured implants. What benefit outweighs the risk of cancer? The FDA needs to send letters to all medical professionals informing them of symptoms and risks of migrated silicone from ruptured implants, gel bleed, or texture flaking off. Why are studies not being done on the over 70,000 of us that have become ill from our implants?

Thank you.

(Applause.)

DR. LEWIS: William Lykins.

MR. LYKINS: Well, good morning, folks. My name is Bill Lykins, and I'm the husband and caregiver to Julie Lykins, a breast implant illness survivor.

As Julie's illness progressed, watching her deteriorate before my eyes, it was an extremely helpless feeling. One examination after another and not a single doctor could figure out what was wrong with her. We suspected a rupture, paid for an MRI, which the results falsely indicated that there was no rupture. It's all in your head, we were told time after time.

Once we finally learned what the cause was through social media, which is sad that it has to come from there, the helpless feeling I had quickly became anger. Doctors continually told us breast implants are the most studied device on the market. There is no way her breast implants were causing the myriad of symptoms, when in fact that's exactly what the cause was. So, was it an indifference or a lack of education on the doctors' part? In my opinion, it was both.

I watched my wife of 35 years become so frail that when I touched her, the pain was unbearable. Her weight dropped to 87 pounds. Her health was so poor that I feared I'd

lose her. But when she explanted, her health almost improved overnight. It's pretty amazing.

About 4 years ago I lost my sister, Terri, who was 55 years old. She had breast implants as well and was suffering from many of the same symptoms my wife and so many of these women here today suffer from. I can't help but think that if medical professionals were educated on this illness sooner, my sister, along with many other women, would still be alive.

As an airline pilot and captain for over 32 years, I'm entrusted with many lives, much like the FDA is. If I knowingly took an aircraft that I knew was unsafe and could potentially take all the lives on board the aircraft, perhaps you or your families' lives, that would be negligent, to say the least. And quite possibly criminal. But that's exactly what's happening every day you allow products to become implanted into a woman's body.

If you continue to permit the sale of textured implants, the product many countries have already banned, while knowing and suspecting -- or suspecting that the product is unsafe, wouldn't you be just as guilty as I if I flew an unsafe aircraft, jeopardizing the lives of all who had trusted in me? How much longer? How much longer do women need to suffer? You're here today because your job is to ensure that the American public is protected from products that harm us. Textured implants are one of those products. The FDA and manufacturers must ensure that medical professionals and patients are educated on the debilitating symptoms and risks of all breast implants immediately. Please protect our family and remove the textured breast implants from the market so they can cause no harm. Now, you folks at the FDA, you have a tough job, and we appreciate what you do.

DR. LEWIS: Mr. Lykins, please conclude. You're a minute over time.

MR. LYKINS: Okay. You've got to deal with this problem. Thank you.

(Applause.)

DR. LEWIS: Dr. Patricia McGuire.

DR. McGUIRE: I'm Dr. Patricia McGuire, a board-certified plastic surgeon. I've been performing cosmetic and reconstructive breast surgery with implants for 28 years.

My identical twin sister is also a physician, and she had breast implants for breast asymmetry 10 years ago. I've seen how her surgery has improved the quality of her life as I've seen in my own breast reconstruction and cosmetic patients.

Over the last few years I've removed implants from patients with systemic symptoms referred to as breast implant illness. These patients have symptoms which vary in type and intensity. Because of seeing these patients and hearing their concerns, I asked my sister to start keeping a journal of any symptoms she's developed since having her implants. Her symptom list included memory issues, fatigue, sleep disturbances, body aches, among others. These are many of the symptoms that I hear from my patients with breast implant illness.

I thought it interesting to keep my own list of symptoms for comparative purposes. I found that as a 57-year-old woman, my list had the same symptoms and the same intensity and severity as my sister who had breast implants. My sister and my story highlight how difficult it is to make this diagnosis and a direct link between breast implants in every case with the numerous and real symptoms we hear from our patients, as these symptoms can also occur in women without implants.

This is an important topic to plastic surgeons. I was one of six international authors on a paper on this subject, published in the journal *Plastic and Reconstructive Surgery* earlier this month. Because of my experience and interest in this topic, I was asked to be a member of the Aesthetic Society's task force on breast implant illness. Our goals include determining potential causes, such as subclinical infection, allergic or neurologic components, to see if we can predict which patients may be at risk, to determine laboratory

values which could be used in diagnosis, which patients would benefit from removing their implants, and whether or not the entire implant capsule needs to be removed. This task force was formed last year to guide research projects and also to educate our 2200 members on breast implant illness in order to promote communication and collaboration between patients and surgeons.

There are physicians who believe that all of these women are crazy and ignore those symptoms. And those who have taken advantage of their fears are recommending potentially risky surgical procedures and expensive detoxification programs that have not been scientifically validated.

Through the efforts of the Aesthetic Society, we hope to encourage a dialogue between patients and their plastic surgeons, as in a video published last week on theplasticsurgerychannel.com, which I highly recommend. We need to obtain sufficient scientific data so we can help our patients make educated decisions when deciding whether to have implants for cosmetic augmentation or breast reconstruction, and also to determine when implant removal may be indicated and the safest procedures for our patients.

Thank you.

DR. LEWIS: Ms. Cathy McLain.

MS. McLAIN: Hi. My name is Cathy McLain, and I'm from Atlanta. First, thank you so much for hearing all this. A small fact about me. I am built like my paternal side, tall and thin, so that's a great thing to many people, but I also had very little breast tissue. Basically none. So, a few years after my third child, a daughter was born, I elected to have breast surgery. In 1996 I had breast augmentation using the saline implants my doctor at the time had recommend. For 17 years I had a great time enjoying these implants. To me, they looked natural and felt natural. Now, to some of you, breast implants might never feel

natural, but if put your hand on the table in front of you, that is what my chest felt like, flat and hard. So, I enjoyed them and never had any issues, feelings mentally or physically, with these implants.

In 2013 I elected to have breast surgery again as treatment for a double mastectomy due to the breast cancer I had been diagnosed with. My doctor decided that saline -- I mean silicone implants would be recommended as the best choice. For 5½ years I have enjoyed the silicone implants. I feel good, I've always felt good, I've had absolutely no issues with them. Both of these incidences, these were my choice. I can't tell you how much that I've just -- I've enjoyed having them. That's kind of weird, but it's a fun part to fill a bathing suit out, to go to a formal black tie event and have an evening gown on that I actually look like my age; I don't have the body of a 12-year-old prepubescent, you know, tall, lanky kid.

I'm thankful that I had a choice to make to have implants in. It would be a sad day, I feel, to take breast implants completely off the market. I respect the other testimonies of women who have not had the experience I've had, but I think there is a compromise out there to keep the breast implants on the market but also continue the research for everyone to have an experience like I had.

Thank you for your time.

DR. LEWIS: Dr. Emily McLaughlin.

DR. McLAUGHLIN: Good morning. My name is Emily McLaughlin, and I have no disclosures. I'm a double board-certified plastic surgeon, and I've been in practice in Fort Worth, Texas for 15 years. I'm a member of both the Aesthetic Society and the American Society of Plastic Surgery. My practice is focused primarily on breast and body surgery. Breast augmentation is one of the most common procedures performed in my practice. My endorsement of the safety of breast implants is very personal beyond my practice as a

plastic surgeon.

I'm a breast cancer survivor diagnosed in 2016 and reconstructed with breast implants. I subsequently had revision of my reconstruction converted from subpectoral to prepectoral for oppressive animation deformity using ADM to cover my implants subpectoral, and now I have far superior aesthetic result.

I fully understand the need for open and transparent communications when consulting with a patient for breast augmentation. Communication regarding informed consent is essential. Information regarding ALCL and BII are discussed between myself and the patient directly, supplemented by brochures provided the society. I follow my patients annually after breast augmentation and recommend MRI per manufacturer protocol at 3 years, then every 2 years. Despite this recommendation, most of my patients do not follow through due to cost. The current recommendations for a protocol of high-resolution ultrasound to replace MRI for implant surveillance is an exciting alternative. I have not had any patients diagnosed with ALCL, although I have evaluated several with a suspicious clinical presentation.

I participate in the National Breast Implant Registry and submit implant data to the manufacturer for every patient. An additional resource made available by the Aesthetic Society is the Aesthetics Neural Network, or ANN, a software system that allows surgeons to assess their practice against their peers and track patient outcomes for all procedures. Soon, ANN will be able download data directly to the implant registry and make it even more informative. These tools allow us to critically assess our own standards and results. Without them, we cannot offer the safest, best care to our patients.

As a surgeon, I acknowledge it is my responsibility to be aware of the most recent data relevant to the care of my patients. The Aesthetic Society keeps members informed of relevant data via email, the website, journals, and in-person meetings. In today's social

media-driven world, it is imperative physicians and patients have accurate data which can potentially diffuse misinformation and together we can make appropriate clinical decisions.

Speaking as a patient, I directed an aggressive approach to noninvasive cancer with a double mastectomy and selected implant reconstruction knowing the benefits outweigh the potential risks. If that's not an endorsement and my belief of the safety of these devices, I don't know what is. I'm eager for this Committee to come to safe conclusions working collaboratively with the Aesthetic Society, ASPS, and patient advocacy groups to make informed recommendations regarding breast implants.

Thank you.

DR. LEWIS: Thank you.

Ms. Joan Melendez.

MS. MELENDEZ: Hi, thank you. Thank you, Panel members, guests, and speakers. I have no financial disclosures. My name is Joan Melendez. I am the founder of TeamEHR. I am honored to be able to speak to you today. I am here today to speak with you about documentation of medical devices, including mesh and tissue.

I am asking for the Panel to require the inclusion of the UDI and the EHR as outlined in CERT regulations to be enforced and that the UDI be required on HCT/P packaging. The UDI should be added to all implants, medical devices, medical devices with tissue, and tissue alone.

From August 1st, 2018 through now, over 8,000 unique adverse events were logged on breast implants. The Panel has asked for numbers, I will provide you numbers by the end of the month, which breaks down all the reports reported on MAUDE by device problem and manufacturer. We are in the process of validation. The data is changing and challenging to pull from MAUDE.

A little background about UDI: UDI went into effect October of 2018 on all medical

devices for Class II and Class III. This does not include just tissue. It's for medical devices, medical devices with tissue.

Tracing of medical devices and implants pose a challenge. As discussed yesterday, the registries, recalls, and adverse event databases are incomplete or inaccurate, and so are the patients' records. Let's see if I can switch slides here.

Sixty-seven percent of medical records contain incomplete medical device details; 90% of medical records document of tissue is incomplete. From the unstructured data model that you use for MAUDE and the recall databases to the missing data and patient EHRs, obtaining medical data information has detrimental downstream effects, as previously discussed.

Let me take you into the operating room where the implant is used. The surgeon and a scrub are taking care of the patient in a sterile field. The circulator is running in the room and documenting the case. During case documentation, the UDI components are typically manually entered in the patient's EHR and the stickers are posted in the OR implant log. Although there may be ability to capture the UDI and registry data, the documentation on implant is done in a surgical theater at the time of surgery. The only application currently on the market is UDI-Xpress, which scans at the time of implant.

In the event of a MAUDE adverse event, the surgical team is led to an adverse event logging on the medical device. Tissue, specifically breast tissue, is purchased as a kit and more so associated with overstatement of charges. And example on the screen shows there is $64,000 of a cost for breast implants in 1 month. That was inaccurately charged where it should have been a distinct charge and that was actually a kit charge. So, $64,000 and over costs were associated.

DR. LEWIS: Ms. Melendez, please conclude.

MS. MELENDEZ: Yes, I'm sorry.

The CERT regulations identify data fields that are to be included, but there are no requirements for measurable data to ensure the information is gathered at the point of care. Until the FDA requires the documentation of the discrete field data, it will not take place. The Panel enforcement of UDI documentation is needed for all implantable devices, not just medical devices. The Panel requirements should include all data elements outlined in CERT regulations as necessary. Until the Panel takes the position, healthcare facilities --

(Microphone turned off.)

DR. LEWIS: I'm sorry, we have to move on.

Dr. Colleen McCarthy.

DR. McCARTHY: Thank you and good morning. My name is Colleen McCarthy. I am a board-certified plastic surgeon practicing at Memorial Sloan Kettering Cancer Center in New York, New York. My clinical practice focuses primarily on post-mastectomy reconstruction. I have no financial conflicts of interest.

Since 2014 I have served as the principal investigator of the PROFILE registry. As Dr. Pusic mentioned yesterday, the PROFILE registry was conceived in 2010 as a result of a collaboration between the ASPS, the PSF, and the FDA shared commitment to patient safety. In 2010, new case reports of women with implants being diagnosed with anaplastic large cell lymphoma prompted the ASPS and PSF to assemble working groups of experts in multiple disciplines. Ultimately, it was determined that structured data collection of confirmed cases of this rare disease entity using a registry model would be the most effective means of collecting and aggregating case information in a systematic and ongoing fashion.

Since the ultimate launch of the PROFILE registry in 2011, complete case history on 101 women with pathologically confirmed BIA-ALCL have been submitted, reviewed, and verified by the study team. This dataset includes detailed information including patients'

demographics, past medical history, comorbidities, past surgical history including all breast implant procedures and all devices implanted, their clinical presentation, their pathologic findings, treatments, and outcomes.

Earlier this month the first manuscript detailing the PROFILE registry data was published in the journal *Plastic and Reconstructive Surgery*. This data helps further elucidate disease presentation. While 94% of registry patients presented with a seroma and/or breast mass, it is notable that 33% were found to have a clinically appreciable capsular contracture at the time of presentation. Additionally, registry patients had low but appreciable rates of concurrent breast erythema, associated skin lesions, and systemic symptoms, all of which were accompanied by either a seroma and/or mass.

The PROFILE data adds other several firsts, if you will, to our understanding of BIA-ALCL. In our recent publication, we report the use of acellular dermal matrices in 8% of cases. We also report the first case of BIA-ALCL detected incidentally during the resection of a breast carcinoma, and the first U.S. confirmed case of BIA-ALCL in a woman of African-American race. And, finally, while bilateral case reports have been previously reported, we present the first series of bilateral BIA-ALCL gleaned from a registry.

The strengths of this registry include the systematic collection of a granular level of detail specifically relating to the disease. We can say that the data in PROFILE is verified. We have a team of registry staff and clinicians that follow up with reporting physicians to clarify inconsistencies in reporting, and perhaps most importantly is our ability using patient health information to rule out duplicate entries, reducing the risk of overreporting of cases. This is a unique and important feature. We look forward to further analyses to continue to provide the best care to our patients, our core mission.

Thank you for your time.

DR. LEWIS: Dr. Nina Naidu.

DR. NAIDU: Good morning, my name is Dr. Nina Naidu. I have no financial disclosures. I'm the National Secretary for the International Society of Aesthetic Plastic Surgeons, also known as ISAPS, and a member of the Aesthetic Society and the American Society for Plastic Surgeons. I perform breast implant surgery in my surgical practice in New York City for both cosmetic and reconstructive reasons. I'd like to speak to you very briefly on two matters: the first is textured breast implants and secondly breast implant illness.

In regards to breast implants, these are FDA-approved medical devices which are widely used by plastic surgeons for size enhancement and reconstruction of the breast following mastectomy. Textured surface breast implants do have specific benefits in terms of a reduced incidence of capsular contracture and tissue integration that prevents implant rotation with the anatomically shaped form stable implants. These devices, by virtue of their surface characteristics, do have the potential to trap bacteria which can lead to chronic inflammation. Studies have suggested that this may lead to malignant transformation causing breast implant-associated anaplastic large cell lymphoma, or ALCL.

Reports exist within the peer-reviewed scientific literature that ALCL does not occur when specific surgical techniques are taken in a large population study to macro-textured implants. Moreover, the organism suspected of producing ALCL are very sensitive to Betadine irrigation of the breast pocket. It is the position of ISAPS that textured breast implants should be kept available for patients provided that there is adequate informed consent about ALCL, specific surgical techniques utilized to prevent implant surface contamination, and a process to manage late-term fluid accumulation around implants to rule out ALCL.

Second, in terms of breast implant illness, this is not a new entity. There have been many reports by patients since the 1990s who have felt that their implants have given them symptoms, including fatigue and myalgias, but without objective findings in all cases. The

safety profile of breast implants is well understood, and definitive scholarly review articles by the Institute of Medicine and within the *Annals of Internal Medicine* journal have not shown an association between systemic illness and breast implants.

I am concerned that some breast implant patients do have odd symptom complexes, but breast implant removal may not cure them of their symptoms. These symptom complexes also exist in women who do not have breast implants.

With the advent of social media and the internet, there are sites that offer medical advice on breast implant illness which can be harmful to patients. I am concerned of sites where women who believe that they have breast implant illness are given fake medical advice to undergo an en-bloc capsulectomy, which is a surgical procedure that has considerable risk and no reported outcome data. The flow of information should be stopped in order to avoid patient harm. Any breast implant illness patient who believes that en-bloc capsulectomy will cure breast implant illness needs to understand that there may be no benefit whatsoever.

In closing, I implore you, as the National Secretary of ISAPS, to keep both smooth and textured surface breast implants available for patients and to curb the flow of fake medical advice regarding breast implant illness. Their benefits to patients far exceed their risks.

Thank you.

DR. LEWIS: Ms. Claudia Nuñez-Eddy.

MS. NUÑEZ-EDDY: Good morning, my name is Claudia Nuñez-Eddy, and I am the Project Manager for the Insurance Assistance Project at the National Center for Health Research.

Since 2015 we have helped more than 6,000 women navigate their health insurance policies for the medically necessary removal of their breast implants. Recently, the number

has been growing dramatically, with more than 200 new women contacting us each week. Most of these women have serious health issues similar to those you've heard at this meeting, including leaking silicone gel; hard, painful breasts; autoimmune symptoms; and ALCL. Some women just recently developed these symptoms, but many have been living with chronic health issues for years. Every day, women tell us how they trusted their doctors when they were told that breast implants were safe and that complications were rare.

Of the thousands of women our organization tries to assist, only 20% are able to get their implants removed. Even fewer get insurance coverage for their medically necessary explant surgery, and the rest use their savings, credit cards or loans, or borrow money from friends and family. Because the FDA has denied a link between autoimmune symptoms and breast implants, insurance companies will not pay for removal for women with symptoms such as joint pain, chronic fatigue, or cognitive problems. As a result, most of the women live with devastating autoimmune symptoms for years, unable to afford to pay out of pocket for their breast implant removal.

The clinical trials funded by manufacturers have many flaws. First, the studies companies submitted to the FDA excluded women with a history of autoimmune disease, and while FDA required patient booklets warning that breast implants may not be safe for women with a history of autoimmune disease, most women considering implants do not receive or read these 60-plus page patient booklets prior to surgery.

Second, most studies only evaluated narrowly defined diagnoses. Most women who contact us report an array of debilitating autoimmune symptoms but do not fit the exact criteria of a diagnosed disease. The National Breast Implant Registry, in its current state, is not useful because it would not include information about these crippling symptoms and would miss the thousands of women who tell us that they desperately need to have their

implants removed but are financially unable to do so.

The number of women getting reoperations is only a small percentage of the number of women who want or need to have explant surgery. If the women have an informed consent checklist to warn about these symptoms, they would consider explant surgery before their physical and financial health drastically deteriorated. The current checklists are vague consent forms rather than specific information acknowledging the risks. Instead, FDA should require patients and doctors sign a checklist that explicitly, clearly, and succinctly states the risks that can occur with breast implants, including the need to remove and replace them and the cost of MRI screening for silent rupture. The FDA should also require the large long-term studies that evaluate the systemic symptoms the patients at this meeting have described.

Thank you.

(Applause.)

DR. LEWIS: Dr. Troy Pittman.

DR. PITTMAN: Good morning, my name is Dr. Troy Pittman. I'm a board-certified plastic surgeon here in Washington, D.C. I'm former director of reconstructive breast surgery at Georgetown University Hospital, and I'm a member of the Aesthetic Society as well as ASPS, and I have no financial interests related to my comments.

I've performed over 3,000 breast reconstructions with silicone implants. The cornerstone of my practice is patient choice, patient autonomy, patient education, and shared decision making. There is this concept of calculated risk in life, in medicine, and in surgery. I've used textured implants in over half of the reconstructive operations I've performed. Why? Because in many cases the benefits of the device outweigh the risks.

With the wide adoption of prepectoral breast reconstruction, a textured implant will oftentimes stabilize the implant in the pocket with the use of less surgical mesh. It affords

greater implant control, gives a more natural result, particularly in thinner patients with little to no soft tissue coverage. Not to mention the abundance of long-term data that show that rates of capsular contracture are lower in textured implants, and in cosmetic patients textured implants are beneficial in women with chest wall deformities or women who have recurrent capsular contracture.

I implore the Panel to give women a choice. Continue to make all implants available to patients. These patients are intelligent women capable of making informed decisions for their bodies themselves.

I explain to women that surgery with breast implants is a capital investment of sorts. I explain that their implants will likely need to be replaced at some point, that they are to remain under the care of a board-certified plastic surgeon for life. In my initial consult, we discuss all of the complications, all of the specific risks, including ALCL. Additionally, I stress to each patient, as I do all women in my practice, the importance of self-breast exam, listening to their bodies, and the importance of routine follow-up. I see my patients at least every 18 months. I follow the FDA recommendations on MRI screening, although I will say it's often a challenge to get women to follow this recommendation, and it's even more of a challenge oftentimes to get their insurance company to pay for the MRI.

Finally, I would like to stress the importance of these operations being performed by board-certified plastic surgeons. You've heard from my colleagues from the Aesthetic Society and ASPS the important initiatives that are being brought out. However, to be a member of these societies, you need to be a board-certified plastic surgeon.

You've also heard from the implant manufacturer that only sells to board-certified plastic surgeons. They presented their data with the lowest incidence of ALCL and superior long-term rupture and capsular contracture rates. This is not a coincidence.

I would ask the Agency to seriously consider a recommendation that breast

reconstruction and cosmetic breast surgery with implants be performed exclusively by board-certified plastic surgeons.

Thank you for your time and the opportunity today.

(Applause.)

DR. LEWIS: Ms. Kerri Reavis.

MS. FOUNTAIN: Good morning. My name is Leigh Hope Fountain, and I am reading the testimony of breast implant patient Kerri Reavis, who couldn't be here today due to her son's health issues. Kerri is 49 years old and lives in Batavia, Illinois. This is her testimony.

"I had my first bilateral breast augmentation surgery with Mentor smooth silicone implants in 1990. After having four children and successfully breastfeeding all of them, I noticed significant breast changes, and I chose to replace my implants in 2004 to achieve a better cosmetic result, again with Mentor smooth silicone implants. I have had Mentor smooth silicone implants for 29 years with zero complications. I am in excellent health, I exercise regularly, and I have no history of breast cancer in my family. Since the age of 40 I have undergone regular mammograms at the advice of my doctors with no complications.

I simply do not understand why the FDA, implant manufacturers, and my plastic surgeon all tell me that I should get an MRI every 2 years to check my breast implants. If I had followed their recommendations, I would've already had six MRIs to date at $1,800 apiece, totaling more than $10,000. I believe that either mammographies or high-resolution ultrasounds would be more than sufficient and far more cost effective. I had numerous ultrasounds during my high-risk pregnancies.

In addition, I happen to have twins with special needs who require an abundance of medical care. I strive to research their condition and give them the best medical care that I can find, despite the fact that services are lacking in my state. I have plenty to do, and I'm busy, along with all of the other women with breast implants. We don't need an

unnecessarily complicated, expensive, and over-the-top step to ensure that our breast implants are safe when there are faster and more cost-effective procedures which are readily available.

As a mom of special need adults, I can say we need to focus on what's more important. MRIs are at the bottom of that list.

Thank you for your time."

DR. LEWIS: Ms. Jennifer Robb.

MS. ROBB: My name is Jennifer Robb. I'm a clinician advocate and third generation of my family harmed by breast implants. My son, the fourth, his lifelong battle began in utero. Devan was born at 32 weeks. My 4-pound baby boy was placed on a ventilator, fighting to survive. Besides respiratory complications, he had food intolerances, failure to thrive, allergies, eye infections, dermatitis, asthma, testing for cystic fibrosis. We both spent our lives in and out of hospitals, doctors' and specialists' offices. We've become dependent on the government to provide financial and medical assistance. I felt so helpless and frightened. Devan, please stand. Before you is the strongest, most courageous young man I am blessed to call my son.

Ladies with BII, cancer, and all mothers with implants, please stand. Today I request, today I speak for the unaccounted children left orphaned, decades of complaints globally, 19 reported deaths from BIA-ALCL, lack of proper testing for those with systemic symptoms now and prior to established guidelines; also, to remind you of the genetic variants thought to increase the risk of developing autoimmune diseases caused by silicone exposure.

For us, the first casualty in our family was my grandmother, who died in 1993 after her disintegrated breast implants were removed. My mother's health wrecked for over 40 years with three different brands of breast implants. Three. In 1993 my breasts were augmented. A rupture went undetected for an unknown period of time, never picked up on

imaging. Ultrasound reported floating debris in my implants. The textured shell was severely eroded and adherence to the chest wall making proper removal impossible. Could mesh not do the same?

I have symptoms of BIA-ALCL, rashes, lung disease, weight loss, masses, enlarged lymph nodes, brown watery fluid in my chest, and the implant and blood tested positive for a rare fungus. However, the fluid was discarded, and specimens never tested appropriately to rule out BIA-ALCL. I was often misdiagnosed, did not return to my plastic surgeon, but instead had several life-threatening emergencies and hospitalizations, including a 3-week stint at Mayo Clinic and Devan finding me unresponsive after being dismissed by an uninformed physician.

It was 2 years after surgery I had pleural effusions, pneumonia, infections, pre-term birth, cardiac arrest, stroke, masses began around the implant at 5 years, my first seroma at 8 years. By 24 years old, I had the first of many visits with a surgical oncologist for concerning breast issues and lists of specialists. Familiar with rare, I did not know I had Ehlers-Danlos syndrome, a rare connective tissue disorder, or the genetic variants thought to increase the risk of developing cancer or autoimmune diseases caused by silicone exposure.

Please immediately recall textured breast implants. Ban the manufacturing, production, distribution, and sale of all breast implants. Demand manufacturer accountability and action. How long does history have to repeat itself? How many lives have to be lost before action takes place? Isn't one life enough? Banning this lethal product is not to limit choice. I repeat, it is not to limit choice. But instead do no more harm.

DR. LEWIS: Ms. Rohland, please conclude, you're way over time.

MS. ROBB: Save lives, prevent disease, inspire the creation of new innovative ideas

with healthier options is not the definition of insanity, doing the same thing expecting different results.

Thank you. I urge you to please listen to our plea.

(Applause.)

DR. LEWIS: Lisa Rohland.

MS. ROHLAND: I'm Lisa Rohland, a surgical technologist and first assistant for the past 24 years from Mesa, Arizona, and founder of the Arizona breast implant and illness information page. In just 8 months I've helped over 500 sick women connect with each other and find qualified explant surgeons.

Informed consent is the most important conversation that patients have with their surgeons. We must improve the consent procedure for breast augmentation with implants. Few patients are health literate. The consent form used by the ASPS is written at a collegiate level. Reading this 13-page form took me 1 hour and 48 minutes. At this meeting in 2002, a video-based informed consent procedure was suggested that permitted a woman to scrutinize the data from the skeptical, not the supportive. This is technologically possible now more than ever.

Risks like fatigue, hair loss, migraines, memory loss, and autoimmune disorders may have been minimized in the consent process, so the implant handbook that I never received. I remember my surgeon saying that these risks never really happen. Then he had me sign and initial a single-page consent form acknowledging that I understood all my risks. I loved my new saline implants but quickly became ill. I spent years apologizing to my children with tears in my eyes that I wished I could be the mother that they deserved. I have almost completely healed since my explant 8 months ago.

I've listened to the testimony of multiple women within the last year that were part of implant studies. I continue to hear that as soon as adverse effects were reported,

patients would receive a letter that they suddenly have been dropped from their implant study or were just never contacted again. Several women have been removed from the study just 2 years into their 10-year study.

We've recently learned that women reporting adverse effects directly to the FDA had their data placed into a repository. As a result, all of that information has still not been made public, not to patients, not to doctors, and not to the media. Transparency regarding adverse effects and the chemicals contained in these implants is essential for women making informed decisions. Patients need to be told about all potential risks for autonomy and the informed consent process, otherwise it is the surgeon and the manufacturers that are making these decisions on behalf of the patient, regardless of how small that risk might be.

I'd like to help you form an advisory committee on informed surgical consent. This committee should have equal members of physicians, patients that have been harmed like myself, and members of the FDA and other governing bodies. All surgeons should use an independent, engaging, and interacting web-based informed consent by 2020 and review and update it annually. FDA, you failed surgeons and patients, and this is your opportunity to make it right. Do your job.

Thank you for your time.

(Applause.)

DR. LEWIS: Lisa Schlager.

MS. SCHLAGER: Good morning, my name is Lisa Schlager. I'm a woman with breast implants and ADM, a cancer advocate, and an employee of Facing Our Risk of Cancer Empowered. FORCE is a national nonprofit representing people affected by hereditary cancers, including those with inherited genetic mutations associated with increase of breast, ovarian, and other cancers.

Tens of thousands of our constituents have undergone mastectomies due to cancer diagnoses or a high risk of the disease. For those who undergo mastectomy, access to reconstruction is crucial. Some women opt for reconstruction using fat, but it's not a viable choice for all. Petite women and those with certain health conditions may not be candidates for that.

When I was facing my own mastectomy, I was assured that the new gel implants were 100 percent safe. After 12 years in cancer advocacy, I know there are caveats. Some women have adverse events, infections, ruptures, capsular contracture, and a small risk of ALCL, but many women don't know this. Better education and informed decision making is desperately needed.

Recent articles on ailments afflicting those with implants have caused alarm and confusion in the community. Even experts don't agree on the findings. Unfortunately, the media amplifies this, further stoking fears. Clearly, more high-quality research is needed.

Confusion also exists around monitoring women with implants. Some organizations endorse regular screening mammograms. This seems counterintuitive given that implants can rupture.

In 2006 the FDA recommended MRI screening for everyone with silicone implants. Conversely, the American Society of Breast Surgeons and American College of Radiology actually recommend against MRI screening for asymptomatic women. It's conflicting information; how are we supposed to make sense of this? I was told to have MRIs every few years, but many women have never heard this, and those who try to follow the FDA recommendations often incur large out-of-pocket expenses as insurers don't pay for implant screening. Perhaps adding coverage of implant monitoring to the Women's Health and Cancer Rights Act could remedy this for at least part of our population.

FORCE applauds efforts to look more closely at these issues. We encourage a

measured approach based on sound science, including balanced information on reconstruction safety, access to well-tested devices, best practices, consensus guidelines, and insurance coverage of implant monitoring, comprehensive high-quality research, and an easy path to report adverse events.

This month's issue of *Plastic and Reconstructive Surgery* features an article proposing a collaborative approach encompassing international alliances, breast device registries, routine surveillance pathways, and better analyses of possible immune-related disease. We support these steps and hope stakeholders will work together to ensure the most accurate evidence-based information is available to women and their providers.

Thank you.

(Applause.)

DR. LEWIS: Ms. Lisa Grande.

(No response.)

DR. LEWIS: Ms. Anne Ziegenhorn.

MS. ZIEGENHORN: We all have something in common here, and I'll get back to that in a moment. I'm Anne Ziegenhorn, the Cofounder of the Implant Truth Survivors Committee. I'm a registered dental hygienist who taught radiology, and I'm a former plastic surgeon scrub tech, so I have inside knowledge of what the industry tells us.

I see I'm not updated on my slides, but okay. How do I go? Okay. So, as you can see, I am a patient as well. I loved my implants. I enjoyed my Mentor textured saline breast implants that were implanted in 1988. Upon looking at radiographs of my mammography, something strange appears in my right breast, and I constantly complained of right and left breast pain, and my left breast would grow two sizes larger than my other. Nobody diagnosed me. My mammograms were said to be clear and clean. As you can see upon explanting, the night that my implants were removed, that is the bottom right photo,

and 6 months later, the upper is what the media projected to be seen.

I have here a report from Dr. Pierre Blais, who examined my implants and confirmed that I had manufacturer faulty valves, both of them, in addition to manufacturer faulty patches. Again, I was implanted in 1998; 1996 there was an investigation, a criminal investigation against Mentor, and that has never been resolved that we can find and that has been proven in a Dallas news article in 2002. I implore you to please research it.

These are my children. Aden is 15 at this time, and Lee is 16. And then I have my Great Dane, my Australian shepherd, and the little Min Pin-Chihuahua. The three at the bottom have no mold or heavy metal illness, but the other two do. My daughter has just received a positive ANA unspecified, and the pediatrician is reluctant to state that she has fibromyalgia, although she displays every symptom of it and every day is in pain. My son almost died from kidney failure while breastfeeding. Both are immune to *Aspergillus* mold. That means they drank it. And testing shows they both have allergies to the same metals that were in my breast implants.

Ladies of BII, please stand. Women around the world have been told saline and silicone are safe. We trust our doctors when they tell us this. They tell us they're safe. Why? Because FDA approves them, and it is a studied object that is the most studied object. BII does not discriminate; it is both smooth and textured implants.

The studies do show that the FDA, James Templer, in 1996, in the year 2000 he quit his job from the FDA because he says that the FDA has gone out of their way to ensure that the women and public do not know the health hazards. And another FDA agent was able to state that she is stuck between a rock and a hard place and that the harshness against the manufacturers is not able to be done. I implore you to look at the chemicals, and I wanted you to know that you, as the FDA that is listening to us right now, please know that we are here to help you, we want to help you. Let us help the survivors form a checklist for the

surgeons and the patient to sign, let you know that their HLA testing can also tell if there is a silicone allergy in the body.

DR. LEWIS: Ms. Ziegenhorn, please conclude.

MS. ZIEGENHORN: A checklist for the manufacturers, if they would stop their 45 to 200 pages of consent information and they can narrow it down, and then if we can educate all. What do we all have in common? I believe we all here are for the health and safety of the public.

Thank you.

(Applause.)

DR. LEWIS: Dr. Scot Glasberg.

DR. GLASBERG: Good morning. I have some slides. My name is Dr. Scot Glasberg, and I'm here representing the American College of Surgeons. I'm also a past president of the American Society of Plastic Surgeons. My financial disclosure is that I am a consultant with Allergan. I'd like to talk to you this morning about the value of using ADMs in breast surgery and also at some point would appreciate if I could answer some of your questions because I think many of the issues regarding ADMs were left open this morning.

The American College of Surgeons is the largest surgical society in the world with 80,000 fellow members in the United States and many across the world.

In 2004-2005, the first ADM was available for use in breast reconstruction. The American Society of Plastic Surgeons started tracking that use in breast reconstruction in 2015, and you can see the number of procedures that were done. ADM has basically become the standard of care in implant-based breast reconstruction with approximately 70 to 80% of those procedures using ADMs.

The potential benefits of ADM use, without going into the technique, are to reinforce the breast tissue pocket, reinforce weak tissues at the breast boundaries, and that

speaks to migration that was brought up and movement that was brought up earlier; decreased expansion time and discomfort for the patient; decreased risk of exposure and extrusion; potentially decreased risk of tissue expander implant visibility and palpability; improving ptosis and natural breast shape; and reduced capsular contracture.

Partial muscle coverage with ADM, which you heard about subpectoral coverage, has over 560 publications in the literature, all reporting on the use of acellular dermal matrices in breast reconstruction published from 2005 to '19.

I would note for the Panel that not all ADMs are created equally. You only mentioned today human versus porcine versus synthetic. However, in those categories as well, ADMs are processed differently and therefore will yield different results, as Dr. Wilkins mentioned that the MROC studies showed.

Currently, there are clearly research limitations. Most of the literature is retrospective analyses, and there's clearly need for more real-world evidence. Registries are clearly an option for doing that and building modules out of the National Breast Implant Registry is one way of doing this.

Surgical techniques and processes are evolving, and you've heard about prepectoral breast reconstruction, which is really gaining momentum in the last several years, and they yield a shorter surgical time, recovery time, decreased length of stay, reduced pain, fewer narcotics use, and improved mobility and better breast shape and form.

Before I conclude, I would like to put one thing into perspective for you. Human ADMs, which are the most commonly used in breast reconstruction, have been regulated under TRG as an HTTP. Okay, they've been used for 15 years. It's only in the last month or two that we've begun to hear about that they're all of a sudden non-homologous use. That has changed and during that time these have become the standard of care.

I would draw your attention to the CBER documents from 2 years ago, which looked

at fat matrices that were put into the breast, and they were considered homologous use in the final guidance document. There's much more to discuss here, and I'd be happy to answer your questions.

Thank you very much.

DR. LEWIS: That concludes our morning public comment. We have to move on with the program. We will now take a 10-minute break, and I would ask the Panel to be back at 10:45 sharp.

(Off the record at 10:36 a.m.)

(On the record at 10:45 a.m.)

DR. LEWIS: I'd like to call the hearing back to order. We have 2 hours for deliberation on two questions. We'll begin and spend the first hour discussing Question 4, which is the Panel will be asked to discuss methods for assessing and addressing breast implant illness symptoms. Yesterday we heard three of the panelists provide a summary and introduction to this. We will therefore move directly to open panel discussion. There are seven sub-questions which the FDA has posed to us. We have 1 hour for this discussion, and we will devote roughly 8 minutes to each of those to try to answer them, and I would ask the panelists to address these as we go. If we need clarification in any of them, we will ask Dr. Ashar to comment or clarify what specific information she needs.

So, let's begin, 4a, steps that should be taken by all stakeholders to characterize implant characteristics and patient factors to better understand the risk of a patient experiencing symptoms consistent with BII. Who would like to begin?

Yes, Dr. Anderson.

DR. ANDERSON: This is a comment that I wanted to make yesterday but needed permission from a patient in order to relay this point and the patient being my wife. It was 5 years ago on March 7, so this month, that our son was being -- starting his sixth cycle of

chemotherapy for Burkitt lymphoma, he's doing quite well, and she developed abdominal pain that I thought was a gallbladder. We took her to the ER, and it turned out it was a clot in her portal vein. She was developing clot throughout her body and had an eosinophil count of 50%, which is highly unusual. She was hospitalized for 3 weeks, it was devastating, and her recovery since then has -- it is almost identical to the description of what we've been hearing. The slide that has the nine points, she has all of them. My wife does not have breast implants.

And the point that I'm getting at is that we're in this debate about is this syndrome due to implants, and I think that there's a much more important bigger picture, which is this is a poorly characterized set of disorders. We went to Mayo Clinic, we learned about fibromyalgia, central sensitization syndrome, chronic fatigue. This is an area that the rheumatologists do not understand very well, but I am absolutely convinced that these patients that are talking to us today, this is real, it's absolutely real, and I've been living with it for 5 years as the spouse.

What I'm also saying is that the idea that this is all the implants, I can tell you from my personal experience, it is not. So, I think we need to be saying something about the symptoms of these -- of this inflammatory disorder that's not well characterized, and we need to say that with implants there appears to be a subset that when the implants are removed, the patient gets better. But if we get just caught into is it the implant, is it not the implant, we are not serving the overall patient community as well as we could be.

DR. LEWIS: From the information we've heard, we can't identify any factors with the implants, saline versus gel, textured versus not, nor even prepectoral versus submuscular, that seem to be factors in the production of breast implant illness. What we have heard in regard to this question and patient characteristics is that patients who have either preexisting or developing autoimmune or rheumatologic symptoms seem, perhaps,

predisposed to it. Are there other patient factors that you feel have been elucidated that we should bring forth?

Yes, Dr. Portis.

DR. PORTIS: I have a question based on your comments, both of your comments. So it's important what you note, that this may happen to people with or without implants, and so one of the things I brought up yesterday, are there precursors we can identify so that when people are going to have implant surgery, that there are some of these precursors already that we can find by blood tests or a family history which would then give us more information to fully inform patients?

DR. ANDERSON: So, the big problem, and I didn't really get this until we migrated to Mayo and heard of it, Mayo's been studying this, this whole entity, and I met a room of people, we met a room of people with these same characteristics and I don't know that any of them had implants. But the big problem here, there is no diagnostic test. Every test is negative, the ANA, the inflammatory, and this experience that these people are talking about that you go to the doctor and he says I don't know what you got, that's exactly what we had been going through. So, this is a -- the problem is we don't do well when we don't have a test that proves it. We tend to say, oh, it must be the patient. Oh, it must be something else. And I watched my colleagues do this as it got more and more mysterious.

So, what I'm getting at, though, is that that's why the description of this, for insurance purposes, we're covered for this because it's an inflammatory something, she had high eosinophils at the very beginning and then they went down again. The problem that the implant patients have is there's no syndrome or diagnosis and so the insurers say -- that's why I think if the FDA said there may be -- there appears to be a subset of patients, we don't know how many, that will get better when implants are removed and -- but I need to say there are some patients that will not get better because it wasn't the implant; it may

have been these underlying predisposing issues. But at a minimum, if FDA could at least say we recognize that this is a real entity that needs further study.

DR. LEWIS: As part of this question, the first part was to characterize implant characteristics which may be related to BII. Would the Panel agree that we haven't heard any evidence of specific implant characteristics that predispose to this? In essence, all the variables around implant characteristics do not seem to be associated.

Yes, Dr. Rogers.

DR. ROGERS: I agree that we haven't heard clearly that one kind of implant is worse than the other in terms of the data that we've seen. I think the statements about recording accurately what implant people have so that we can start to have that data, maybe with a Q -- you know, the scanning of the information with the QOL or however that is gathered is going to be critical because we need to know really a lot more about the exposure and we talked a bunch about that yesterday, and I would agree that people copying numbers over in the OR and etc. is not, you know, is not always done well. So, characterization of the implants in some standardized fashion so that we can start to make sense of the exposure is critical.

DR. LEWIS: Dr. Ballman.

DR. BALLMAN: Yeah, I agree, we definitely need that and, you know, just as we discussed yesterday, we need some baseline patient characteristics, you know, that might predispose patients to this and those were discussed yesterday. But we also need a control group, as was mentioned, because, you know, there are individuals that are developing this without having breast implants and it's hard to tease apart the two groups without a control group. And so, we need that definitely. And then we need follow-up that follows up these symptoms, and it looks like it's got to be relatively long. Some women, we've heard today and yesterday, now it's 10 years out that they're developing it. You know, a

study that just ends after 2 years looking at acute sort of complications and not collecting this information will not be useful for addressing these questions. So, if this really wants to be addressed, you know, there are individuals that know how to do this, but these are some of the basics that are going to be needed.

DR. LEWIS: Before we move on to (b), are there any other patient characteristics that people think we should be talking about other than this potential presence of rheumatologic or autoimmune disease?

Yes, Dr. Ashar.

DR. ASHAR: We appreciate the comments of this Panel and the recognition that a subset of patients who have these symptoms will get better. Yesterday's discussions brought up the prospect of studying patients who subsequently have their implants removed with a resolution of their symptoms, you know, is a starting place because while we can recognize that a subset will get better, we certainly want to drill down on that and understand which patients will get better and which ones won't. Can the Panel elaborate on if a study along those lines was taken further, how we should proceed? Because there you wouldn't have a control arm.

DR. BALLMAN: But you would have the individuals that had explants that did not get better. I mean, so that would be useful.

DR. LEWIS: We really have heard no testimony of a consistent percentage of patients who improve after explantation. We've seen, from various studies, numbers as low as 20% and as high 75%. So I really think there's a paucity of data regarding that question and that certainly needs to be recorded in any registry. For a patient who presents with BII and has implants removed, that data following would be essential in terms of symptom resolution.

Yes, Dr. Lippman.

DR. LIPPMAN: I realize I may be a slightly broken record here, but I just think it's extremely important to emphasize controls, not simply whether symptoms go away when you stop. I'd like to tell you, in 30 seconds, a large randomized study done in breast cancer for women receiving aromatase inhibitors. These drugs are widely believed, on every public website, to cause all kinds of aches, pains, chemo brain, everything that you can think of.

In the IBIS trial, which was double blinded, placebo controlled, 26% of the women on an aromatase inhibitor had serious complaints; 24% on the placebo controlled had serious complaints; 6% on the aromatase inhibitor discontinued because their complaints were so severe that they would not tolerate the drug; 4% on the placebo controlled discontinued because of intolerable side effects. The differences between the 26 and 24 and the 4 and 6 were actually real, the study was powered sufficiently to answer that question, but the majority were not, and I just feel that there may be some truth lying in the bottom of these horrible complaints that women are telling us about, but without a control we are just not even treading water.

DR. LEWIS: Yes, Dr. Gallagher.

DR. GALLAGHER: So, I'm wondering, one of the things I didn't hear is the numerical difference between those women who might have been implanted because of breast cancer versus those who implanted otherwise. So, I think that would be an important question to see whether or not there's a constellation of these events in different ways in those groups.

DR. LEWIS: Yeah, excellent point.

DR. GALLAGHER: The other thing that I heard was about the genetic marker CD30, and so I'm wondering if some kind of trial related to having some of these women being willing to do genetic testing to see whether or not that was some kind of marker or if there were other genetic markers involved.

DR. LEWIS: Dr. Li.

DR. LI: Just to throw in my materials comments, I think it would be important to track actually what implant these women had. If there was a suspicion of any kind of leak or anything else that was implant related, that might have something to do with whether or not the symptoms disappear after a revision.

DR. LEWIS: Let's move on to (b), potential basic research questions warranting consideration to determine potential mechanisms of causation or association between breast implants and symptoms of BII and if present, the recommended studies (e.g., genetic, immunologic, in situ allergy testing prior to and after implementation). So, a basic science question, what issues should we recommend be addressed?

Dr. Burke.

DR. BURKE: Well, I think without a doubt, first of all, we can take a medical history if they have allergies and sinusitis as their own history or a history of any connective tissue disease. Some people have transient Hashimoto's disease at some time in their lives and it's resolved. But those are very important questions. Or if I had a history of these diseases. And there are several genetic markers that have been mentioned in various publications. I think the gene 2q23 and an HLA type, HLA-B8 or something, that -- I mean, we could consider that and also maybe everyone should have a sed rate and an ANA. I mean, those are not expensive tests and they're easy to do.

DR. LEWIS: Yes, Dr. Anderson.

DR. ANDERSON: The problem with that is that the ANA is going to be negative. The panel of tests is consistently negative and that -- and so I think we really -- from a research perspective, it's very difficult. How do you measure something where you can't actually describe or define the disease by a test as we do with blood sugar and diabetes? It seems to me, though, that from an FDA perspective, this is not a research body, this is -- their job is safety and efficacy of the devices, it's about informing the public, and I think there's really

interesting research that's going to be coming down the road in a broader perspective, but I just don't know that this is the place. I think we have great difficulty recommending specific research.

DR. LEWIS: We're at a disadvantage in that we don't have an immunologist on the Panel or a rheumatologist who has this specific area of expertise, so we may have to recommend to the FDA that that's -- those are the specialties that need to be consulted in regard to basic research questions.

It does seem to me that one of the issues here is the concern about basic toxicologic studies with silicone. Those that were done were done 50 years ago and there were some exhaustive studies, but they were limited, I think, largely to rodents, and I don't know if anything further is needed because several people have addressed here the possibility of silicone dissemination. Certainly, we know that in ruptured implants it may disseminate into local lymph nodes and basic toxicologic studies in regard to that, even though that would normally have been done long in the past, may be an area that needs investigation in view of what we're hearing about the patients who are affected by this.

Dr. Leitch.

DR. LEITCH: So, I think, for those patients who have the implants removed, to evaluate the capsule around it more, you know, pathologically as well as looking for contaminants or fungus or other things that could be cultured from the tissue to see if we can identify something in that regard that would shed light on the development of these symptoms.

DR. LEWIS: Dr. Jaffe.

DR. JAFFE: Yeah, I'd just like to go back to the point about lab testing and you're saying that ANA is negative or a sed rate is not useful, but you do want to separate out BII from other more well-defined illnesses such as dermatomyositis. So, having an ANA might

help you say, well, this patient does not have BII, has lupus or, you know -- so I think a broader laboratory testing would be useful in sorting out this syndrome from other potentially more recognized illnesses.

UNIDENTIFIED SPEAKER: That's a good point.

DR. LEWIS: Dr. McGrath.

DR. McGRATH: My only concern with that would be we don't know that there's any entity that's associated with a breast implant and an elevated sed rate or ANA, and I would be very sad to have to turn down a patient seeking breast reconstruction after a mastectomy on the basis of that laboratory test because we don't yet have evidence that there's any linkage, and until we have that, I don't think we should start testing people.

DR. LEWIS: Dr. Burke, did you have a question?

DR. BURKE: I was looking through the paper, but in reading lots of background papers after literature searches for this Panel, I mean, there's some papers that say there's even 47% positive ANA for BII, but I'll find that, and I'll give you that reference. I have it in this bag somewhere.

DR. LEWIS: Dr. Ballman.

DR. BALLMAN: I just want to follow up a little bit. I mean, I agree there should be testing to make a decision as to whether or not someone should get implanted, but if we don't have the testing up front, we won't be able to -- for a small subset we wouldn't be able to determine whether or not it predisposes people to BII later on, if that makes sense.

DR. LEWIS: Yes, Dr. White.

DR. WHITE: Since the question is about potential basic research questions, I would just mention that I think there might be some consideration given to doing some animal model studies that might help guide the identification of potential parameters that could be looked at in the clinical setting. We heard at least one presenter talking about certain

animal models of autoimmunity that responded to developed symptomatology and signs to implanted -- to implants. And so, I think if you could identify through animal models either some changes in circulating T-cell profiles or subsets or something like that, it might identify, then, a marker that could be looked at in humans.

DR. LEWIS: Go ahead, Dr. Rogers.

DR. ROGERS: I know this isn't about breast implant illness, but I think that some basic science energy should be placed on its effect on breast milk, implants, both silicone and saline based. We really didn't get much information about that, but since a large number of young women are choosing to have these implants done and then are breastfeeding, I think that that warrants further investigation.

DR. LEWIS: Okay, let's move to (c), how to characterize the relative risk for symptoms of breast implant illness considering the wide variety of symptoms in breast implant recipients compared to the general population. We really have had a variety of statistics provided in regard to women's satisfaction with breast implants, which reportedly ranges from sort of 85 to 97%, implying that 10% or less are having problems with breast implant illness in terms of incidence. Who would like to characterize, to respond to that question and perhaps even, Dr. Ashar, you might tell us what --

DR. ASHAR: Sure.

DR. LEWIS: -- you hope to learn here.

DR. ASHAR: Right. So, we've heard from women that suffer these symptoms that there could be a constellation. The list is about 90 symptoms long, and so that poses a challenge when trying to, you know, take a few steps in the right direction to start characterizing this illness. So, you know, do we start with the top five symptoms? How do we break it down into something that's manageable where we could actually deliberately get results and then move forward from that point?

DR. LEWIS: Well, directly related to the discussion we're going to have later today, which is the consent question, because what you're asking is what should be told to patients in the consent session to make them aware of this hazard.

DR. ASHAR: Actually, it's a step prior. If we want to -- certainly we have to inform patients or recognize that this is occurring, but if we want to take steps in the right direction of understanding which patients might suffer these problems and which patients may not and if removal of their breast implants, you know, remedies the situation, where do we start given that there's 90 symptoms that we're looking at? How do we start to study it? It's a studying question here.

DR. LEWIS: Right.

Dr. Ballman.

DR. BALLMAN: So, I mean, that could be one approach. I mean, it depends upon what the study design is. I mean, it could be a very, very focused study, and you may not need that many patients and you could go deep. Or do you just want to cast a wide net and then it would have to be maybe the top sort of, you know -- again, I think, in consultation with people that know rheumatology and things like that, as to what this undefined sort of syndrome is and what are the top sort of characteristics of it because then you could start picking up the signal and if that signal is there, then do a deep dive. So, I think there are a couple options that could be taken.

DR. LEWIS: In the data reported, the material given prior to the meeting from the implant makers, the adverse symptoms relative to breast implant illness that had been reported by the different manufacturers were actually all worded differently and so they, each of them, reported somewhere in the neighborhood of the high teens or 20 of the symptoms. It was notable that there was a fair difference in the frequency, the frequency ranged from 1 or 2% for many of them up to -- the highest was around 30%. But perhaps

when we are characterizing it would be to start (a) with a more consistent listing of the commonest symptoms that are reported so that the wording is not different for everyone and so the specific symptoms that are present are characterized and then to look most closely at the highest frequency percentage, the top 8 or 10, perhaps, that simply are reported most frequently in starting to characterize it.

Dr. Rogers.

DR. ROGERS: I think that a plea needs to be made for standardized patient-reported outcome and symptom severity scales because that would achieve exactly what you were talking about, Dr. Lewis, and without those we don't really know what we're measuring with ad hoc questions.

DR. LEWIS: Yeah.

Dr. Ballman.

DR. BALLMAN: And just a quick follow-up. I mean, again, there needs to be a control group, you know, with all I said before, but I was assuming that there were women that had implants and women that did not in those studies.

DR. LEWIS: Any further comment on that point?

(No response.)

DR. LEWIS: If not, we'll turn to (d), the workup and evaluation of patients with breast implants possibly experiencing symptoms of BII and how this information should be used to inform both individual patient treatment decisions as well as our overall understanding of this issue. Basically, this gets at the question of making patients more aware of what they're experiencing and making doctors more aware of the presence of the symptoms and then of counseling in regard to removal or not and the likelihood of improvement with that.

Dr. Portis, do you have any comments?

DR. PORTIS: Well, I think we keep -- it keeps looping back on itself, but I think of your story about your wife and I think it elucidates the point that we need to listen to women that something is happening and if we can start out by finding some kind of informed consent to talk about with patients that these things might happen, and if we can get a manageable list of symptoms and then we have laid the groundwork to have a conversation with women and not dismiss them, and I think part of what's happened is that women have felt dismissed. And so, yes, I think if we can characterize it, we can at least acknowledge that something real is happening. I think, though, we also go back to the kind of chemical soup that we have found out or I found out over these last 2 days that goes along with implantation. It's hard to separate out what's what, but I think first giving validity to the reality of people's symptoms.

DR. LEWIS: Dr. Ashar.

DR. ASHAR: This question was getting at the fact that several of the patients that testified indicated that they -- it was a diagnostic odyssey to understand that they were having breast implant illness symptoms, and it's equally frustrating for caregivers and healthcare providers to satisfy the patient because they don't quite know what to do, either. So, what are steps? If you had a patient come to you with these symptoms, what should a clinician do? We can be empathetic and understanding, but are there some basic things that we can start assessing?

DR. LEWIS: Dr. Leitch.

DR. LEITCH: So, I think you would do a rheumatologic workup. I mean, that would be kind of a start-point to see if you can identify a specific disease entity that could be treated and to get a handle on things to look for -- you know, by physical exam, to look for some changes relative to the implant, the skin around the area of the implant or else around the body, some of these rashes are reported diffusely. Now, rashes are common

and, you know, we see them in a lot of circumstances dealing with -- you know, cancer patients a lot of times come in with various rashes which aren't going to be -- but, you know, kind of putting everything together, you know, things to "look for" and to be able to talk with patients about you may not in that finding any specificity from these tests, but that would be a start point to come from.

DR. LEWIS: Yes, Dr. Engebretson.

MS. ENGEBRETSON: What I keep hearing is that patients don't know. You know, they'll go to the general practitioner, they'll go to a rheumatologist, you know, maybe recommending to these patients to go back to the surgeon or surgeon-type group that placed the implant and put the responsibility back on the breast surgeon or the plastic surgeon. I don't mean responsibility, but maybe just having a more general understanding of what these illnesses are versus a general practitioner that's going to look at this patient and be like, where do I even begin, and maybe they're not even going to know that the patient has an implant. A lot of our patients don't like to disclose that they have implants. So, you know, maybe putting some responsibility back on the patient to educate them to go back in to see the plastic surgeon or the surgeon who placed the implant.

DR. LEWIS: So, we have, then, at the moment, recommendations again for something similar to what we talked about before, which would be a workup along rheumatologic and immunologic lines, looking for any characterization of that in patients who are complaining of this.

It's interesting that we have not heard, in either the material provided or the testimony, of any spontaneous remissions of BII absent removal of an implant. It could, of course, be case selection, and the patients who got better don't come here to talk to us, and so we really have no knowledge of that. But if that's true, then part of the counseling of patients would be that they're not going to get better spontaneously, and therefore the

only therapy that is potentially effective at this point would be removal of the implants. We haven't heard that point specifically made, but it would seem to be valid from what we know.

Yes, Dr. Gallagher.

DR. GALLAGHER: So it's not specific to, you know, what should the clinician do, other than to say I am aware of some women -- I live in Houston, but we see a lot of patients from rural areas, and they'll talk about how they had to travel to the big city somewhere, even to get their breast implants, they don't have immediate access to somebody. So, one of my concerns would be that your general physician, your family practitioner, the person who might be available won't even know to ask the question about breast implants. So, I think if we think about the general provider of healthcare, we should add to the list of things that they would even ask if a patient comes in with something of an unknown etiology or something whether or not there are breast implants.

DR. LEWIS: Seeing no other comments, we'll move to (e).

(Off microphone comment.)

DR. LEWIS: I'm sorry. Excuse me, Mary.

DR. McGRATH: I think perhaps, Dr. Frank, you went a little bit far in your summary comment there with the -- the issue is that we still don't know. It's really, we're still at a stage where this is a putative breast implant illness. We don't have an understanding of what this is, and to proceed from that and to accept it as an entity and then recommend surgery based on that because you can't get better from it, I think, is going way too far right now. So, I would take exception with what you said. I think that would not be a good service to do at this point.

DR. LEWIS: Okay.

Yes, Dr. Anderson.

DR. ANDERSON: One way to address the education of the physician community might be to go in the other direction, which is to say this has so much in common with fibromyalgia, chronic fatigue, it might be to alert the rheumatology community that when they're working people up for this, a question you should ask is do you have breast implants, because if the rheumatologists don't know about it, then there's really nobody.

(Applause.)

DR. PORTIS: And I think in terms of gathering information, we need to know what implant they have because, again, we don't have any clear data about if it's true that these illnesses are true across all implants and then the mesh issue, which we still have to talk about.

DR. LEWIS: Question (e) is really perhaps a further extension of the one we just discussed, which is the extent of the workup and factors to be considered when you specifically are considering implant removal as opposed to just diagnosing a disease and counseling the patient. Is there anything additional that should be raised or tested in the patient where that becomes a question?

Dr. Lippman.

DR. LIPPMAN: So, I think that the Israeli data are about the best that we have seen, suggesting that some proportion of symptoms are explainable in some sense by implants, and I think that's more likely than not, and in the sense of being cautious, I think I'd have to conclude that some of these complaints are implant related.

I think in terms of a workup, common things happen commonly, and women can get lupus and Hashimoto's and thyroid disease, which are all amongst many others, and certainly before you would agree that because someone had symptoms you would remove an implant, you ought to have a competent physician say that they have excluded those totally legitimate causes. So even if you say there's no blood test for this implant-

associated set of concerns, there's certainly a blood test for a hell of a lot of other things and that ought to be excluded. I think they need to see what we used to say, you need to see a doctor, a real doctor who knows what they're doing.

I think if those things are excluded and you are left in this grab bag of things that look vaguely like chronic fatigue and stuff for which there are no tests and may or may not exist, I think you can very legitimately say to a patient here's an option, some women seem to improve, I can't tell you whether you will or not, but I certainly would support you in doing such a thing. I would feel that way as a physician.

DR. LEWIS: So, you speak to the need for testing to exclude known diseases?

DR. LIPPMAN: Absolutely.

DR. LEWIS: Dr. Leitch.

DR. LEITCH: I think the other thing, it seems like a lot of the people who have spoken have talked about the rupture of the implants and not knowing about that and attributing the fact that the implant was ruptured, that that could contribute to the development of symptoms. So, it would also give you more rationale to remove an implant if you knew it was messed up. So, getting some type of test, and we'll be talking about that more today, which to get to assess whether the implant is intact and that that would be one of the things to look at in terms of informing your decision and recommendation to the patient about removal.

DR. LEWIS: I don't know. And let me question that. Have we actually had any evidence that a ruptured implant is more likely to give rise to BII than a non-ruptured implant? I don't recall that, if that's --

DR. LEITCH: You know, because a lot of what we're hearing today is anecdotal, so I don't want to say that there's "evidence" that says that this just occurs with a ruptured implant, but I think this is -- this is a complaint in the constellation of many of the people

who have testified today of having a ruptured implant that was unknown to be ruptured for years or something like that. And, again, you know, if you're going to make a decision to remove an implant, having a really discrete reason to remove it, being that it's ruptured, justifies the surgery. You know, if you're kind of on the fence about should I remove the implant in this circumstance, if it's ruptured, you have -- you have further impetus to say removal of the implant is a reasonable thing to do.

DR. LEWIS: But I don't really think we have any information even from all the testimony that all of the people who develop severe BII have a ruptured implant. We've heard several people --

DR. LEITCH: No, I get that. Like I said, it's been anecdotal comment that's made, and I think for the person trying to make that recommendation for removal of the implant, if you knew it was ruptured, you would feel -- you know, you thought maybe you accomplished two goals.

DR. LEWIS: Okay. Let's move on to Question (f), postoperative information that should be captured regarding patients who undergo implant removal surgery for preoperative symptoms of BII.

Dr. Ballman.

DR. BALLMAN: Well, first of all, I mean, it would be helpful if someone's going to undergo an explant because of preoperative symptoms of BII, to document what those preoperative symptoms are in this standardized version and then, you know, post-surgery -- and I don't even know what to recommend for a time frame, maybe 6 months, maybe 1 year post-surgery to reevaluate using a standardized instrument, those same symptoms, to see if there has been resolution. And then, finally, I think there needs to be, you know, testing of the tissue that was removed.

DR. LEWIS: Well, I think long-term tracking, since many of these patients continue to

have symptoms, the exact time schedule to be determined, but long-term tracking rather than short-term tracking is something we should recommend.

DR. BALLMAN: Well, I agree but, I mean, you know, most people said that they had resolution right away. But I think long-term tracking couldn't hurt, but I don't know how many women, you know, it took like --

DR. LEWIS: Yeah.

DR. BALLMAN: I agree.

DR. LEWIS: I'm not speaking to those who have remission of symptoms, they might indeed be short term, but since the substantial majority have continuing symptoms, some characterization of that would be needed. Is there any other definition?

Dr. Li.

DR. LI: You could probably say it all with me now, but I think it's critical that when you get this information that the implant should be specifically identified. So, we talk about tracking and that this little label is with every implant, that should be a part of all these reports. Not only would it track, you know, global -- there's something inherently wrong with the design, that if there's a batch problem or anything like that, that that could be found.

DR. LEWIS: Yes, Dr. White.

DR. WHITE: Yeah, I just would say that I think we have to be careful not to say that women that have certain markers of potential other autoimmune conditions that are first identified after the presence of their -- after their implants, that those conditions are either clearly a known autoimmune syndrome that is unrelated and that they won't respond to explant of the implant. I think we don't know that, we don't have -- I mean, it's certainly something that should be -- maybe you shouldn't automatically just expect that they're going to get better with that, but I think we have not explored this question enough to

know that -- I mean, we can turn people's ANAs positive with some medications that we give, so it's possible that the implant is causing a syndrome like this.

DR. LEWIS: Dr. Leitch.

DR. LEITCH: Well, I think if you identify a specific disease entity with your testing, then you treat that, treat that entity first and then see if that's successful. If it's not, then you go to the next level, "well, could the implant be the cause of this," you know, and kind of, you know, go through in a measured way before you commit to saying, yeah, let's try the implant removal as the treatment. You would do the normal treatments for those diseases.

DR. LEWIS: Dr. McGrath.

DR. McGRATH: One final thought before we leave this topic. Dr. Ballman, I think it would be ideal in a good clinical trial or study to look at the tissue, but I don't want to leave that as a general recommendation because there are expense associations here, and I don't want to give the impression that every person who has a breast implant removed should have a study of that tissue because there are going to be a lot of issues for clinicians to try to figure out how patients will be covered or pay for that.

DR. LEWIS: That last question is discuss opportunities to leverage existing social media platforms and other technologies such as artificial intelligence, text mining, mobile apps, digital health, to collect and analyze data on BII symptoms.

Dr. Ballman.

DR. BALLMAN: I mean, I think novel ways of doing things, you know, should be looked at and these should be considered, but I think they need to be validated. You need to know what you're getting. I mean, garbage into something that's fantastic is still going to be garbage out even -- I mean, just being new doesn't necessarily mean it solves the problem. But, again, though, I think there are ways of using these things and I think they should be looked at, but just with some caution.

DR. LEWIS: Dr. Jaffe.

DR. JAFFE: Yeah. So, I'd like to go back to the point about tissue. I mean, I think that any time an implant is removed, that the tissue should be examined, including the capsule, for --

(Applause.)

DR. JAFFE: -- you know, undiagnosed infection or malignancy. I mean, it's an additional expense, but it's a relatively minor expense related to the other procedures that we're talking about in terms of the surgical procedure, MRI, sonogram, all the other procedures that we're doing to work up the patient. If you're going to take the patient to the step of removing the implant, I think that you have a burden to examine that tissue for any pathology.

DR. McGRATH: A lot of patients simply choose to have them removed at a certain point in their life; they're older, they're heavier, they don't want them anymore, and that would be an additional expense really with no indication for doing it.

DR. JAFFE: Well, I don't know. In our hospital any tissue that is removed has to go to pathology, and it has to be examined by a pathologist regardless of the indication, even if it's normal tissue. I mean, I think the CAP guidelines strongly recommend that for any tissue that's removed should be examined by a pathologist.

DR. McGRATH: I don't want to, you know, pursue this too far, but actually I think that most pathology departments have committees that make these determinations, and we do not routinely, for example, send the skin that we take off in a facelift, we don't send the tissue that we take out with liposuction, we don't send the tissue we take off with abdominoplasty, and you can kind of go on and on with quite a long list of things that, in fact, are not required by the Joint Commission or by hospitals to have to submit for analysis.

DR. LEWIS: Any further comments?

DR. ROGERS: I think looking at the capsule locations with this constellation of symptoms is different than looking at the capsule of folks who decide they just don't want it. So that's a different thing. Maybe they would serve as controls and, you know, patients have removal and capsulectomies separate from -- you know, as compared to patients who have removed the implants because of the constellation of symptoms.

DR. LEWIS: Dr. Chevray.

DR. CHEVRAY: I think sending the implant capsule of all patients who have a capsulectomy is just completely impractical. The majority of breast implants are placed for cosmetic use. Those patients who have them explanted often are paying out of pocket for that surgery, and the cost to have that tissue examined by pathology is not insignificant. It can approach 10 to 20% of the total cost of that explant surgery. I think any reasonable plastic surgeon who's doing a capsulectomy with a concern of ALCL or a patient with symptoms of BII would send the capsule to be examined pathologically, and I think it should be the clinical decision of the surgeon and the indication for removing the capsule. If you just blanketly say you have to send all breast implant capsules for pathologic examination, I think that would be unwieldy and not practical.

DR. LEWIS: Dr. Ashar, have we provided enough information on this question, or do you have further questions of the Panel?

DR. ASHAR: No, I thank you.

DR. LEWIS: We'll move to Question 5. The Panel will be asked to discuss the evidentiary requirements for assessing the safety, effectiveness, and benefit-risk for the implantation of surgical mesh for breast reconstruction and/or mastopexy procedures. The two discussants of this are Dr. Chevray and Dr. Li.

Dr. Chevray, would you please lead off?

DR. CHEVRAY: Yes. So, the term surgical mesh needs to be clarified. Traditionally,

when you say surgical mesh, you mean a synthetic material, for example, polyglycolic acid, known as Vicryl, which is an absorbable synthetic mesh, or polypropylene, commonly known as Marlex, which is a non-absorbable synthetic mesh. Those are commonly used in general surgery to repair hernias. Those are rarely used in breast surgery.

What we're talking about when we say surgical mesh for breast surgery are generally -- the vast majority of the meshes that are used are biologic. By far, the most common are human and porcine or pig dermis and those materials or those tissues have been processed by proprietary methods by the manufacturers. I think I believe that at least some of this processing is mainly cross-linking the proteins in these tissues. Anyway, so when we're talking about surgical meshes for breast reconstruction or breast surgery, both cosmetic and reconstructive, it's really tissue-derived from human or pig, for the most part, the dermis.

Now, this is a relatively recent technique, so 20 years ago -- well, let me back up. Most breast implants are placed for cosmetic use. A minority are placed for breast reconstruction. The vast, vast majority of mesh, biologic mesh, used in breast surgery is for reconstruction. So, I'm going to speak almost entirely about the situation where a patient has had mastectomy and we're reconstructing the breast with an implant and mesh.

So, 20 years ago when you did this, there was no mesh involved. Almost in every case, a textured tissue expander was placed underneath the pectoralis major muscle in a first step and then subsequently you expanded the breast tissue, skin, and muscle and then at a second step replace the tissue expander with an implant. That was 20 years ago.

In the last 20 to 5 years, surgeons starting using biologic mesh to improve the cosmetic outcome of the breast reconstruction by allowing the lower half of the breast to be expanded by the tissue expander to a greater degree than the upper half and the technical reason the mesh helped, the biologic mesh helped, was that you could allow the

lower portion of the pectoralis major muscle to not be attached to the chest wall anymore, so when you filled the tissue expander, it expanded the lower half of the breast more so than the upper half, which is what a breast normally looks like. The lower pole projects greater than the upper part.

And so also between roughly 5 years to 20 years, there were some surgeons who used textured tissue expanders under the pectoralis major muscle with no mesh and there were some surgeons who used textured tissue expanders under the muscle with mesh.

It's been a relatively recent technique, I'd say really only with any substantial degree in about the last 5 years, where tissue expanders are not used, that step is eliminated, and a breast after a mastectomy is reconstructed with an implant placed either below the muscle or, even more commonly now, above or in front of the pectoralis major muscle. Now, before the use of biologic meshes, if you placed an implant above the pectoralis major muscle after a mastectomy, the only thing covering it was the skin and a little bit of fat of the breast skin and barely uniformly that led to a poor cosmetic outcome because of capsular contracture. And so, the biologic mesh is now used usually to wrap the implant, in some cases completely, and that's supposed to decrease the risk for capsular contracture and allow fixation of the implant in the correct position so it does not move. So those are the two main reasons for using a mesh today in a prepectoral implant reconstruction, is to prevent capsular contracture, which can adversely affect the cosmetic outcome, and to keep the implant where you want it.

Many surgeons still reconstruct a breast with an implant under the pectoralis major muscle, and whether you use an implant or a tissue expander, the main role of the mesh is to allow the muscle to move away from the chest wall to obtain a better cosmetic result and also, to some degree, to keep the implant or tissue expander medial on the chest where cosmetically that's where you'd like it.

My synthesis of the published literature over the last 20 years has been that there is not -- let me say this correctly. There is not a substantial benefit cosmetically to the outcome of a breast reconstruction when using mesh, or it's not been proven, I should say, in my view, and that the use of mesh in a tissue expander reconstruction, there is a slightly higher risk of seroma and implant infection. And that really mirrors what the MROC study that was presented today more or less shows. I think use of mesh in a prepectoral breast reconstruction with an implant is new enough that there is not adequate data to conclude whether it's safe or beneficial.

So why have biologic meshes been used increasingly in breast reconstruction? I have seen over the last 20 years that the manufacturers of these biologic meshes market them very heavily, and there's a generation of young plastic surgeons who are residents who were exposed to this marketing which continues, and there are a handful of highly compensated plastic surgeons -- or sorry, plastic surgeons who are compensated heavily by the manufacturers to speak about the use of these meshes. So, my personal opinion, my personal professional opinion, is that there's probably little risk but the benefit is questionable. The benefit is hard to garner because it is, again, largely a subjective opinion of the patient and the surgeon as to the outcome, the cosmetic outcome, of the breast reconstruction. Instruments like the BREAST-Q certainly help in measuring and therefore studying that question, but it's been difficult. It's very difficult in any area of plastic surgery to prove that one things looks better than another, so that benefit is difficult to prove.

DR. LEWIS: One quick question. Does anyone ever use the mesh to cover a textured implant?

DR. CHEVRAY: Yes, absolutely. Tissue expanders mainly, but if you use a textured implant you would cover that. If you use a textured implant, which is unlikely today, in a prepectoral reconstruction, you would cover it with dermal matrix or a biologic mesh. But

in the past, when tissue expanders under the muscle were the main way to reconstruct a breast with an implant, almost all the tissue expanders were textured, and if you were going to use mesh, you covered at least a portion of that tissue expander with the mesh, that textured tissue expander with the mesh.

DR. LEWIS: Dr. Li.

DR. LI: The use of biological mesh is quite a bit beyond my comfort zone, so I'll defer to my surgical colleagues on the biological mesh. My concern is the synthetic mesh, which I understand is a relatively small percentage of the current use, but perhaps that's because there is actually no approved synthetic mesh that one could use. My concern is that if the FDA provides a pathway for the development and approval of a synthetic mesh, that, in fact, they will grow like every other synthetic substitute of a biologic does, and the question then is how does one set some guidelines or some approval process for a synthetic mesh? And this is where I'm a little bit stymied. A couple of things, though, that I think I would need as somebody who might develop such a thing is what is my endpoint? In other words, Dr. Chevray listed several reasons why one would use a mesh. So, when you develop a synthetic mesh, which one or more of those endpoints are you trying to achieve? Are you trying to stop motion? Are you trying to get shape? Are you going to use it in conjunction with a smooth or a textured breast? Those all would likely have an influence on the materials or design of the synthetic mesh that you choose.

The other thing I would recommend is that you define what a mesh is. If you read through the literature, a mesh is everything from some piece of plastic with holes literally punched out close together, to woven silk and they're all really kind of generally characterized under the category of textured. And, again, we, the last couple of days have been using the word textured as if it were kind of one very well-defined thing. In fact, texture is an infinite range of surfaces, so one would have to define what would be, in fact,

a surgical mesh and once you define that, so what's an acceptable texture? Is it pore size, is it roughness, is it the three-dimensional structure?

If it's woven, one of the problems we've had industrially with anything woven is that when the woven cloth, when it moves even a little bit, you get wear, and wear of generation of small polymeric debris particles is something that is notoriously bad in biological systems. So, I think if you go to synthetic and then you superimpose upon that the materials of choice, Vicryl is resorbable, so the question is how long does it need to stay around? One of the problems with resorbable is you don't have great control over how fast the resorption is. So, depending again on the endpoint, is it too fast or too slow? And the rate at which it resorbs, oftentimes even in things like resorbable pins for fracture fixation, occasionally they resorb so fast you get a very local severe inflammatory response, which is, again, you're putting this in an area where a lot of stuff is going on already, so the material of choice is also going to be critical. I'll stop there, but the list is rather impressively long of the things that you want to consider, and it makes me nervous to put it in an area with a breast implant where there's already a lot going on that we're not exactly sure what the etiology is and now we're going to put something else in on top of it, that the dermal fillers, as we heard this morning, don't always -- it's not obvious that they provide a big benefit.

DR. LEWIS: Dr. Ashar.

DR. ASHAR: I just want to -- I appreciate Dr. Li's comments. The level of complexity here is very great and to help simplify things for the Panel's discussion, we're focusing this question largely on ADMs because that's the issue that we're being confronted with at the moment. For your background, we consider surgical meshes from a regulatory perspective kind of as devices for this intended use. Certainly, depending on the manufacturing and the construct of the material, we would have a unique set of questions for each and every material. But our purpose is, is really the circumstances of how to demonstrate a favorable

benefit-risk profile clinically to make a decision regarding supporting or justifying an intended use associated with breast reconstruction.

DR. LEWIS: Do you distinguish between human- and animal-derived ADMs?

DR. ASHAR: For the purposes of this discussion, we do not. There is a category of human-derived tissues that are subject to other regulations, but for the purposes of our discussion talking about clinical benefit-risk, we're putting in the same category all ADMs.

DR. LEWIS: And you're treating this, in essence, as a new device?

DR. ASHAR: That is correct.

DR. LEWIS: Dr. Lippman.

DR. LIPPMAN: While obviously the combination of an ADM with a breast implant is different from an ADM alone, there is an awful lot of literature, I assume, on the safety of ADMs in lots of other body places which might supply some data. I mean, are there reports of anything looking even vaguely like breast implant illness with ADMs used for hernias or vaginal repair or anything else where they're used?

DR. LEWIS: Dr. Rogers.

DR. ROGERS: I don't believe that -- I'm not aware of this syndrome of complaints after absorbable grafting material, although there are wide arrays of complaints that patients have after mesh implantation in the pelvis. I think my concern is really about not so much safety but as efficacy. And I think that you have to have comparator studies, preferably randomized, where you could convince surgeons that the answer must be -- the question must be answered, is this offering additional benefit, and if it's not, then including the cost, which is quite substantial, doesn't make sense, right? I don't think there's any -- we haven't seen any data to say that outcomes are better, maybe not worse, or that the proposed benefits of the mesh have been validated.

DR. LEWIS: Well, that statement, if we look at Question 5, the last sentence in that

paragraph, FDA has not evaluated the safety and effectiveness, which is what you're addressing, 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 reconstruction. So that's a pretty clear statement that they're treating this as a new drug -- I mean new device, as we just heard.

Dr. Ashar.

DR. ASHAR: And then to take it further, Question 1 -- Question 5a is taking it -- trying to pick up where FDA has left off. We have advised manufacturers that they should justify their claims by providing the data that meets the requirements of Items (i) through (vii) below. Unfortunately, it goes on to a second slide, but if you have your questions in front of you -- and what we're looking for in this question is to understand whether what we are asking for is appropriate or if you have recommendations modifying this list.

DR. LEWIS: Are those seven things standard for devices in general?

DR. ASHAR: It was created specifically to understand the benefit-risk profile for ADMs for breast reconstruction. So, it is not -- it's unique to this situation. We tried to develop a framework that sponsors could use to go back and develop clinical trials that might meet these criteria, or even use existing data that might meet these criteria that we could consider to justify benefit-risk.

DR. LEWIS: Okay. I'll ask people to read (i) through (vii). As we go along, we'll try to briefly touch on each one to see if people feel that anything is unreasonable in those.

Dr. Sandler.

DR. SANDLER: I mean, assuming that this is a new indication and that manufacturers are interested in marketing for this indication, then I think what you've outlined is perfectly reasonable and presumably, some of these seven bullets could be, you know, tweaked or negotiated a little bit but fundamentally, I think you would need a statistically valid study

that would demonstrate safety and effectiveness, and I don't see any reason why you should step away from that relatively high standard.

For better or for worse, the products are already 510(k) approved, 510(k) cleared, and so physicians are using them in this setting without, you know, perhaps this kind of data. So, you know, it may be that the manufacturers are not highly motivated to test their device in this setting for fear that it might turn out not to be any better. So, it is sort of -- it's almost like, you know, the cat is out of the bag. Is that the right metaphor, the cat's out? And so, it may be too late to, you know, to try to get everything carefully controlled and studied at this point.

DR. LEWIS: Dr. Ashar.

DR. ASHAR: It would be helpful for us -- a colleague reminded me, it would be helpful for us, Dr. Lewis, if you wouldn't mind reading the seven points so that we have it --

DR. LEWIS: Right.

DR. ASHAR: -- in the record.

DR. LEWIS: Let's go through the points one by one and we'll try to briefly address each one. Number (i), a comparison of patients treated with the subject device to a breast reconstruction group, control group, that does not receive mesh. Does that seem reasonable to everyone?

Yes, Dr. Leitch.

DR. LEITCH: So, I guess that we need to be talking about two situations. So, one is the subpectoral and one is the prepectoral. So, for the subpectoral, it may be actually easier to do the control of no mesh versus mesh given the data from Dr. Wilkins, you know, that there might be more enthusiasm for surgeons to say, well, that data looks like there wasn't that much difference, let's do it in a randomized fashion. For the prepectoral, I wonder how that's going to work, and maybe Dr. Chevray could comment about that, if

people would be willing to do prepectoral implant without something else over the device than just the skin.

DR. CHEVRAY: I think that would be very difficult to accomplish because it's generally held by plastic surgeons that the results of placing an implant prepectoral, the outcomes are poor. So, you'd be randomizing patients -- so no surgeon really does that or very, very, very few and otherwise, if you create a study, you'd be randomizing patients to a treatment that is generally held to not work well or lead to a poor outcome.

DR. LEWIS: In the submuscular placement that we heard from Dr. Wilkins, his was not randomized but he had a roughly equal number of patients based on surgeon choice. Are you saying that in the prepectoral space that would not be true?

DR. CHEVRAY: Correct. Absolutely correct.

DR. LEWIS: So, in the prepectoral, nearly everyone uses a mesh surrounding the implant?

DR. CHEVRAY: Yes.

DR. LEWIS: Dr. McGrath.

DR. LEITCH: So, in that circumstance you'd have to --

DR. McGRATH: Yeah, I was just going to make the same comment. I mean, it would be improper to put an implant between the skin and the pectoralis muscle as your only option. It wouldn't just be a bad result; it would be the wrong thing to do. You will get terrible capsular contracture, and it's creating a deformity that would really be unacceptable.

DR. LEWIS: And would a textured implant alter that statement?

DR. McGRATH: I'd have to think about all the clinical pieces that go with that. Part of the use of the -- in that position, part of the utility of the ADM is that you can sew it to the muscles to help stabilize things. You can't sew an implant; you can't touch the implant.

So, I'd really have to think about that, Dr. Frank, to be sure.

DR. LEWIS: Okay.

Dr. Ashar.

DR. ASHAR: Just so that you're aware, 5b has that question for you in a different way. For prepectoral breast reconstruction with mesh, could the control arm be subpectoral implantation without mesh, just given the practicality of trying to find some sort of control arm?

DR. LEWIS: Well, it sounds like the ability to do the study with controls, subpectoral has perhaps been answered by Dr. Wilkins's study and what we're hearing is that subglandular prepectoral placement may not be possible although there's some question about textured implants.

DR. ASHAR: The question is, you know, we'd like to abide by having clinical trial equipoise and have the same procedure in both arms. But in this circumstance, given the, you know, plastic surgeons typically not doing prepectoral without mesh, could you use the control arm of a subpectoral implant placement without mesh as your control in comparison to the prepectoral?

DR. CHEVRAY: It would be a poor choice because it's not identical except for the use of mesh because you -- it's a different operation. The prepectoral would use -- typically uses substantially more mass or surface area of mesh and the submuscular surgery raises the pectoralis major muscle and puts the implant under that muscle.

DR. ASHAR: What other option do we have?

DR. McGRATH: And it would give you some information about the behavior of the biologic material in the environment, so you would derive some information. It would not be exactly the same, but it would have utility to answer a number of questions.

DR. CHEVRAY: Yes, that study would be useful for plastic surgeons and, you know,

the study of breast reconstruction, for sure, because it could answer whether prepectoral reconstruction was any better than submuscular reconstruction in terms of aesthetic outcome. But for examining the mesh, if you're studying the risks of the mesh, the prepectoral surgery has a lot more mesh involved, surface area and mass of mesh, so the control with submuscular using a lesser amount of mesh wouldn't be a good control.

DR. ASHAR: It would be submuscular with no mesh, excuse me, because unless there's another option, that's why we're coming --

DR. CHEVRAY: Right, there probably is not a better option. That may be the best option for a controlled study.

DR. LEWIS: That would --

DR. BALLMAN: I mean, since it sounds --

DR. LEWIS: Dr. Ballman.

DR. BALLMAN: -- like it's not clear, which is better from sub versus the pre and so forth, why not do all three arms at once rather than two individual trials which would be inefficient because you would have to have two controls. I mean, you couldn't reuse a control from the first trial for the second trial. So, I mean, why don't you think of it as three different entities? I mean, do you know what I'm saying?

DR. ROGERS: I have a question. So prepectoral is never -- has never been done without mesh?

DR. CHEVRAY: Yes, it's been done in the past, isolated cases. I'm sure many older -- I'm old, okay, older plastic surgeons have done that, but it's not very -- it's never been very popular and --

(Off microphone comment.)

DR. CHEVRAY: That's generally held to be the case, yes.

DR. McGRATH: It's absolutely the case. That was an error that when I was starting

out people did, and it was disastrous. It was called subcutaneous mastectomy. You would take out the breast and put this implant under the skin, and it was catastrophic, and that was absolutely stopped, and we stopped doing that, goodness gracious, back in the '70s. So yes, it's a historical comparison that younger plastic surgeons have never seen. But to do that now would be really improper to go back and just put an implant under the skin.

DR. LEWIS: So, Dr. Ashar, it sounds like a control group and a prepectoral location is going to be difficult.

Number (ii), inclusion and evaluation of relative adverse events for both the treatment and control arms. I think that's reasonable, but again, the assumption of a control arm may be possible, so adverse events might be limited only to one limb.

Number (iii), assess --

DR. BALLMAN: Just one question. I mean, assuming these are going to be followed then long term, I mean, maybe for preapproval it's fine, but long term to see if there's issues with BII and so forth, otherwise you'll get into the same sort of perhaps situation with the different types of textured versus not.

DR. LEWIS: Yes, Dr. Portis.

DR. PORTIS: I'd like to almost go back to the statement in the beginning that none of these devices have been cleared or approved in breast surgery and reconstruction and yet they're being routinely already used. And as somebody said, the cat's out of the bag. I don't know how we get the cat back in the bag, but I'm very concerned. I really implore all of us and FDA to really think about safety and efficacy and to not once again get into the situation where we are using women who are not informed even that the mesh is there, as guinea pigs in this, and I'd like us to go back to the precautionary principle and get --

(Applause.)

DR. PORTIS: -- some real data, preapproval, about safety and effectiveness. I mean,

we see what happened with the -- some of these implants wanting post-approval studies done that, as we discussed yesterday, were not done. So, I really hope that people will take that seriously and look at this and get the information we need.

DR. LEWIS: Dr. McGrath.

DR. McGRATH: I don't want you to get the impression that people have done this without thought. That is not the case at all. We've used these products for years for hernia repair and plastic surgeons do ventral hernia repair with regularity, usually with the general surgeons, and we found tremendous utility for synthetic permanent materials and also, particularly in infected patients and patients with GI -- other issues on the abdominal wall, we found the ADMs to be extremely useful. You can use them in the face of infection and so forth. They've served very well, and we have a long track record with them. So, instead, what we've done is we've taken them up to the chest wall. Now, think about it, after a mastectomy, you have skin going down on muscle, which isn't a whole lot different from what you've got on the abdomen; it's just 12 inches away. So, what we started doing is we're using it in a different area, yes, but in a way biologically it's very similar to the way we were using it in the places that we're very accustomed to and we're using it every day on the abdomen. So just to clarify, I think that may help you understand that this wasn't an experimental work by any stretch of the imagination.

DR. PORTIS: Thank you, I appreciate that. And then do you have any comments about the different types of mesh, then, given the history?

DR. McGRATH: There's a huge difference, as Dr. Li pointed out, between the polymeric permanent meshes and the absorbable meshes and the ADMs. I think they all would have to be looked at very differently. If I understand from Dr. Ashar, we're focusing today on the dermal matrices, is that correct, the ADMs and not on these other ones which would carry different risk profiles and we know that from the work on the abdominal wall.

DR. PORTIS: Just a last comment going back to the studies presented. All of this discussion and yet the efficacy based on this one study, we heard that people weren't reporting better outcomes, though I hear there's some surgical realities to what needs to be done to have an effective surgery.

DR. LEWIS: Dr. Lippman.

DR. LIPPMAN: Two points. If I understood correctly the report from Michigan, we heard pretty clearly that Brand A, B, C, and D were not equivalent. So even in that setting, there are obviously -- I'm going to accept completely the validity of the study, reasons to know what A, B, C, and D were and let patients know. I mean, I don't see how that could be kept secret.

Secondly, I think it's entirely reasonable to say that if this cat is partially out of the bag, that women are at least allowed to see, in an informed consent, that a mesh is going to be used or is proposed to be used and that the FDA has not yet made a determination about this mesh in combination with an implant, whether it or may or may not give a superior result, and that's something you need to discuss because maybe it's not quite the technically correct use of the term, but it's an off-label use.

(Applause.)

DR. LIPPMAN: And so, to me, that's something, whether you use the word that it's an experiment on the woman or an off-label use, I think that consumers, patients, women, are entitled to know that this isn't just a routine thing that they should gloss over.

DR. LEWIS: We have a great deal of material to cover in a limited amount of time, so Dr. Burke.

DR. BURKE: I just have one pressing question, and that is just like we see breast -- there's possibly breast implant illness, have there been reported cases of abdominal mesh illnesses or pelvic support illnesses? I mean, has that been reported in the medical

literature since you have this long history with various ones?

DR. ASHAR: We haven't done a search of our MDR database to see -- we haven't done the same analysis that we did in preparation for this Panel meeting on breast implants, looking at breast implant illness symptoms with mesh.

DR. BURKE: But have the surgeons here -- Mary, maybe I could ask you. Have the surgeons here seen any kind of mesh implant illness? I mean, has that been reported in the surgical literature at all, because there are so many abdominoplasties, and there are so many hernias, and there are so many pelvic wall repairs with these meshes.

DR. McGRATH: I'll defer to Dr. Frank, who's a general surgeon, but to my knowledge, it has not been reported in the -- in the general surgery literature where these are used routinely.

DR. LEWIS: The use of meshes in the abdominal wall for hernia repair of whatever type is principally -- there are severe complications which occur in the inguinal area, but they're not related to mesh reactivity, they're related to chronic pain syndromes and involvement with the sensory nerves which pass through the inguinal area, and it's because of the scarring of the mesh over time in relation to the nerves which traps the nerves, produces traction on them and produces pain. And so that's not true of ventral hernia placement, but it is true of inguinal placement. And mesh, in those characteristics, is virtually always a polymeric permanent mesh. It's not acellular dermal matrices, which are not used there.

DR. McGRATH: Yes.

DR. LEWIS: The dermal matrices in the abdominal wall are useful principally in an infected field where they dissolve over time, whereas if you use a permanent mesh, it results in a chronic infection which cannot be cleared otherwise, so they're different situations. But in terms of reaction to the mesh, in terms of any of the things we're

considering relative to BII, the answer is no, that's never been reported.

Dr. Engebretson.

MS. ENGEBRETSON: I think we have to do due diligence in our control group because we're being told that the surgical mesh is being used on smooth implants as well as textured, and the reports that we have had have only been over 2 years. So, our ALCL, is that going to be able to be studied effectively if you are wrapping textured implants in mesh and smooth implants in mesh? So, I think we have to take that into consideration because that's not going to take away some of the problems with using textured implants.

DR. LEWIS: Well, if the texturing, as we have heard some of the testimony, is relevant to ALCL, putting dermal matrix over it would not be expected to change those characteristics. It might perhaps add to them, but it wouldn't change them.

MS. ENGEBRETSON: I think we need -- I feel that we need to know those patients, though, that are getting the textured implants with the surgical mesh to see if --

DR. LEWIS: Oh, yeah.

MS. ENGEBRETSON: I mean, I think that that has to be declared.

DR. LEWIS: Okay.

Yes, Dr. Brummert.

MS. BRUMMERT: Are patients made aware that mesh is used for their surgery before the surgery happens, and if they are, can they opt out of it? Are there other options that they can use that are safer, because there's a lot of patients who are not comfortable using the mesh.

DR. LEWIS: Are you referring to breast implantation?

MS. BRUMMERT: Yes.

DR. McGRATH: Yes, because usually when we're having a breast reconstruction conversation we cover not only the mesh and the position of the implant, but also the

options of using their own tissue, autologous tissue. So, yeah, it's a very comprehensive discussion. The mesh is part of that because it helps to drive where we go relative to the muscle.

DR. LEWIS: Dr. Ballman, did you have a question?

(Off microphone response.)

DR. LEWIS: Okay. Number (iii), assessment of the effectiveness of the mesh for breast reconstruction compared to no mesh control. We aren't sure we can have a control, but certainly, we would probably recommend testing for effectiveness even if it's one arm of the study, it sounds like.

Number (iv), pre-specified statistical analysis accounting for reasonably obtainable relevant confounding variables including radiation, chemotherapy, patient demographics, medical history, type of reconstruction, type of mastectomy, type of breast implant, etc. The analysis would potentially allow identification of specific patient populations or methods for use that result in a favorable benefit-risk profile. How do people feel about this? It's a lot of information.

Dr. Ballman.

DR. BALLMAN: No, I agree with it. Nothing more to add.

DR. LEWIS: Dr. Gallagher.

DR. GALLAGHER: So just one thing. Some people include the new immunotherapies as chemotherapy and others do not, so I would specify that it should be another set. Thank you.

DR. LEWIS: Any further comment?

(No response.)

DR. LEWIS: Number (v), an analysis comparing treatment and control on a per-breast and per-patient basis --

DR. LIPPMAN: Excuse me. That point should not be overlooked because of the rising use of immunotherapies and you could, retrospectively, not prospectively, simply ask whether women with implants treated, albeit in a metastatic setting for the moment, with checkpoint inhibitors had either worsening of their complaints or those complaints are rising, and I think that's an extremely important point that we can make a recommendation about.

DR. LEWIS: Okay, we pass Number (v). Analysis comparing treatment and control on both the per-breast and per-patient basis where feasible and appropriate. Is there any feeling that's a problem? It sounds appropriate.

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

Do people feel that 12 months is adequate?

Dr. Leitch.

DR. LEITCH: You might need to indicate a certain time post-completion of the entire reconstruction because if, you know, you get your first step done at the time of mastectomy and then exchange of an implant subsequently, so you kind of have another event that the person has to heal from. So, I guess I would say 12 months from the last reconstructive procedure.

DR. LEWIS: Yes, Dr. Jaffe.

DR. JAFFE: Yeah, I mean, in terms of assessing for implant-associated anaplastic large cell lymphoma, we've already discussed that the timeline has to be substantial and that most of these cases occur 10 years or more after. And if you're asking a question whether adding mesh in increases risk, I mean, I think that has to be part of those studies. So, it's a different question. But when we were talking about analyzing risk of implant-

associated anaplastic large cell lymphoma, I think we have to include the use of mesh as part of that equation.

DR. LEWIS: I don't believe we have any evidence that dermal matrix mesh is associated with ALCL.

DR. JAFFE: Well, we don't, but we don't know exactly what causes the increased risk. I mean, if you're collecting the data, you know, we've heard about the large-scale PROFILE study, and if you're collecting data on the type of implant, why not collect data on the use of mesh at the same time?

DR. LEWIS: Well, I think --

(Off microphone comment.)

DR. LEWIS: Dr. Burke.

DR. BURKE: Well, Dr. Chevray said that there seemed to be more seromas when you have the mesh. And we know we diagnose the ALCL from the seroma fluid, so we don't know if there's a correlation between more seromas or earlier seromas and ALCL because, I mean, the etiology might be that you just get lots of T-cells there, and then some T-cells mutate and then you get the lymphoma.

DR. LEWIS: Dr. Ballman.

DR. BALLMAN: Just a follow-up. I took this to mean premarket, and that was my recommendation, was once the premarket is done they have different phases, that the postmarket, you know, they continue to follow these patients past the premarket time for BII and BIA-ALCL.

DR. LEWIS: Good. Last point, evidence of a favorable benefit-risk profile for breast reconstruction with a subject device compared to reconstruction without the use of mesh. Again, I'm not sure we can do the second part of that, but you could ask for a favorable benefit-risk for the one limb.

Dr. Rogers.

DR. ROGERS: I think at the very least you could compare the different kinds of ADMs and/or the amount used, right? So, we heard yesterday about people having different strategies to reduce -- or, you know, of placing the graft on the implant. So, I think there's opportunity for some comparisons here. I don't know.

DR. BALLMAN: But since this is sub, I don't understand why there isn't an opportunity to have a no mesh part. I mean, this isn't the pre. I mean, this is all -- so I don't understand that comment.

DR. LEWIS: We've heard from Dr. Chevray and Dr. McGrath that people don't --

DR. BALLMAN: But that's the pre, that's not the sub. We're talking sub here.

DR. LEWIS: Well, we have Dr. Wilkins's data relative to the submuscular placement.

DR. BALLMAN: Yeah, but that's not randomized clinical controls, and I can show you many sorts of observational studies with patient selection bias that come out with vastly different results. So, I thought we were talking about clinical trials of --

DR. ASHAR: Yeah, to clarify, you know, a couple of points I wanted to raise actually on the last question, Question (vi). Just so you know, the duration of follow-up has to do with premarket clinical follow-up. So, provided that the company, the trial sponsored by the company, follows their patients out, as you recommended, perhaps 12 months following after their last mastectomy procedure and provided that there was complete resorption of the device or quiescence of the inflammatory response well beyond that time, that would be -- that's potentially suggesting that FDA's approval of that product could occur after 1 year. So, I just wanted to emphasize that point.

With respect to, you know, comparative analyses using different treatment strategies, which would be very informative and beneficial for the surgeon, we definitely understand that, but the purpose of this discussion is to tell manufacturers what testing

they need to do on their device that is least burdensome to justify a favorable benefit-risk profile. So, ideally, I imagine that they would be most interested in having single control arms since they're invested in demonstrating the benefits and risks of their device.

DR. LEWIS: Do you have any other questions?

(Off microphone response.)

DR. LEWIS: Okay, Dr. Chevray.

DR. CHEVRAY: So, these biologic meshes, these ADMs, acellular dermal matrices, there are several different kinds. You're considering them as devices. To obtain approval by the FDA to use these devices in breast reconstruction, I would think that all seven of these points that were asked of us would all be appropriate, and you should consider these devices like you considered breast implant devices in 2005, 2004. The manufacturers should perform studies comparing the surgery with their device with the ADM to the same surgery without the ADM and show that there's benefit and -- or the ratio of the risk to benefit is low. The risk to benefit or the benefit to risk is high. There's not much suspicion right now in this room that the ADM causes ALCL or illness on its own, so it would be -- you know, I think 12 months follow-up would be fine after implantation of this mesh to make sure there's no serious adverse consequences of placing this in a person. So, if the risk low, they wouldn't need to show much benefit. There may be benefit, there may not be much, I don't know, but they could use the BREAST-Q and document that. But I think you should treat it like you treat any other device.

DR. ASHAR: Thank you.

DR. LEWIS: And we move to (b). This is a very complicated question. I'm not sure we have adequate time to even deal with it. Considering the number of combinations of different surgical mesh breast implant surgical reconstruction procedures (i.e., prepectoral, submuscular, direct-to-implant, tissue expander to implant) possible, discuss the extent to

which each combination should be studied separately.

Dr. Chevray.

DR. CHEVRAY: No, I think you should concentrate on the mesh. So, if they're seeking approval for the mesh, they should study the mesh and not every combination of Mesh A with four different kinds of implants placed in different positions in the person. Just study the mesh.

DR. LEWIS: And, basically, since a control group is not possible in the prepectoral placement, that would simply be a one-arm study.

DR. CHEVRAY: Well, the best situation to study it in, which is still being performed, is a submuscular breast reconstruction with or without mesh because that's the way it's still done. It's not being done as often as it was 5, 10, or 20 years ago, but that surgery is still done fairly commonly, so submuscular breast reconstruction using an implant and you can use mesh or you cannot use mesh.

DR. LEWIS: Any other comments?

DR. ROGERS: If it wasn't efficacious in the subpectoral muscle, then it could not be extrapolated to the prepectoral implants, right? Because, I mean, we just heard --

DR. CHEVRAY: The main purpose of the mesh in a prepectoral reconstruction is different than the main reason for using a mesh in the submuscular. In the prepectoral reconstruction, the most important reason for having mesh there is to prevent -- or minimize capsular contracture. So, they're different.

DR. LEWIS: Dr. Ashar.

DR. ASHAR: Yes. Does the breast implant make a difference, though? While we're going to be agnostic regarding the actual operation, but whether it's Brand X mesh with a specific breast implant, should those combinations be -- or should we consider all breast implants the same?

DR. BALLMAN: How do you consider them now? Do you consider them all the same now? I mean --

DR. ASHAR: The feedback that we provided to manufacturers is between, you know, what we discussed, Items (i) through (vii). I imagine these types of topics would also come up, so that's why we're asking this Panel for your opinion.

DR. LEITCH: Well, I think you should at least have an indicator of what implant was used. That should be a factor that's -- you know, that's examined as part of the study information you would have. I think you've got to have that. Now, it sounds like it will be 90% smooth and 10% textured is what will likely be the case.

DR. LEWIS: Dr. McGrath, any comments?

DR. McGRATH: Yeah, I agree with that, and you wouldn't want to set it up where the manufacturer is obliged to find a certain number of a certain kind of breast implant to go with the mesh because if trends continue there may be a paucity of a certain kind of implant to use. So, I agree, I think that could be observed after the fact rather than building it into the design of the study.

DR. LEWIS: Dr. Li.

DR. LI: I don't know how important a question this is, but if you're doing a study of an approved product and you have a mesh and an implant and there's some complication that requires a reoperation, as far as the FDA goes, how do you decide if that is a failure of the mesh or a failure of the implant, or does it matter?

DR. ASHAR: Well, I think the breast implant manufacturer would blame the mesh and the mesh manufacturer would blame the breast implant, and we have difficulty with that all the time. So, we look at all adverse events whether or not we think it's associated with a device.

DR. LI: Assuming this becomes an approved device, the mesh, and there was a

complication, what would the FDA want the reporting to be? In other words, because right now, you know, they're not even telling you what implant they're using. So, if you have a mesh and an implant and you get a report that there's a complication or a reoperation, what information would the FDA want in there for it to be useful to you?

DR. ASHAR: Yeah, this would be for the purposes of a premarket clinical trial where we would be reviewing all the case report forms in that IDE study beforehand, where we would make sure that there were line items where they were specifying precisely what implant was used, what mesh was used, so we expect that we would obtain all of that information. It's very different in a postmarket setting obtaining voluntary adverse event reports where a narrative is provided by any individual who finds that they have been harmed or they suffered an adverse event which may not have all the fields filled out. That's more of a passive way of obtaining that information than the clinical trial construct that this question is about.

DR. LI: I was just curious if there was a way to collect the data in some manner that you would have a better feel for if it was the mesh or the implant or some combination.

DR. ASHAR: If this Panel has specific recommendations, we would be happy to consider them, and that's why we're here.

DR. LEWIS: That question actually pertains to (c), but let's ask Dr. Ballman the question first.

DR. BALLMAN: Just a quick comment. I mean, I think given that people are expressing sort of potential difficulties of doing such a randomized trial in the first place that, you know, I think you collect the information on the type of implants and you look at subgroup analyses to see if there's issues, and it may be required for their studies if there are issues, but not put it up front just because you got to get one study sort of done.

DR. LEWIS: We need to move on to (c), given that implantation of the mesh for

reconstruction involves the implantation of two devices, i.e., mesh and the implant, please discuss if it's possible to consider benefit-risk for each separately or as a single item, which relates to the question you just asked, Dr. Li. How do people feel about that?

DR. BALLMAN: Just a comment. Again, I think you look at it together as a whole at first, and then you look at subgroups to see if there's any signal coming in, and if there is, then you dive deeper.

DR. LEWIS: Dr. McGrath.

DR. McGRATH: One other thing I would throw out there that hasn't come up at all, we use mesh around expanders and then go back and exchange the expander for the permanent implant. That usually occurs certainly within a year, and you might want to think with some experts about whether that offers any opportunity for seeing what's happening with the mesh.

DR. ASHAR: What do you mean precisely, maybe taking a biopsy of the mesh at that time?

DR. McGRATH: It's just a unique opportunity to be seeing the mesh at time intervals over the year.

DR. LEWIS: What's the purpose of the mesh with an implant since contracture is not an issue?

DR. McGRATH: That's exactly the same as with the implant.

DR. LEWIS: Positioning?

DR. McGRATH: Positioning, yes.

DR. LEWIS: Because, I mean, we heard that the mesh is used to reduce contracture, but contracture's not an issue with an implant. I mean, with an expander.

DR. McGRATH: Oh, it is. It's much less uncomfortable if the expander isn't being encapsulated.

DR. LEWIS: Oh, I learned something. (d) 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 postmarket studies, to characterize the benefit-risk ratio and safety and effectiveness over time.

DR. PORTIS: Can I go back and ask a question of the surgeons?

DR. LEWIS: Dr. Portis.

UNIDENTIFIED SPEAKER: Can you advance the slide? Thank you.

DR. LEWIS: Dr. Portis.

DR. PORTIS: I just wanted to go back and ask a question of the surgeons. What condition do you find that mesh in after 6 to 12 months of an expander? Could you say anecdotally what you see, Dr. McGrath?

DR. McGRATH: It varies with when you look because it's incorporated over time into the patient's own tissue, but I just still think it would be an interesting observation.

DR. LEWIS: Dr. Chevray.

DR. CHEVRAY: So, these are biologic meshes in the manufacturer's claim, and I do see clinically that generally they are incorporated into the tissue of the patient. Unlike a synthetic mesh or a breast implant, the body does not form a scar capsule around it. Actually, blood vessels start to grow into the mesh, which is a process dermis and it really heals to the surrounding tissue. I mean, typically, there's a breast implant on the other side of the mesh, but the undersurface of the breast fat and skin the mesh heals to.

DR. LEWIS: We haven't really answered this question yet. What do people feel would be appropriate measures for the benefits? These would obviously include multiple factors of satisfaction and quality of outcome, as well as psychological factors, much as we heard Dr. Wilkins discuss today. But do you have specific recommendations for the FDA as to what should be used to quantitate benefits?

Dr. Chevray.

DR. CHEVRAY: So, again, in my mind, the benefits are questionable, so the main issue is whether there's much risk or not and I think that can be ascertained within the 12-month time frame from the date of implantation of the mesh. To ascertain the benefit, which is a cosmetic -- the benefit is to improve the outcome of the reconstructed breast and to ascertain that, you need at least 2, 3 or more years of follow-up of the patients.

We know from other studies that certain types of breast reconstruction using implants tend to be great over many years. Another way to say that is patient satisfaction decreases over years to decades and autologous tissue reconstruction, the patient satisfaction seems to increase over years and decades. And so, you really need years of follow-up to ascertain whether a patient is more or less satisfied with their breast reconstruction versus another method or a method without mesh.

DR. LEWIS: Dr. McGrath.

DR. McGRATH: I agree with that in terms of the outcome and what the patient sees. The thing that's tricky here is the person that you would have to ask is the surgeon because I think there clearly are technical benefits to using it. Let's talk about subpectoral. If we're not using a piece of mesh as a sling or a hammock to hold the bottom of the implant, then we're going to cut the pectoralis muscle and use that or we're going to lift up the serratus muscle, and any time that you can maintain anatomic integrity of the muscles, it's always better than when you have to transect it and move it around. So, I don't know how you're going to answer that question unless you ask a surgeon to comment on it. I suppose that could be part of the study.

DR. ASHAR: I think we're looking for tangible patient benefit, and so I'm wondering what you all think about things that are maybe perhaps more immediately in the postop, like reduction in pain or other sorts of things that may be observed, maybe you've observed

in your practice.

DR. LEWIS: Yes, Dr. Leitch.

DR. LEITCH: Operative time to be looked at and that would be something that could be perceived as a benefit. Pain, pain management. Time in hospital, although it's just short. I mean, it's usually hard to demonstrate differences in that because it's usually pretty short, but that would be something you could look at.

DR. LEWIS: It's going to be difficult to separate the benefit of the mesh added to an implant from the implant alone, obviously. Again, it seems Dr. Chevray is right that the main thing we're concerned about is risk and that would appear to be low from what we know so far.

DR. ROGERS: I don't think the only thing that we want to know about is risk because if it's low risk, but it doesn't have proved benefit, then why are we doing it? I mean, you know, what's the value, I mean, of using something without benefit even if the risk is the same? So I don't know, I would -- I still think that a patient-focused outcome measure is critical and what the follow-up time for that should be, it sounds to me -- and I'm not a breast surgeon -- that the two procedures are really very, very different so they really have to be considered differently, but I would just encourage because if it's not a clear benefit to patients, then why are we putting it in?

DR. LEWIS: Dr. Chevray.

DR. CHEVRAY: So, I agree completely. The FDA is always interested, for the patient's sake, for the population's sake, about this benefit, the ratio between risk and benefit. So, I just said that I don't know that the benefit is great for using a mesh, so we have to focus on deciding whether the risk is substantial or not. Having said that, if there is not a benefit, right, why are we doing this? And I think there are other forces at work as to why it's being used. But aside from that, the benefits of the mesh are largely touted because the mesh

now allows you to place an implant wrapped in the mesh in the prepectoral position and we've just been saying how it's going to be very difficult, if not impossible, to study that compared to a group, a control group, that has no mesh but an implant in the prepectoral position. But, anyway, the benefits of the mesh are largely touted because now you can put an implant in the prepectoral position so now you don't have to dissect the pectoralis major muscle and lift if up off the ribs, that hurts less, potentially you could get the patients out the hospital faster because they use less narcotics and they have less pain. I think those were the two main benefits.

DR. LEWIS: Yes, Dr. Anderson.

DR. ANDERSON: I'd like to make a comment as a non-plastic breast surgeon. In our cancer operations, things we do are very standardized, and it's hard for us to vary a lot. The oncoplastic techniques are probably the biggest deal, but because it's cancer treatment, it's different. Working with plastic surgeons, I see a tremendous amount of variability which I think relates to the art of what they do, this transition, for example, from it was we never put it in front of the muscle until all of a sudden we were always putting it in front of the muscle, and I don't think that's going to change any time soon. It's like trying to tell an artist what pen, what brush they should use, and I think we'll continue to see changes. That's why I think sticking with this idea of we just need to know, when you put in the mesh, do people get hurt? I think we have to keep that bar low because they're not going to start suddenly standardizing what they do because of the artistic nature.

DR. LEWIS: Dr. Lippman.

DR. LIPPMAN: Also, apologies, I have trouble cutting my own dinner much less being a surgeon.

(Laughter.)

DR. LIPPMAN: I'm concerned, in harkening back to the need for a control group,

whether or not there's a way to imagine a control group with autologous reconstruction in which there are no implants and no mesh used. I know that there are reasons for choosing a TRAM flap or a DIEP or whatever you're doing, but there has to be some overlap in patients, I would imagine, that could be subjected or offered a trial with one that's just their own tissue and one that it's not, and that would answer an awful lot of questions, it seems to me.

DR. LEWIS: Let's turn to the last question. 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 interfaced with existing registries.

Dr. Ballman.

DR. BALLMAN: I'll take a first stab. I think it should just be part of the National -- the registry that's being set up and being captured as to what is being implanted and what type of mesh and so forth and so on, and then sub-studies can be done off of this just like, you know, that are being proposed for the registry as it currently stands.

DR. LEWIS: So, integration into the NBIR?

DR. BALLMAN: Completely.

DR. LEWIS: Dr. Leitch.

DR. LEITCH: And that's the only way you're going to get the prepectoral info is by a registry format.

DR. LEWIS: So, it looks like there's agreement that the answer to that is yes.

DR. ASHAR: Thank you.

DR. LEWIS: Dr. Ashar, is there anything else you'd like us to address?

DR. ASHAR: You know, I'm sorry to delay. Are there any unique situations or items that we need to consider for mastopexy? I know we haven't touched on that a lot simply

because this topic on reconstruction was so pressing and so involved, but specifically with mastopexy, if you have any recommendations, we would appreciate it.

DR. LEWIS: Dr. McGrath.

DR. McGRATH: I think the use of mesh with either breast reconstruction or breast mastopexy is completely different. We're dealing with different tissue and I think that needs a robust discussion. But just on a very quick -- my personal quick comment on it is that I would keep that separate from this discussion and think about it in more depth and what that would require because it's going to be very different in terms of breast tissue surveillance and all kinds of things if you use it in that setting.

DR. ANDERSON: You're saying different because mastopexy is a lumpectomy, you're leaving breast tissue behind, you're rearranging it versus whole breast reconstruction we're removing the entire gland. That's what is making it different?

DR. McGRATH: In mastopexy, you may not remove any breast.

DR. LEWIS: Dr. Chevray.

DR. CHEVRAY: Right. So, Dr. Anderson, you're speaking about mastopexy in conjunction with the lumpectomy for breast cancer care, oncoplastic. So that would be a minority of mastopexy of mastopexies that are done in the country. So, the majority are cosmetic surgeries to lift the breast to improve a patient's appearance, and I agree completely with what Dr. McGrath said. That's different; you should view it as a different use or a different indication for this mesh device and study it and approve it separately.

DR. ASHAR: Thank you. We have other means for getting expert opinions on this at a later time. Thank you.

DR. LEWIS: I call the morning session to a close. We will adjourn and resume at 1:15. Thank you.

(Whereupon, at 12:46 p.m., a lunch recess was taken.)

A F T E R N O O N S E S S I O N

(1:19 p.m.)

DR. LEWIS: I would call the Panel back into session for the afternoon session of the second day, and our first presentation will be on the history of silent rupture screening and informed consent for breast implants by Dr. David Krause, the FDA.

DR. KRAUSE: I'm tall. So good afternoon. Thank you for taking time out of your busy schedules to attend this meeting of the General and Plastic Surgery Devices Advisory Panel. The FDA sincerely appreciates your attendance and your advice. My name is David Krause. I'm the Deputy Director of the Division of Surgical Devices in the Center for Devices and Radiological Health of the FDA.

This afternoon, the FDA will ask you to provide your advice and recommendations regarding the statement located in the labeling for silicone gel-filled breast implants recommending that implant recipients get an MRI at 3 years post-implantation and then every 2 years thereafter. You will also be asked to comment on the patient informed consent materials provided in the current silicone gel-filled breast implant patient labeling, but first, I'd like to provide a bit of history to put this into context.

After Congress voted and approved the legislation and President Ford signed the bill establishing the Center for Devices and Radiological Health in 1976, breast implants were placed into Class II by the original classification panels and were regulated through submission of a premarket notification and determination of substantial equivalence. Thus, approval of silicone gel-filled breast implants was not required. It was necessary for applicants to establish substantial equivalence to an existing device by comparing the device characteristics and the labeling.

At that time, the labeling for silicone gel-filled breast implants did not include a recommendation for MRI screening but did include information for patients, which was

fairly short and identified certain risks that a surgeon should relate to the patient. However, there was no page that both patient and surgeon could sign providing evidence that the patient and the surgeon had discussed these issues.

In 1988, due to emerging safety concerns, the FDA reclassified breast implants to Class III requiring premarket approval. However, silicone gel-filled breast implants continued to be reviewed through the submission of a 510(k) and determination of substantial equivalence. Each marketing clearance letter included a statement that FDA would be call for premarket approval applications. This continued until the FDA finally issued a final rule calling for the submission of PMAs in April of 1991.

In January of 1992, the 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. The manufacturers agreed to this and silicone gel-filled breast implants were no longer made available.

In April of 1992, the FDA concluded that none of the PMAs submitted for silicone gel-filled breast implants contained sufficient data to support approval. However, the panel had recommended to the FDA that silicone gel-filled breast implants continue to be available for patients undergoing reconstruction procedures. Thus, in the United States, from April 1992 on, silicone gel-filled breast implants were only available to women undergoing breast reconstruction procedures through entry into a clinical study. However, during this time of the moratorium, saline-filled breast implants remained available for augmentation and reconstruction, and new devices could attain marketing clearance via submission of a 510(k) and determination of substantial equivalence to existing devices.

After FDA called for PMAs for saline breast implants in May of 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. Because these were saline-filled breast implants, there was no recommendation for MRI screening. However, the panel expressed a concern that patients should be adequately informed regarding the risks, so a patient brochure was included in the labeling, but it did not include a page where both the patient and the surgeon could sign the document.

In October of 2003 and April of 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. There was also a recommendation that a patient focus group review the labeling and provide recommendations to the manufacturers that the labeling be updated after the focus group review.

In November 2006, acting on these aforementioned recommendations from the panel, FDA approved Allergan's 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 2 years thereafter and included informed consent documentation that was much more comprehensive than those previously provided and included a page the patient and the surgeon could sign once they had discussed all the potential risks of breast implants with their plastic surgeon.

And it's important to note that this labeling was reviewed by a focus group made up of patients and the recommendations of that focus group was included in the labeling.

Thank you.

DR. LEWIS: Thank you.

We'll now hear from industry representatives related to the core study MRI data and patient education and informed consent. We'll begin with a presentation by representatives from Allergan.

DR. BROWN: Okay. Good afternoon, Advisory Committee members, FDA, and breast implant patients. I'm Dr. Stephanie Manson Brown, a plastic surgeon, and I'm the Vice President for Clinical Development for devices in Allergan.

Today I'm going to speak about three important topics. First, I'll address patient communication and informed consent. Then I'll discuss MRI for detecting silent rupture. And we'll finish with a brief section on ADMs, as we are a manufacturer of ADMs and we'd like to address this.

As we heard from patients yesterday, they are not being adequately informed of the risks of their breast implants before or after their implantation. Currently, Allergan has several tools available to encourage effective dialogue between patient and surgeon. These include detailed surgeon directions for use, which outlines risk information that the surgeon is expected to provide to the patient; a summary patient brochure that patients and surgeons can review together during consultation; a detailed procedure-specific patient brochure that the patients can review online following their initial consultation; and additional tools for facilitating surgeon-patient conversations, such as brochures and webpages.

We also conduct live education sessions with surgeons on informed consent best practices. And in all labeling documents, 1 to 2 weeks between consultation and surgery are suggested to allow the necessary time for a woman to understand the information and make an informed decision considering all the risks and benefits.

These are just some examples of the additional patient materials we provided, and we have these and others available on the natrelle.com website.

A patient's informed consent is a process that starts before she's considering breast implants and continues just before her surgery and endures past her implantation. Based on what we've heard from patients, we will continue using focus groups to evaluate the content and the delivery methods of our patient labeling.

It's important to facilitate communication between healthcare providers and patients who've already had implants. We do this through education of surgeons and primary care providers on a variety of topics, including BIA-ALCL.

As we heard yesterday, primary care providers are particularly important because they are often the ones who see women, if the women then develop symptoms related to their implants.

As we heard yesterday, one of the complications that can occur with implants is rupture, and I'll now speak to you about MRI screening and silent implant rupture.

Implant rupture is an important concern for patients. Silent rupture occurs when the implant ruptures without any reports of signs or symptoms. Labeling recommends regular MRI screenings at 3 years post-implantation and every 2 years thereafter. When diagnosed, the labeling indicates that the surgeon should advise the patient to have her implant removed.

What we see in practice is that MRI compliance is low, and I know that has been mentioned quite a few times over the last day or so. The baseline of our post-approval study has an assessment of real-world MRI screening compliance. Shown in this table are the percentages of patients having MRI within the follow-up year, and as you can see, patients getting an MRI scan as per the screening recommendations in the label is low, which may be due to many reasons.

Surgeons report that satisfied and asymptomatic patients typically do not return for MRI due to high costs, low insurance coverage, and the inconvenience it poses to patients.

However, our premarket studies indicate that the majority of ruptures are silent, which underscores the need for periodic screening. To improve compliance, the need for screening should be reinforced, and we support lower-cost alternatives to MRI such as high-resolution ultrasound.

And then the third and final topic of the presentation is acellular dermal matrices, ADMs. ADMs have been utilized in the breast from around the early 2000s, as we heard earlier. The utilization of ADM has allowed for the improvement and evolution of breast reconstruction surgical technique from previous approaches.

Today in the U.S. it's estimated that around 70 and actually possibly up to 80% of prosthetic breast reconstructions are performed with an ADM. These are associated with two specific reconstructive techniques which we heard quite a bit about in the Panel discussion previously. One is using partial muscle coverage where the implant is placed over the pectoralis muscle, and two, prepectoral placement where the implant is placed on top of the pectoralis muscle.

There have been reports in the literature that there are several benefits associated with using ADM with partial muscle coverage, and these include reinforcement of weak tissue at the breast boundaries, improved breast shape, reduced expansion time and discomfort, decreased risk of exposure and/or extrusion, and decreased risk of implant visibility and palpability.

The introduction of ADMs has also allowed the surgeons to develop the prepectoral technique and this allows maintenance of the integrity of the muscle. As you heard from Dr. McGrath this morning, maintaining the integrity of the muscle and avoiding transection is often associated with better outcomes, and we can see this in the literature where there have been potential benefits reported using ADM in prepectoral breast reconstruction. For example, shorter surgical time has been reported, as has decreased recovery time, reduced

postoperative pain and therefore less narcotic use, and the elimination of animation deformity. All of these benefit particularly the patient but also the healthcare system.

The most common complications reported in the literature with ADM used in breast reconstruction include seroma, infection, skin necrosis, and implant or expander loss. Recent literature suggests that complication rates are equivalent to other previous techniques.

We at Allergan are committed to the generation of additional data supporting the use of ADMs in breast reconstruction, and we are working with the FDA to define clinical endpoints that ensure optimal outcomes for patients.

And so, to summarize the three topics that have been discussed today. Informed consent must be improved by involving patients even more in the material development.

Continuing education of patients post-implantation is critical, as informed consent should not stop at implantation.

Patient compliance with MRI screening is low in the real world, as we've seen from our postmarket data. However, screening is important to detect silent rupture, and more work should be done to reduce the costs and inconvenience to patients.

And evolving technology like high-resolution ultrasound may provide a lower-cost alternative that could enhance compliance.

And, finally, ADMs are an important evolution in breast reconstruction, and we are fully committed to demonstrating patient outcomes and safety through further data collection.

Allergan has and will continue to actively support research, education, and informative labeling to promote and advance the safest use of breast implant products. We appreciate the opportunity to speak on these topics and look forward to working together with patient groups, the Agency, industry stakeholders, and the medical community.

Thank you for your time.

DR. LEWIS: Thank you for the presentation.

We will now hear from representatives of Mentor.

MS. DAURIA: Good afternoon, Mr. Chairman, members of the Advisory Committee, and the FDA. I'm Raina Dauria, Vice President of Regulatory Affairs supporting Mentor. Bear with me, the slides are not moving.

(Pause.)

MS. DAURIA: Thank you for your patience. Before I begin, I'd like to acknowledge the powerful stories that we heard from the women who traveled here yesterday and today and reaffirm our commitment to identify additional ways that we can continue to monitor and further the understanding of breast implant safety and improve patient education. Nothing is more important to Mentor than the health and safety of the women who choose our breast implants, and we take that responsibility very seriously.

Today I'll talk about the utility of MRI screening and surgeon and patient communication as it relates to the informed consent process.

FDA has asked Mentor to comment on our experience with the utility of MRI. We conducted a review of MRI results for patients participating in our MemoryGel and MemoryShape core studies. Our data show, while MRI was a very effective method for the detection of silent ruptures, compliance with MRI screening in both core studies dropped off significantly 5 years after implantation. A review of patient feedback indicated that there are multiple reasons why women with breast implants do not comply with MRI screening guidelines, ranging from cost to claustrophobia.

As indicated in the physician and patient labeling, MRI screening is currently recommended for all women with breast implants 3 years post-implantation and every 2 years thereafter. Clinical studies have shown that the vast majority of ruptures occur

6 years or more post-implantation. Based on this finding, it may be of value to consider an adjustment to current screening timeline recommendations with appropriate postoperative follow-up and screening based on the individual patient risks, needs, and preferences. We encourage exploration of validated patient-centric solutions such as high-resolution ultrasound.

Turning to patient and surgeon communication and informed consent, I would like to share with you some of our efforts to communicate risks associated with breast implants so surgeons and their patients can make informed decisions.

At Mentor, we take seriously our responsibility to communicate potential risks associated with breast implants to patients. We heard the testimony yesterday, and we understand that there may be a gap between what we are providing and what information is reaching the patients. We believe the best way to ensure patient understanding of risk is for them to have a conversation directly with their surgeon. To that end, Mentor provides all surgeons with a patient education brochure as a handout for patients. We've provided copies of this brochure to the Panel for your reference.

Along with extensive information on risks and benefits, this brochure contains links to where patients can find more information about their breast implants, including a link to Mentor's summary of safety and effectiveness which is on the FDA's website. It's a public website, and anyone can gain access to it. The SSED does include a table of general device materials for our breast implants.

The brochure also contains, in the back, two copies of an acknowledgement of informed decision checklist. One is a tear-out for the patient's medical file and one that remains in the brochure for the patient to take with them. This checklist is to be signed, ensuring the patient has reviewed the contents of the brochure, understands the information, has considered other options, and has had time to discuss the information

with the surgeon. We request they wait 1 to 2 weeks, but we know that they can take longer.

Mentor also makes available a two-page, easy-to-understand patient risk information booklet. This is to go together with the brochure because we know the brochure can be cumbersome. It has a lot of information, so the two-page risk information booklet clearly lists breast implant considerations and risks such as BIA-ALCL and breast implant illness.

We know that women typically seek their own information on breast implants for nearly 2 years before deciding to move forward with the procedure. Knowing this, we have invested significant time and resources in making up-to-date transparent information about the safety of breast implants readily available for women online through websites and via social media.

Likewise, we want to ensure that surgeons have the latest information to consider and share with their patients. All new customers are trained by Mentor on the proper use our implants as well as the risks of our implants. In addition to the patient information brochure I just described, we also provide updates to surgeons as new information becomes available via regular email communications, evidence-based perspectives, our corporate website, surgeon portal, and direct education through professional society meetings.

Also, taking the FDA's lead in reaching out to all types of healthcare professionals, Mentor is exploring opportunities for further outreach to medical societies and congresses that include primary care physicians to increase awareness and encourage physician-patient communications even more, and long term where they might not be coming back to their plastic surgeon.

As patient safety is Mentor's first priority, we support open and transparent dialogue so that women have all of the information needed to make informed choices about their

breast surgery. We would like to emphasize that we see this effort as a shared responsibility. We look forward to working with FDA, physicians, patients, and surgeons to ensure that patient education and safety is making the most informed choices.

Thank you for the opportunity to speak on these important topics.

DR. LEWIS: Thank you.

MS. d'INCELLI: Good afternoon, ladies and gentlemen, distinguished Panel, and members of the audience. Sientra is pleased to present today to the General and Plastic Surgery Devices Panel of the Medical Devices Advisory Committee.

My name is Rosalyn d'Incelli. I'm Vice President of Clinical and Medical Affairs at Sientra. I'm joined by my colleague JoAnn Kuhne, Vice President of Regulatory Affairs and Quality Assurance, and Dr. Bruce Van Natta.

Today's presentation will include the following requested topics: Sientra's core study, MRI outcomes, and an overview of our comprehensive patient informed consent decision process.

Sientra's patient and physician labeling follows current FDA MRI recommendations. The first MRI should be performed at 3 years postoperatively and then 2 years thereafter. And if a silent rupture is suspected, the recommendation is removal. Alternatively, as we discussed, the American College of Radiology states that MRI is not appropriate for asymptomatic patients.

While MRIs are effective in detecting silent rupture and have the potential to identify ruptures earlier, they do present limitations. The limitations include a higher number of false positives that can lead to unnecessary operations and implant removal. It is a costly diagnostic procedure with limited healthcare coverage, and at this time it's unclear what the optimal period or intervals are for undergoing screening for MRI silent rupture.

As discussed, potential solutions to address these challenges could include assessing alternative imaging technologies that may be effective, such as high-resolution ultrasound, and another option could be to follow the ACR recommendations and only recommend diagnostic MRIs for suspected ruptures.

Within the core study, our patients received MRIs at regular intervals every other year. These MRIs were then interpreted by a local and central expert radiologist. If either the local or the central radiologist indicated a suspected or a confirmed rupture, then that patient is reported as ruptured in our data.

Through 10 years there is an 8.6% rupture rate in the MRI cohort, which included 571 patients. Additional rupture analysis through 10 years showed that 41% of the study ruptures came from three surgeons and these three surgeons only enrolled 16% of the total study subjects. This data supports the technique-dependent variable of this complication and highlights the need for further assessment as some of the factors may be controllable via best surgical practices.

Analysis of the MRI data showed that 39% of the suspected ruptures were found to be intact at explantation or follow-up MRI. In other words, this means that one-third of the patients thought to be ruptured were actually not ruptured, and many patients underwent unnecessary surgery to determine that. Through 10 years and across all 1,800 patients in the study, there were 36 ruptures confirmed via explantation. All of these were intracapsular except for one, and a majority of these were silent and first detected by MRI.

Sientra is committed to supporting a comprehensive informed decision process. The patient labeling is a key source of information for the informed decision process. It was developed with patient focus group input and approved by the FDA. This 80-page brochure presents a comprehensive review of all the benefits, risks, and considerations of breast implants and breast implant surgery. It is provided directly from the surgeon and is also

available on our website. While extremely thorough, many advocacy groups and patients are not being fully informed of all these risks, as has been discussed at this Panel. We designed the brochure to be comprehensive and to empower a fully informed decision.

The educational brochure includes a page titled *Acknowledgement of Informed Decision*, with checks yes and no and instructions to be signed prior to surgery by both the patient and her surgeon, indicating the patient reviewed and discussed all of the information with her surgeon and was fully informed prior to surgery.

We reviewed data from our new enrollment post-approval study and were able to learn about their experience with our informed consent process. Interestingly, 97% of participants felt the educational brochure helped them understand the risks and benefits of breast implantation and 97% felt that the educational brochure, in addition to discussions with their plastic surgeon, provided the information needed to make an informed decision. These results are from over 4,000 study participants.

When asked, 19% of the participants did note that they would prefer their brochure had more information in certain areas. The top three areas that the patients listed were implant longevity, more information on reoperations, and other potential complications. This feedback provides very useful information to focus on during this critical step in the decision-making process.

Our website is also a key source of information for our patients and surgeons. Sientra's commitment to safety website aims to increase awareness and understanding of the benefits and risks of our implants. Several resources are provided, including our 10-year clinical data, information on BIA-ALCL, all of the labeling and multiple other helpful links for patients. We also connect with our community of patients and physicians through a variety of online platforms including Instagram, Facebook, Twitter, and LinkedIn. As demonstrated through our digital initiatives, we encourage patients to ask questions and be

informed about their surgical options. And we provide many other resources such as reconstruction educational videos and information developed by the plastic surgery societies.

In conclusion, we would like to thank the Panel for the opportunity to participate in this important forum and to the women for sharing their very personal stories. We are committed to providing accurate and thorough patient labeling and education in order to allow patients to make a fully informed decision. And making a decision to undergo breast implant surgery is a very personal decision. We take our responsibility seriously and pledge to partner with the surgeons, patients, and FDA to address these important topics of awareness, education, and research.

Thank you.

DR. LEWIS: Thank you for the presentation.

Lastly, we'll hear from the Ideal company.

DR. HAMAS: Good afternoon, I'm Dr. Robert Hamas. I'm a board-certified plastic surgeon.

All ruptures are silent, and only later do they become symptomatic. The real question probably is more about how women feel about having a ruptured implant. So we engaged a third party to do a randomized online survey asking about women's feelings about it, and we surveyed about almost a thousand women, 45% were nurses to get a sense of people with some medical background, and not surprising to us, at least 97% of the women would want to know if their silicone gel implant had ruptured, and 95% of those would want to have it removed if it was ruptured, even if asymptomatic.

Silent rupture of silicone gel implants is kind of an interesting problem because the FDA has approved intact implants as safe and effective, but ruptured implants have not been approved. There is not a 10-year trial of ruptured implants, and it might be

interesting to look at that subgroup of women -- and we've touched on it a bit this morning -- that have ruptures to see if the incidence of, for instance, autoimmune disease is higher within that subgroup, just as we've seen problems with ALCL in a subgroup of patients with textured implants.

Silent rupture creates a dilemma for both surgeons and patients. Do they reassure the patient and say leave it in because there's been a lot of studies saying that silicone gel implants are safe? But those implant studies are done with intact implants. Or do you remove it, as FDA has recommended? And many surgeons would do that as well, and it seems to be what women prefer based on their surveys.

It seems kind of obvious, though, in a way. If a surgeon opens an implant package like this one here in the operating room and you looked in and you saw a ruptured implant, I think any surgeon here would say, gee, that's defective, and you'd send it back to the manufacturer for a credit. So, if it's not okay to put in a ruptured implant, then why, after 7 or 8 or 15 years, is it okay to leave in a ruptured implant?

How extensive is the problem of silent rupture? This isn't talked about very often at meetings and things, but we did an estimate based on procedural statistics that are publicly available from ASPS and ASAPS. Each year they publish how many cases are done using breast implants and what percentage are silicone gel. And assuming just a conservative 1% per year rupture rate, you get about 150,000 women or more just since gel implants were reapproved in '06, and of course, we know very few get MRI.

Now, warranty funds are available to replace a ruptured implant, I think $3,500 is kind of the average, but what a dilemma for a patient. Do you spend the money for an MRI to find out it might be ruptured to get the warranty money? It's kind of an awkward situation. So, effectively, I'm sure many women just don't bother doing it, you know, don't know if it's ruptured and the warranty money doesn't get spent.

Is high-resolution ultrasound an option? I've heard a number of people talking about it. It was very, very interesting. Marc Salzman from Louisville did a very nice presentation at the last plastic surgery meeting, and he confirmed rupture at surgery in 49 of the 50 patients that showed rupture on MRI -- excuse me, on high-resolution ultrasound.

Now, this little unit pictured is a small inexpensive handheld office unit. It costs all of $5,000, projects the image on an iPad screen, and it gets stored in the cloud, and it seems like a really cool way to do screening in a plastic surgeon's office or anybody's office, for that matter, and our company decided to take a leadership role in this area and have actually already started a study. We're screening 1,000 women at 9 plastic surgery sites here in the United States.

And we're going back to the year 2000 because the implants that were approved in '06 were actually manufactured in '99 and 2000. So those implants, we're going to look at implants that potentially are 18 years old, and there's very little long-term data available, and we're looking at asymptomatic women that will be called in from these practices.

What I think will be very interesting, also, is these women all have the gel implants, they're asymptomatic, and we're going to do surveys both before and after the screening to again find out their feelings. See, even old guys get used to thinking about that.

I'll move on to the informed consent process. What's optimal? Well, it's optimal if the surgeon listens to the patient's concerns and presents all three implant options, both the saline, the water balloon, the silicone gel implant, and the structured saline implant. I mean, they're three different technologies and present them all. It's best if it's presented in an unbiased and objective way as part of our ethical informed consent as physicians to give women all their choices and all their options and not limit them and let the woman choose the implant that she feels is best for her, of course with the help of her surgeon in consultation.

Sometimes the informed consent process can be great in the office, but then the hospital interferes, and some hospitals limit the number of vendors and implants that are available. We have recently run into a problem with purchasing people who don't care one bit about differences in technology. They regard our implant with a structure inside that supports the shell the same as a saline water balloon because they're both filled with saline. And all I can say, that's like saying a chocolate milkshake is the same as a glass of milk because they both contain milk, which doesn't make sense.

Some hospitals block companies that have physician stockholders. We have some. HCA, Tenet, Intermountain, huge hospital chains will not allow our product in because HHS has a policy or has made a recommendation that hospitals not purchase any products from a company that has even one physician stockholder. So, what's the effect of that? Women may want to have three choices, but they're going to end up with two at those hospital systems which serve an enormous number of women.

Sometimes informed consent can be altered by surgeon bias. Some surgeons dismiss women's concerns. Silent rupture, for instance, they may not think is an issue and don't want to worry about it or talk about it. Some surgeons say they'll only use silicone gel, they're very resistant to change, which has really surprised me for plastic surgeons, but that's true. They like to use what they've been using and that's that. And some just outright discourage the use of any saline-filled option, so that's off the table and again limits women's choices.

I think Steve Jobs had a great quote. "People don't know what they want until you show it to them." So, I think informed consent should simply be show all three choices.

Thank you.

DR. LEWIS: Thank you.

We'll now have a presentation from the FDA on core study MRI data and patient

education and informed consent by Sung Yoon, Dr. Sung Yoon.

DR. YOON: Good afternoon, my name is Sung Yoon. I'm a double board-certified plastic surgeon in practice. I'll be discussing two topics in this presentation. First will be the patient education and the informed consent, followed by the core study MRI data for reassessment of the current FDA labeling recommendation for MRI screening to detect silent rupture of silicone gel-filled breast implants.

As a background, there are five silicone gel-filled breast implants which have been approved for use in patients. The data from the approved PMAs are referred to as the core studies. In general, the core studies have a 10-year follow-up, and each study includes an MRI cohort for MRI assessment of silicone gel-filled breast implant rupture.

The five approved silicone gel-filled breast implants were approved between 2006 and 2013. These devices were approved for breast reconstruction in women of any age and breast augmentation for patients at least 23 years old.

We understand that choosing to undergo breast implant surgery is an important decision for patients. FDA requires all breast implants to have a labeling for physicians, as well as patients who are considering breast implants. Labeling includes information such as risk of breast implants, potential surgical complications, as well as the results from the PMA core studies.

When the silicone gel-filled breast implants were first approved in 2006, as a condition of approval, focus group studies were conducted to evaluate patients' understanding of the labeling. As an additional condition of approval, an informed decision process survey to assess the informed consent process was completed.

In 2011, when the FDA was made aware of the breast implant-associated anaplastic large cell lymphoma, BIA-ALCL, we required language regarding BIA-ALCL to be included in both physician and patient labeling. On the FDA website we have information for patients,

including patient labeling of each of the implants, as well as information on potential risk of having breast implants. We encourage patients to visit the website prior to making choices to undergo breast implant surgeries, in addition to discussing your options with your physician.

One of the potential risks mentioned in the labeling is breast implant rupture. Rupture is one of the most reported device problems for breast implants in the MDR. Ruptures are categorized as symptomatic or silent. Silent ruptures refer to those without any noticeable changes.

For saline-filled breast implant ruptures, the implant deflates when saline is absorbed by the body, which may be noticeable. However, for silicone gel-filled breast implants, ruptures may be silent.

Silicone gel-filled breast implant ruptures are categorized as intracapsular when the gel remains within the scar tissue that forms around implants or extracapsular when the gel migrates outside that scar tissue.

MRI is considered the most effective method for detecting rupture of silicone gel-filled breast implants. Based on literature, MRI sensitivity for detecting rupture ranges anywhere from 64 to 89%, specificity ranges from 77 to 97%. And because ruptures in silicone gel-filled breast implants are often silent, recommendation for MRI screening to detect silent rupture is included in both the physician and patient labeling.

The FDA has recommended that physician and patient labeling for all approved silicone gel-filled breast implants include the recommendation of MRI screening at 3 years and every 2 years thereafter to detect silent rupture. However, several reports have challenged the role of MRI as a screening tool for the evaluation of silent rupture, citing concerns, as you heard, about compliance, cost, and reimbursement.

With this presentation, FDA seeks recommendations from the Panel regarding two

questions: first, on the level of evidence of clinical benefit that would be required to support current FDA recommendation on MRI screening for ruptured silicone gel-filled breast implants, and second, on whether FDA should continue to have manufacturers make specific recommendations in their labeling about MRI screening of silicone gel-filled breast implants. And if so, what should those recommendations be?

In the next few slides, results from the five core studies conducted by three manufacturers are presented, which include MRI and non-MRI cohorts for assessment of rupture rates. Each core study included four different indications of augmentation, revision augmentation, reconstruction, and revision reconstruction.

Although the company Ideal also manufacturers approved breast implants, for the purpose of this presentation which focuses on MRI screening for silent rupture of silicone gel-filled breast implants, rupture data on saline implants by the company Ideal are not presented.

Please also note, direct comparisons cannot be made between manufacturers or implant types due to the differences in the study design, which includes size, methods in which the ruptures may have been detected or confirmed, durable overall study compliance rates, different MRI screening schedule and its compliance rate, and methods for analyzing and presenting the data.

This table summarizes the five core study results, which followed patients for 10 years post-implantation. In general, the overall study compliance decreased with time and varied between 55 to 81% at 10 years by indications. However, the MRI compliance, as you can see, by the end of the study showed a wider spectrum ranging from 42 to 100% by indications.

As you can see in these two rows, when reporting rupture rates, the majority of ruptures in both MRI and non-MRI cohorts were considered silent.

In the first two columns, Allergan reported on all explanted ruptured devices, of which 73 to 100% were reported intracapsular.

As shown in the middle two columns, Mentor reported on all silent ruptures on a patient level, which showed 67 to 85% were intracapsular ruptures.

The Sientra core study reported on all explanted silent confirmed ruptures, of which 96 to 100% were reported as intracapsular rupture.

In general, according to the data in this summary, most of the ruptures in the core studies were silent and intracapsular.

Now, in the next five graphs, the cumulative incidence of rupture rates on Kaplan-Meier rupture rates over 10 years for each of the core studies that are presented for the MRI and the non-MRI cohorts.

First, for Allergan Natrelle, the cumulative incidence of rupture shows that prior to Year 4, the rupture rate is less than 5% and then increases at a variable rate afterwards. Each line represents the four indications where the lines in red are in the MRI cohort and the non-MRI cohort are in blue.

A similar trend can be seen in Allergan Natrelle 410 implant study graph of the cumulative incidence of rupture rates.

For Mentor MemoryGel, again, the cumulative incidence of rupture rate shows a variable increase starting at Year 4 to 6. Some data points for the non-MRI cohort are not shown because the data was not provided.

This graph represents the Mentor MemoryShape core study which again shows a similar trend of increase in rupture rate the longer an implant is in place.

For Sientra round and shaped implants, the trend of variable increase in rupture rate can also be seen.

In this graph, the 10-year rupture rate between MRI and the non-MRI cohorts within

each indication of each core study are depicted in red and blue. As you can see, by the wide and generally overlapping confidence intervals, in general, there does not appear to be a difference of K-M rupture rates between the two cohorts.

However, additional comparisons by indications or by manufacturers or implant types cannot be made since the studies are inherently different in their study design, including size, methods in which the rupture rates may have been detected or confirmed, variable overall study compliance rates, different MRI screening schedule and its compliance rate, and methods for analyzing and presenting the data.

In conclusion, rupture is one of the most reported device problems for breast implants.

Data limitations restrict statistically robust interpretations of rupture information presented in the interim as well as the final core study reports, as seen in the core studies table.

Rupture rates increase the longer implants are in place. Overall, core study rupture rates generally are less than 5% before Year 4, then increase around 4 to 6 years post-implantation. After Year 6, the rupture rates continue to increase at variable rates, as seen in the graphs.

The majority of rupture events in the core studies were silent and intracapsular in nature regardless of the cohort. In general, there does not appear to be a difference in the 10-year rupture rates between the MRI and the non-MRI cohorts in the core studies, as seen by the wide and overlapping confidence intervals of the 10-year rupture rates.

Next, we have a representative, Dr. Destounis, from the American College of Radiology, who will be discussing their 2018 recommendation for detection of breast implant rupture.

DR. DESTOUNIS: Good afternoon. I'm Stamatia Destounis. I'm a radiologist, and I'm

here as a representative for the American College of Radiology. Thank you for inviting us to this very interesting discussion.

So as a bit of a background, in the 1990s the American College of Radiology saw a need for national guidance for appropriate use of imaging technologies. So, the ACR task force on appropriateness criteria was formed at that time, and several expert panels made of multidisciplinary healthcare providers, including those representing other specialty medical societies such as OB/GYN, oncology, internal medicine, and surgery were invited to be members of the panels.

So, guideline development and revisions were made by extensive literature review and also application of established methodologies such as the RAND/UCLA method and also grade.

So, on occasion, the evidence may be lacking, or the literature may not be quite clear, so at that point expert opinion and consensus supplemented some of the ACR appropriateness criteria that were formed.

So, after extensive research and deliberation, the panel will give an appropriateness rating for imaging and treatment procedures for specific clinical scenarios and for specific medical conditions.

So, currently, the ACR appropriateness criteria committee includes 186 diagnostic imaging and interventional radiology topics and 914 clinical variants and over 1600 clinical scenarios. Because medicine is a dynamic field, yearly reviews and revisions are made to this, and new topics are introduced frequently, and this past year, the breast implant evaluation criteria was introduced.

So, this was intended to really guide radiologists and the radiation oncologists and the referring healthcare providers in making decisions regarding radiologic imaging and treatment. And the ultimate decision regarding appropriateness, however, has to be made

by the referring physician and the radiologist in light of all the circumstances that are presented for that individual patient, for that individual exam.

So, breast MRI has high spatial tissue resolution. Because of no radiation and the ability to emphasize the signal from the different tissues, which is water, fat, and silicone, really you're able to look at implants in an ideal way. So, you're able to suppress the water and the fat and really look at silicone and it's able to characterize implant rupture very well. However, if you look at the peer review literature, there's variable sensitivity and specificity and accuracy reported, as already has been mentioned.

And I have a few articles here, one by Rietjens. The accuracy they quoted was 94% for implant ruptures. Scaranelo, however, had a sensitivity of 64% and a specificity of 77%. Holmich looked at the same thing and found accuracy of 92% and the sensitivity was 89% and specificity of 97%. So, when you look at the literature, you will get very different sensitivity and specificities.

So, the 2018 ACR appropriateness criteria by the expert panel, which predominantly has radiologists, OB/GYN surgeons, and oncologists and also internal medicine physicians, they looked at what they would consider appropriate for MRI for breast implant evaluation.

So, MRI is felt to not be appropriate for the evaluation of saline implants. There's no imaging that's indicated for the asymptomatic patient. So, if the patient has no symptoms and they have saline implants, there's no role.

If the patient has symptoms for saline implants, it's very easy to look at a contour change or a deflation of the implant in that case, and then there's no role for MRI in this case; also, mammography or ultrasound, for the symptomatic patient. That takes care of that diagnostic concern.

If you have the patient, according to the ACR criteria for silicone implants in an asymptomatic patient and evaluation of that patient, the benefits of screening for rupture

are controversial, the data is limited, and no clear role at this time for silicone implant evaluation for a patient with no symptoms. Some of the authors in the peer review literature also discuss shared decision making, which may be appropriate, and a patient-centered decision versus a more generalized recommendation.

So, we do know that rupture is one of the main complications of implants. The risk will increase with the age of the implant, and most ruptures will occur somewhere around 10 to 15 years post-placement. So, if you have a symptomatic patient with silicone implant and you want to evaluate that patient, MRI is indicated.

The ACR appropriateness criteria, which you can also go on the website and look at yourself, I have an image there, they look exactly like that. So, when you look at silicone breast implants and you have a suspected implant complication and the patient's younger than 30, for initial imaging, MRI of the breast without IV contrast is usually appropriate. Ultrasound of the breast is usually appropriate. In younger age less than 30, mammography with a digital breast tomosynthesis or diagnostic mammography is not appropriate, and contrast is not appropriate. Let's see. Yes, so MRI of the breast without IV contrast, appropriate.

For patients 30 to 39, for initial imaging and you have a suspected implant complication, MRI of the breast without IV contrast again is appropriate. Mammography, however, in this age group also may be usually appropriate whether it's tomosynthesis or 2-D mammography, and ultrasound of the breast is usually appropriate.

If the patient is 40 or over, again, we look at MRI of the breast without IV contrast as usually appropriate, and in this case, tomosynthesis, you know, the 3-D mammography or diagnostic 2-D mammography is appropriate. In the group of 40 and over, for the ultrasound of the breast, it may be appropriate. It was given a rating of 5 because there was such a disagreement amongst the panel whether they thought breast ultrasound was

indicated in a woman over 40. When there was concern about implant rupture, for most women over 40, usually mammography is indicated or the MRI.

Okay, so I wanted to show you, for MRI image evaluations, when we look at it as radiologists and interpret, you know, breast MRI all the time, you want to -- if you're diagnosing rupture, you have to confirm it in two planes. This is the axial plane, and what may look as rupture where you see -- I don't know if you can see my arrow, so I'm sorry. Oh, there we go. So, where you can see these curvilinear lines on both sides, well, those actually may look like rupture, but they're not; they're folds. So, you need to include axial and sagittal images to really diagnose something that may be a rupture and not a fold and you need to include silicone-specific sequences and also a water sequence.

If you're looking to evaluate with MRI for intracapsular rupture, obviously, it's very challenging to diagnose this with ultrasound, and there's variability in the ability of sonographers to do the ultrasound for the implant patient, and you're looking for intracapsular rupture with ultrasound if the step ladder appears, which can be very variable. Mammography typically is not routinely used to look at intracapsular rupture, so it does require the breast MRI evaluation.

For breast MRI you're going to see the multiple curvilinear low signal intensity lines, and you're looking specifically to look at the silicone to be bright, and that's the T2 images and that's the Linguine sign, and I will show what that looks like, that's complete rupture intracapsular. That's the collapsed implant membrane. You may have cases where it's not collapsed at all or minimally collapsed, the intracapsular rupture, and there's a keyhole and you have a teardrop sign basically.

But this is what the intracapsular rupture would look like, and you can see here these curvilinear low signals, and that's the Linguine sign, and you can see the same thing here on the opposite, the sagittal view, and that's what an intracapsular complete rupture

looks like.

For the extracapsular rupture, when you're looking with MRI, these patients may present with palpable masses or other changes in that breast contour, and the diagnosis can usually be made by mammography and/or ultrasound because you'll see high-density silicone outside of the capsule. And on ultrasound, there will be the snowstorm pattern, which actually ultrasound can be very good for the extracapsular silicone.

When you look with MRI in those cases of extracapsular rupture, you will see discrete foci of low signal or isointense intensity on the T1 images and high signal intensity when you suppress the water and you're looking at silicone.

This is what the extracapsular rupture would look like. You'll see that there is the implant and you see the bright little line outside. And I'm sorry, the lights are on. I don't know if you guys can see that well, but you'll have this little bright signal right here, and that's the free silicone outside of the capsule.

And I know you discussed the anaplastic large cell lymphoma for the suspected breast implant associated, so I just wanted to say a little bit. This is a newly recognized entity by the WHO, and the data is limited and evolving, and most of these cases are with textured implants. It's a rare T-cell lymphoma. It usually will present with an effusion a year after surgery. Early recognition here is critical, and we do need to make the diagnosis usually from the cytological analysis of the fluid. And when the disease is limited around the capsule, the implant capsule, the patients have a better diagnosis. So, the ACR committee did have appropriateness criteria for also this case.

So, if you're suspecting that the patient is presenting with this rare T-cell lymphoma and there's no warmth to the skin or skin changes or erythema to suggest inflammatory breast cancer or infection and you're really looking at seroma fluid swelling and mass and pain, then ultrasound usually is the way to start. The committee felt, the panel of experts

felt, starting with ultrasound usually is most appropriate. And tomosynthesis, 3-D mammography, may be appropriate. Mammography may be appropriate. There was disagreement here for 2-D mammography a little bit, and with and without IV contrast for MRI may be appropriate.

And I wanted to thank you for your time.

DR. LEWIS: Thank you, Dr. Destounis.

We'll now have Dr. Jonathan Green of the NIH present on patient consent best practices.

DR. GREEN: Great. Thank you for inviting me to speak this afternoon. My name is Jonathan Green, and I'm the Director of the Office of Human Subjects Research Protections at the National Institutes of Health. Just a disclaimer. My presentation today is purely my own opinion. This does not represent the opinion of the government, of the Department of Health and Human Services or the NIH, and I have no conflicts of interest. And most importantly, I am not a lawyer and not giving anything resembling legal advice here.

So, I was asked to speak to you about best practices for obtaining informed consent in a clinical circumstance. So, I think it's important that we place that in the context of the doctor-patient relationship. So, the doctor-patient relationship has some unique features, and it's really characterized by this imbalance of power and this imbalance of knowledge and the fact that patients come to us in this extremely vulnerable state of illness. And because of that, we think of the doctor-patient relationship as a fiduciary relationship, which is a relationship that is based upon trust.

And so what is it that we're trusted to do, and the first is that the patients trust that we have special knowledge, that we, in fact, did go to medical school and that we did attend class and that we have the knowledge necessary to diagnose and treat their condition; second, that they trust that we will act in their best interests, that all of our

actions and decisions will be geared towards promoting their best interests; and then, third, they trust that we will put their best interests ahead of our own self-interests. And so, these are really the core tenets that govern our relationship as clinicians with the patient. So, when we think of informed consent, we really need to put it in that context.

So informed consent is really an incredibly powerful thing. It's transformative. It can take something that is completely impermissible and turn that action into something that's okay to do, right? And that's true not just in medicine; it's true in everyday life. I think we can all think of examples where if we were to act in a certain way without that person's consent, we would be in jail. But the mere act of that person providing consent turns that action into something that's completely okay to do. So, really, consent has this transformative power.

And when we think about informed consent in the terms, again, of the doctor-patient relationship, it is a way that we respect patients and we encourage them to exercise their autonomy, and in fact, it's one of our strong obligations as clinicians to promote our individual patients' autonomy with the goal of allowing them to make decisions that are congruent with their own goals and values.

So, consent is really about making a decision and we have an obligation to provide the necessary information. Again, remember, we have this imbalance of knowledge, and so we have to impart information to our patients so that they can exercise autonomy and make decisions that are then consistent with their own goals and values.

And in this process, you know, words really do matter. Prior to my current position, I worked at a teaching hospital, a large teaching hospital, and every day I would hear my residents say I'm going to go talk to this patient or this family and I'm going to go get consent. And what that means, to me, is that the decision has already been made, the decision has been made by the clinician that the right thing to do for that patient, for that

family to do, is to agree to what it is that I'm going to go offer them, as opposed to the idea that what we're really trying to do is to gain an understanding of that individual's goals and values and assist them in making a decision for themselves that is consistent with that.

So valid informed consent really requires five things. It requires that consent is given in a truly voluntary manner; that the individual of which we're asking consent from is competent and they have adequate decision-making capacity to provide that consent; that there's been disclosure of the necessary information for them to make such a decision and that it has been given in a way that there is true understanding; and then that that individual provides the authorization for the procedure or the decision that's been made. So, all five of these are necessary for informed consent to be valid.

But the reasonable question to ask, you know, is consent always required? When is consent required? Is it for everything that we do? And it really does depend upon the nature and the consequences of the decision. So, we can think about this in terms of about whether a decision involves ends or means, where an end would be something that involves an important patient value consideration whereas a means would be the way that we get to that end.

So, for example, I might decide that I'm going to get a haircut and I go to the barber; it is a decision for me what style I want my hair cut in. Or I go out to dinner, and I can make a decision as to what I want to eat that night, what I'm going to order. Or I go to the physician, my doctor, what treatment I might undertake for the disease or condition that I have. So those would be important. And whereas the means might be, you know, I'm not -- it's not up to me what scissors the barber uses or how the chef prepares the dinner or how the surgeon, what instruments they use in the course of that operation. So, consent is really always required when it's a decision that's about an ends that involves an important patient value.

Another question that I think is relevant here is when must we be certain to disclose a rare risk of harm? And I think, again, it depends on the nature of that potential harm. What is the likelihood and the magnitude of that harm? The greater the likelihood and the greater the magnitude, then the stronger our obligation is to make sure that that is presented. And what is the likelihood that that disclosure is going to alter a decision? Is it a make-it-or-break-it decision for that patient?

So, we might consider a circumstance. Let's take, for example, an adverse reaction or the risk of an IV contrast infusion. So, the overall risk of that might be about 1 in 1,000 for an adverse event and somewhere on the order of 3 in 100,000 for patient death. So when would we have to disclose that? Consider, perhaps, a patient who comes in and asks that they want to do a whole-body CT scan to look for any potential tumor that they feel concerned that they might have, as opposed to the patient who presents with a sudden unexpected loss of consciousness and needs a head CT. So, I think that the obligation to be sure that that decision is informed, but those facts vary, really, depending upon the circumstance of that patient.

So, I think of this when I see patients and talk to their families, that it's clear that patients really have a varying degree of informational need and people live somewhere on a spectrum and some patients may really have a high degree of informational need and they want to know everything, they need to know every single detail about what's going to happen, whereas others are much more comfortable down the other end of it there and they don't want to know. Doc, you just make the decision, tell me what I need to do. And similarly, clinicians live on the same spectrum where some are much more comfortable providing everything, every possible thing to the patient, and others really want to just give the bare minimum. And, of course, our role and our obligation as a clinician is to find that sweet spot, and we really have to determine for each individual patient where is it on the

spectrum that they are. There is, of course, some minimum necessary amount of information that we're not going to let the person out of the room without them hearing this. There's some body of information that everybody has to know, but then we do have an obligation to tailor that to each patient that's there and find for them what is their sort of key information.

And the most important thing we have to do to get that is we really have to listen, we have to be willing to sit and take the time and listen and understand for each patient where it is that they live on the spectrum.

So, thank you.

DR. LEWIS: Thank you.

We'll next hear from Dr. Lynn Jeffers, who will discuss the American Society of Plastic Surgery and the Plastic Surgery Foundation's commitment to patient education, safety, and research.

DR. JEFFERS: Thank you for the invitation today. I'm Dr. Lynn Jeffers. I'm a practicing board-certified plastic surgeon in Ventura County, California. Most of my surgical practice is breast surgery, and the safety and well-being of my patients is, of course, of paramount importance to me.

But exactly 1 year ago to the day, actually, it became very personal when I was diagnosed with breast cancer. In the last year I've had surgery with tissue expanders, radiation, and I'm actually still actively undergoing chemotherapy and my last dose a week ago. So, as you can imagine, this explains the hat, and as you can imagine, I'm very happy to be here for many reasons but especially to talk to you about the commitment of the American Society of Plastic Surgeons and the Plastic Surgery Foundation to patient education, safety, research, and advocacy.

As a past board Vice President of Health Policy and Advocacy, I'm very proud to be a

part of ASPS. We are the largest plastic surgery specialty organization in the world. ASPS represents 93% of all board-certified plastic surgeons in the United States, including international members from more than a hundred countries. The Plastic Surgery Foundation, as you heard earlier, is also the philanthropic and research arm of ASPS.

We believe in fostering innovation in plastic surgery, setting the highest standards for the practice of our specialty, and advancing the quality of life for our patients through education, research, and public awareness.

We strive to be the go-to partner and collaborator for our physicians, patients, industry, and government, starting with the FDA. As Dr. Pusic noted yesterday, we worked closely with the FDA to develop both the PROFILE and the National Breast Implant Registry. We've also been an active and interested partner in the FDA's Medical Device Epidemiology Network, which led to our invitation to the Women's Health Coordinated Registry Network as well as the other organizations above. Our society has a proven track record serving as a trusted collaborator on patient safety, quality research and advocacy, and we look forward to continuing this leadership in this important work.

These are some of the tools that our society has developed to protect our patients and ensure quality. Our Patient Safety Committee monitors and evaluates health policies, accreditation standards, and publications that impact patient safety. Our Quality and Performance Measurement Committee actually produces clinical practice guidelines and establishes validated performance measurements that are used nationally for plastic surgery. Concurrently, we have a BIA-ALCL Committee and a Women's Health and Devices Task Force that continues to research ALCL and other implant-related issues.

For the last 2 days you've heard about the need for more research and more data and ASPS/PSF has a robust research program which funds over $900,000 of investigator-directed research each year. And through our clinical trials network, our infrastructure

allows us to conduct our own studies, including multicenter trials.

As you've heard over the last 2 days, we've invested nearly 20 years into creating and evolving our patient registries, and ASPS does agree with the Panel that the registries are an important part of the future of patient safety, quality, research, and health policy.

Now, recognizing that integrating with physician workflow is important, the EMR integration with our registries was launched actually in 2018, currently with select EMRs, so that when the data is entered into the surgeon's EMR, it automatically populates into our registry. We will be extending this to the NBIR and to other EMRs in the future.

The goal with our registries will always be to gather structured, validated, quality data so that we may reach conclusions with the assurance that they are backed by good science.

So, as I was sifting through some of the recent key events that have occurred in terms of implant science and education to present today, I realized there really are three main timelines that are parallel but interrelated. So, they're infrastructure, science, and education. And as you can see, one event in one area actually supports advances in the other.

Evidence-based determinations take time, as we all know, but good quality research is crucial for the safety of our patients. And our decades-long commitment to laying down these blocks has led us to where we are in the world of quality research and education today. ASPS/PSF looks forward to utilizing this infrastructure and this culture of safety to address the quality and research needs of our patients and our surgeons.

We firmly believe that patient voices are critical to the integrity of our work. In fact, we have actively sought our patient perspectives and inputs. We actually have three public members currently on our board and on a number of our committees, including our Women's Health and Devices Task Force and the National Breast Implant Registry steering

committee. Their voices have been critical to our mission and strengthen what we do.

ASPS also believes that outcomes reported by patients are an important consideration in research. And, in fact, back in 2015 and 2016, PSF convened the Patient-Reported Outcomes in Surgery Conference dedicated to this very topic. The PSF has funded the study and development of validated patient-reported outcomes that you heard about earlier, and these tools such as the BREAST-Q, FACE-Q, and WOUND-Q, which have been used and have been able to merged into our registries where applicable.

So, this is a missing link, we've talked about it, the link between clinical outcomes and the outcomes as the patients experience them. And as a patient now, I certainly now have a much better multidimensional perspective on the procedures that I just performed so routinely in my last 17 years.

I became a doctor to improve my patients' lives, and ASPS and PSF seek to understand that patient perspective and advocate for our patients. Just as we advocated for the Women's Health and Cancer Rights Act, which mandated coverage for mastectomy reconstruction, which I'm very thankful for, and the Breast Cancer Patient Education Act, we will also advocate for the coverage of BIA-ALCL patients and other medically indicated breast implant-related issues. In fact, in 2017 we developed an insurance coverage criteria document for BIA-ALCL, and additionally, a resolution is currently being crafted to be presented to the American Medical Association in the upcoming year as one step in this advocacy effort.

It's our belief that advocacy starts with education and includes not just the halls of government, but also public space and surgeons' offices, and ASPS is committed to surgeon, patient, and public education utilizing current and emerging tools.

So to that end, we know that everyone learns differently, people get their information from different sources, so we plan to continue to use our in-person venues

such as our annual meeting and clinical symposium, as well as our publications such as our journal *PRS*, which is the leading plastic surgery journal in the world, reaching 17,000 subscribers monthly, and our *PRS Global Open*, which reaches approximately 24,000 visitors to our website each month. And, in fact, in 2019, *PRS* published a supplement dedicated to ALCL. We're looking to issue regularly updated advisories, as we have, and in addition to our usual society communications.

Next, for our patients, our ASPS website is a trusted resource for more than eight million visitors annually. Plasticsurgery.org features news from the specialty, procedures from options and public Ask a Surgeon program. Specifically, regarding breast implant safety, plasticsurgery.org helps inform patients with a downloadable brochure, quick facts, and patient safety advisory which is updated at least twice a year with new clinical insights.

The ASPS website also hosts dedicated ALCL resources for physicians, including NCCN guidelines and free CME courses. In addition to the website, we will continue to advocate and educate through our social media platforms and through our partnerships with patient groups and other organizations.

Yesterday and today we heard from women who called out the importance of proper informed consent. We wholeheartedly agree that women should be fully informed by their surgeons. And ASPS has actually created standardized patient consent forms for over a hundred common plastic surgery procedures, including at least eight that deal specifically with breast implant procedures. All of those consent forms include ALCL among the other complications that are listed. Our Patient Safety Committee subject matter experts actually regularly review and update this content. This is just a sampling of what comes from that consent form.

However, as we just heard, we all know that informed consent is not just a piece of paper. It's a process centered on the patient. And informed consent is only successful if

the patient understands it on their terms. We will continue to champion the education of our surgeons and our patients and offer tools to facilitate this informed consent process.

Patients each have different needs, different experiences, different outcomes, which sometimes makes standardized policies and approaches a challenge. As data and research improve, we should strive to move science forward so that each patient is presented with options tailored to that particular individual. We've talked about subsets of populations today. The infrastructure that we have built is an important part of that vision. ASPS/PSF will continue to partner with you, our surgeons, our patients, and the public in the pursuit of patient safety, quality, research, and advocacy.

Thank you.

(Applause.)

DR. LEWIS: Thank you very much, Dr. Jeffers.

Last, we will hear from Dr. W. Grant Stevens regarding the American Society for Aesthetic Plastic Surgery and Aesthetic Surgery Education and Research Foundation, in regard to data collection and scientific data-driven research to support physician education and patient access and choice.

Dr. Stevens.

DR. STEVENS: Thank you very much. Good afternoon to all of you. My name is Dr. Grant Stevens. I am the President of the Aesthetic Society, a board member of the Aesthetic Surgery Education and Research Foundation, also known as ASERF, and a board-certified plastic surgeon. The Aesthetic Society is the leading membership organization for cosmetic plastic surgeons certified by the American Board of Plastic Surgery. As such, we are the go-to organization for education, research, and advocacy involving all cosmetic procedures, including breast implants. The Aesthetic Society has more than 2,000 active members. We conduct, support, and disseminate independent data-driven research which

facilitates ongoing communication between patients and surgeons, vital to the care of our breast implant patients.

As the representative of the Aesthetic Society and of ASERF, I want to address some of the top issues and concerns that I have heard yesterday and today, including the need for more better data and the need to preserve patient choice and to trust the women to make their own decisions which have been so well articulated by the patients throughout this meeting.

At the Aesthetic Society, it is part of our mission to improve the data and the overall information sharing amongst our physicians, enhancing their education and training in regard to BIA-ALCL and other potential breast implant-associated systemic conditions.

Tracking of ALCL emerged in 2011, but for far too long, too many physicians were unaware of its existence, let alone how to screen for it and how to talk to patients about it. Physicians need to be aware of the latest data regarding this condition, or any other breast implant-related issues, to better serve our patient community. That is exactly why ASERF was founded in 1993, to identify and pursue issues relevant to advancing the safety and effectiveness of aesthetic medicine. We do this through independent, unbiased, and directed research as well as groundbreaking education.

ASERF has funded 36 clinical studies in the past decade alone. Currently, ASERF is funding three breast implant studies. One led by Marshall Kadin on the pathogenesis of ALCL will shed light on the detection and the quantification of cytokines as well as help characterize cells producing these cytokines. This can facilitate the identification of premalignant precursors to ALCL. It will also help identify IgE targets to shed light on the pathogenesis of ALCL and potential strategies for tumor prevention.

The second study is being led by Dr. William Adams. Dr. Adams will scientifically evaluate different breast implant irrigating agents for biofilm prevention as well as establish

biofilm eradication.

The third study is being led by Dr. Robert Whitfield, President Elect of ASERF. His study pertains to BII or systemic symptoms in breast implants and will examine specific genetic markers like the MTHFR gene.

We all need the best science available to facilitate both physician and patient education. This is informed consent in the true sense of the words. Patients deserve to know the benefits as well as the risks of different types of breast implants.

At this meeting I've also heard that we need a patient checklist to facilitate informed consent, a patient follow-up, and ongoing patient monitoring. As you heard yesterday and today, at the Aesthetic Society we have embraced a new digital technology as a means to this very end, to improve informed consent and to add to our growing body of data. Three years ago, the Aesthetic Society partnered with technology development firm Anzu to develop the Aesthetic Neural Network, also known as ANN, a unique, user-friendly, electronic, fully automated data collection system that can gather and evaluate customized long-term data, both retrospective and prospective.

Today, ANN is a very robust data-sharing cooperative that members of the Aesthetic Society can join to share their unidentified practice data and learn from experiences of other surgeons. ANN now features 240 data sources, 3.6 million standardized mapped procedures, and more than 730,000 patients, including more than 144,000 breast implant patients.

Yesterday you heard Drs. McGrath and Rogers say that the single biggest problem with registries is the need for manual data entry and subsequently, physician compliance. We believe we have solved the problem with ANN. ANN allows for automatic data extraction, what we call frictionless data entry, all built around the physician's practice calendar. This means I can scan my implants at the time of surgery and the data fill will

automatically self-populate with a template customized to my practice, and it still allows me the chance to change the details if I need to.

That, in itself, is so exciting to me personally, but ANN is much more than just this. Patient survey forms and peer-reviewed articles and videos are also featured on ANN. Physicians can join a study or activate a patient in a study protocol. ANN also features long-term breast implant tracking and surveillance with data that can be shared with the National Breast Implant Registry.

All patient data collected in ANN is anonymized and de-identified in compliance with HIPAA Safe Harbor laws. ANN also includes a patient app which can facilitate the collection of data from patients and improve long-term monitoring and follow-up. For example, instead of having to come in for a visit, a patient can answer a few simple questions on their app, which would be entered in ANN. This is a win-win for everyone seeking credible, quantifiable data with discernible sources as a support to the national registry.

While ANN will embrace our communication with our patients, nothing will ever replace the face-to-face dialogue that occurs between a physician and their patient. I want to emphasize that as plastic surgeons, we listen to our patients. It is the core part of who we are as physicians. I am pleased to say that the Aesthetic Society was the very first organization to ever reach out to the largest expert ALCL patient advocacy community led by Jamee Cook and Terri McGregor, who you heard from yesterday. Member surgeons of the Aesthetic Society, in conjunction with the Plastic Surgery Channel, have partnered with this impressive group of patient advocates to further awareness and education about ALCL as well as the key challenges and the advancements of its treatment.

There's one last issue I'd like to address here today, and that is the issue of informed patient choice. We strongly support patients who have testified here over the last 2 days in their drive for more data and information. Implants are patient's personal choice, and we

want to ensure that they are well informed when making their decisions.

Importantly, we must be cautious in making any decision that would ever hinder our patient's right to informed choice. Textured implants or, in certain cases, specific brands of textured implants have been banned in a few countries overseas. Should we be taking away options from women seeking breast implants?

As Dr. McGrath said yesterday, there are certain clinical situations where we need textured implants to get the very best result for our patients. Individual patients have specific needs, goals, and other factors driving their personal decisions. They deserve to be informed of the risks associated with implants and the various choices available. Provided with the most up-to-date information, they are well equipped to make their very own informed decision. We believe that ASERF's funding of pertinent research and the inclusion of ANN will benefit all patients and the field of plastic surgery in this and many other ways.

On behalf of the Aesthetic Society and of ASERF, I would like to thank the members of this Panel and the FDA for overseeing the ongoing process to evaluate the risks and benefits of breast implants. All of us here today share common goals, increasing transparent informed dialogue and collaboration between physicians and patients, embracing new technologies to better fuel the data collection, and sharing and conducting more research to get better answers on all fronts.

Thank you very much for your time and attention.

DR. LEWIS: Thank you very much, Dr. Stevens.

I'd like to now ask all of the presenters this afternoon if they would assemble behind the podium. We have about 15 minutes for questions from the Panel. It can be directed to any of those who have presented. We heard a good deal of information, and I suspect there will be quite a few comments.

I would like to actually lead off with a question for Dr. Destounis. If you would come

to the podium microphone, I'd appreciate it. In your presentation you did not make a clear distinction between ultrasound and high-resolution ultrasound, and I want to ask if that's because there is no difference between them or if the two are actually different technologies, and if so, is there a limitation to the availability of high-resolution ultrasound?

DR. DESTOUNIS: So, at the time that the ACR committee panel met for the appropriateness criteria, they discussed ultrasound, which is the high-frequency breast ultrasound that we perform, whether handheld or the automated, but we did not specifically look into high-resolution ultrasound. The technology looks very promising and very interesting, but it's evolving and currently, the studies are small studies that are out there, and it has not been considered as the standard of care for implant evaluation.

DR. LEWIS: So high-resolution ultrasound equipment, then, is not generally available at the present time?

DR. DESTOUNIS: At this time, I mean, a very busy practice, we see, you know, over 100,000 women a year, and all I do is breasts, and we do not have high-resolution ultrasound at this time; it's not available to us, no.

DR. LEWIS: Okay. And then just a last question. You presented several different scenarios about women who have symptoms, but specifically now, is your recommendation from the college that women who are asymptomatic and perhaps beyond a certain duration would be adequately served by ultrasound as it is currently available in most places as a screening tool?

DR. DESTOUNIS: So, the American College of Radiology appropriateness criteria that came out for implant evaluation, there was no indication for screening for asymptomatic women. That's why I concentrated on if the patient comes in with symptoms, does it change in the breast exam, then we discuss the different scenarios that were age related. Less than 30, you would do a breast MRI, no contrast, or ultrasound may be indicated; 30 to

39, MRI, no contrast, ultrasound or mammography, whether 2-D or tomosynthesis; and the women over 40, diagnostic mammography, 2-D versus tomo, you know, and also the MRI. But yeah, for asymptomatic women, there were no criteria for screening.

DR. LEWIS: So, you don't support the current FDA recommendation of substituting ultrasound for MRI in asymptomatic women?

DR. DESTOUNIS: So, looking at the current literature, which is a pretty extensive review that this expert panel went through, they found that many of the studies had quite a selection bias and most of them included symptomatic patients and not just asymptomatic, you know, silent rupture patients. So, they looked at, you know, several hundred articles and meta-analyses, and they came up with a bias of the data that was a bit conflicting, so there was no recommendation at the time given for asymptomatic patients.

DR. LEWIS: Okay. Thanks for all that clarity and what you presented.

DR. DESTOUNIS: Okay, thank you.

DR. LEWIS: I would like to turn now to other questions.

Dr. Portis.

DR. PORTIS: Can I follow up with you, Dr. Destounis? So, you said then that at age 40 up, that there's -- and your slide said there's disagreement about using ultrasound for breasts, so why does it change at that point?

DR. DESTOUNIS: So, for the 40 and over group, the thought was that really if there was -- so intracapsular rupture with ultrasound is very operator dependent and, you know, when you see the step ladder appearance, you're like great, but you frequently will not see it for many reasons. So, really, MRI you need if you're looking for intracapsular rupture, but for the extracapsular rupture, typically mammography is very good for the women 40 and over, and it wasn't that there was disagreement amongst the panel that ultrasound is not good for extracapsular rupture, but you'll see the snowstorm appearance. They were just

thinking about do you need to do that? You can just do the mammography, and that's what -- and plus, the women 40 and over are of the age for screening guidelines and for -- you're looking for cancer, also. So, they thought come down, you know, hard on the mammography.

DR. PORTIS: A follow-up. So, for women who have had implants for reconstruction, though, mammography would not be an option?

DR. DESTOUNIS: So that's true. That's true. So, mammography would not be, unless there was -- you know, you can certainly image a reconstructed breast with mammography, and if there was extracapsular rupture, that could be identified.

DR. PORTIS: Thank you.

DR. LEWIS: Dr. Anderson.

DR. ANDERSON: So, about the screening question. If we're using MRI to look for rupture and these are breast cancer patients, what you told us was actually we don't use contrast when we're looking for rupture; if we're not looking using contrast, we're not using gadolinium, and that means we're also not looking for cancer.

DR. DESTOUNIS: So, if the patients, if you're also looking for cancer, obviously these are breast cancer patients and there's concern there, we would be using contrast, with and without, absolutely, not -- these were screening patients. Sorry, incorrect.

DR. ANDERSON: So, the reason I got to that is that there's a lot of debate about screening with MRI for cancer because MRI has a 20 to 30% false positive rate. So in the scenario you get the MRI, oops, she's a cancer patient, I'm going to add contrast, oops, 1 out of 4 of them are going to need an additional workup and potentially an MRI-guided biopsy. Now, if insurance covers that, that would be good, but if somebody's paying out of pocket, I mean --

DR. DESTOUNIS: Right, it gets -- I mean --

DR. ANDERSON: -- you're saying, in our places, you can't just have one MRI.

DR. DESTOUNIS: It becomes cost prohibitive, obviously, for the patients if the insurance may not cover it. If we walk through this together, there's a patient that presents and they're a breast cancer patient and there's a finding and that patient then, if the finding is identified on MRI, frequently they can have a targeted ultrasound, which then may identify the abnormality or answer the question. It's a cyst, it's a cluster of cysts, it's benign, or there is something that could be evaluated further with ultrasound. Then the biopsy becomes under ultrasound and not an MRI-guided biopsy.

DR. ANDERSON: But it would not work for non-mass like enhancement, for example?

DR. DESTOUNIS: Right, for non-mass, absolutely. If you do have non-mass enhancement, then you would -- you know, you would have to proceed with an MRI-guided biopsy. I do think that a lot of the false positives with MRI, maybe there's a lot of -- there's a lot of differences in the literature and the peer-reviewed literature about the false positives and I do think that that is an issue. I feel like with improvement in the techniques and the technology of MRI and also the improvement with the high-frequency ultrasound, I think a lot of these questions could be answered without the MRI-guided biopsy. But for the non-mass enhancement, I agree with you; they have to go to MRI-guided biopsy.

DR. LEWIS: Dr. McGrath.

DR. McGRATH: I'd like to ask the manufacturers or the leadership of the societies to answer this question. All of you made presentations about how much information you make available and it's quite extensive, but we heard a lot of patients over the last 2 days say they get too much information. How are we going to solve this puzzle of meeting both the provision of the details that they're already getting and the sense that it's overwhelming?

DR. JEFFERS: Well, as you already know, having been recently a patient, but of course I had an advantage since this is what I do. But I can tell you that, you know, I didn't need as much talking about the plastic surgery part, but when it came to oncology and radiation and everything else, even though I'm part of the center, I never thought about some of the details and the exact permutations of those choices. And this is my personal bias. I usually fall on the side of more information is better.

However, to your point, Dr. McGrath, it's important, that's why they come to us, right? I mean, that's the difference between looking up everything and talking to all your friends, which are great sources of information, but then it's our job as physicians, when they come in, to help them filter that, help them figure out what parts of those things are relevant to them and what parts of those things aren't relevant to them.

So, whether it's an answer we want, basically we have to tailor what we say to each individual patient. Even if a patient presents with you with the same stage and the same breast cancer, you and I all know that all patients are different, and each patient's tolerance for what information they can take in for that moment is different, and part of the art of practicing medicine is learning that and understanding what your patient's needs are. But at least in the backdrop, we give them the website, we give them brochures and so that when they are ready to take in that information or if they wish to look at that information, it is available to them. Does that answer your question?

DR. LEWIS: Dr. Leitch.

DR. STEVENS: Thank you, Dr. McGrath.

I'd like to elaborate on that. I agree entirely with Dr. Jeffers, but also in addition to that, at the Aesthetic Society, with the use of ANN and the patient app, the patients will be able to download and interact and communicate in ways that up until now we've never been able to. So, it will be interactive, they can refer back to their app whenever they wish,

prior to, during and after their procedures, and ongoing communication will be relevant and contemporaneous and will keep up to date. So, this new way of communication will facilitate better informed consent as an ongoing process, and as we discover new issues, perhaps, and new ways of monitoring, we can communicate with our patients through this wonderful app called ANN.

MS. d'INCELLI: One thing to add a little perspective from the manufacturer side. All of the content in the informed decision brochure is required content through the FDA and through studies, so it's every possible potential risk, benefit, all of the data, all of the considerations, the different types of surgery and risks from surgery, it is all in there. It was reviewed with a patient focus group to try to best understand the best wording. It's worded at about a tenth-grade level, so it's intended to be understood by the patients.

And we do understand it's a lot of information. That was one of the feedbacks from the patient focus group. And, in addition, there's a smaller version, it's about an eight-page summary version of it that does include the key points within that, so those are provided as well, in addition to instructions that the surgeon should discuss all of these with the patient and sign the consent. So, clearly, that isn't always transpiring in that way, the intended way, but that's the current status and so I look forward to some collaborative discussions on a way to improve that.

DR. LEWIS: Dr. Jeffers and Dr. Stevens, we've heard from the audience on three sessions that one of the big problems is not only the adequate informed consent for patients but awareness of doctors in multiple specialties in regard to an awareness of breast implant illness and ALCL. There seems to be generally a very widespread unawareness of much of that. Do either of you have strategies in your organizations for any doctor education that would improve that?

DR. JEFFERS: Well, of course, we base our, you know, core -- one of our core

missions on education. So, as I said in my talk, first, in general, that education, as I stated, I think everyone learns a bit differently. Especially in this modern age, we have to make sure that we are providing education in a way that people want to learn. So, in addition to the traditional in-person meetings that we have, we have a big annual meeting, but we also have a number of clinical symposia that are dedicated to certain topics or certain topic areas. In fact, one we have is a breast and body symposium. We also dedicate time to, of course, publications, our websites and social media. So, we're trying to utilize everything we've got in our toolbox to get people -- get the information out there.

As far as people being informed, and as far as especially about ALCL, I happen to be on the board about -- well, a little bit, almost a decade ago now, when ALCL first came to our attention and I remember sitting there and a lot of us talking about what to do with this because it just had been a random report and we were concerned that, you know, how do we get to the bottom of this because we want to know, as patient advocates, we want to know if there's an issue. And so, there was constant talk about how to get this education, how to get more data, but then how to do a measured education of our physicians without alarming people because we didn't know enough data, as we don't know enough now, but we certainly knew even less then. So, there's that fine line in learning to -- when to educate and how much information at that time until we knew.

What I will say is that since that time, as I showed in some my slides there, we built that infrastructure in the three different timelines of having an ALCL committee working with other organizations, working with other outside organizations, creating the PROFILE database registry and trying to get down to figuring out how to disseminate this information. I do think that we have -- we've put in a number of -- I definitely think that the awareness of ALCL is much higher now, especially in the groups that I'm in and the social media groups that I'm in that discuss this.

DR. LEWIS: Okay, thank you.

Dr. Stevens, if you could make it short, we're just about at the end of the session.

DR. STEVENS: Yes, sir. In addition to the areas that Dr. Jeffers was talking about, the Aesthetic Society has a task force specifically for ALCL, another one specifically for BII, and we have our meetings. We also have the ASERF, and as I mentioned before, ANN allows us to communicate with our physician members and keep up to date. But that's not the problem here. The problem is the lack of informed information to the non-board-certified plastic surgeons.

I would appeal to this Committee to consider to raise-the-bar and to appeal to the companies to distribute these products to the highest level, the most trained physicians and surgeons who are uniquely board-certified plastic surgeons. It's more than simply putting it in. It's putting it in, monitoring, and taking care of the patient for the duration of the time that it's in the patient, and finally, in that unlikely event that they need help, it's accurate and prompt diagnosis and treatment.

When these devices are distributed to non-board-certified plastic surgeons, we have no way of educating them. We don't know how they're putting them in; we don't know if they're using accredited facilities. How do we educate them on an ongoing basis, and how are they possibly going to know how to take them out when they're not surgeons in many cases? I would appeal to the Committee to go back to their original feelings that they did that last time you met and reconsider asking these manufacturers to distribute to the very best trained board-certified plastic surgeons. Thank you.

(Applause.)

DR. LEWIS: Thank you.

I want to thank all for an excellent series of presentations. We're a little over time, and we've got a lot to cover still, so I have to call an end to this session. We'll now take a

10-minute break and return at 3:20.

(Off the record at 3:09 p.m.)

(On the record at 3:21 p.m.)

DR. LEWIS: I'd like to call the Panel back in order, please. Everyone please take their seats.

(Pause.)

DR. LEWIS: We will now proceed with the afternoon session of the Open Public Hearing. For the record, all Panel members have been provided written statements received prior to the meeting for their consideration. During the hearing, public attendees are given an opportunity to address the Panel, to present data, information, or views relevant to the agenda.

Commander Garcia.

CDR GARCIA: Thank you, Dr. Lewis. Everybody please take your seats. We're beginning the meeting.

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the Open Public Hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentation. For this reason, FDA encourages you, the Open Public Hearing speaker, at the beginning of your written or oral statement, to advise the Committee of any financial relationship that you may have with any company or group that may be affected by the topic of this meeting. For example, this financial information may include a company's or a group's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you, at the beginning of your statement, to advise the Committee if you do not have any such financial relationships. If you choose not to address this issue of financial

relationships at the beginning of your statement, it will not preclude you from speaking.

Thank you, sir.

DR. LEWIS: We'll now proceed with the public hearing under the same ground rules as we've had for the others. We need a strict 3-minute limit. We have 22 speakers scheduled, and we have an hour for this session, so we need everyone to adhere strictly to the schedule in order to allow the later speakers to be heard. We'll begin with Dr. Michele Shermak.

DR. SHERMAK: Good afternoon and thank you for allowing me to address the FDA today. I have no conflicts. I'm a board-certified plastic surgeon who trained at Johns Hopkins. I was a fellow in Nashville focusing on breast surgery. After this extensive training, I was on the staff at Hopkins for 11 years, and I'm now in private practice in Baltimore. I am the reconstructive surgeon for a very active community-based breast cancer practice at the University of Maryland St. Joseph Medical Center in Towson, Maryland.

Plastic surgeons increasingly depend upon silicone gel implants for their patients. Relative rates of silicone gel breast reconstruction are rising, particularly in centers that used to primarily perform tissue reconstruction. Why is this? Because silicone gel implant reconstruction is associated with lower morbidity, length of stay, and cost than flap reconstruction for abdomen, back, or buttock. In my practice, I also depend on the excellent track record for gel implants with cosmetic breast augmentation patients and massive weight loss patients, who suffer significant breast deflation and chest deformity.

Nipple-sparing mastectomy has increased in prevalence over the past 2 decades and has become our go-to mastectomy for women with breast cancer. It pairs optimally with a media gel implant and ADM reconstruction. It allows for a one-and-done reconstruction with aesthetically superior results. Recovery is short with limited morbidity, and with the

more cohesive gel implants, they feel more breast-like and lead to less rippling, particularly relative to saline implants.

Prepectoral reconstruction with round gel implants and ADM limits animation deformity and discomfort. Prepectoral placement with ADM results in far less contracture after radiation therapy. Furthermore, implants are great for contralateral match in reconstruction, and implants with scaffold provide better symmetry. Our breast cancer reconstructive patients are achieving high-level aesthetic outcomes with off-the-chart levels of confidence and satisfaction.

In my 21-year professional experience, I really have not seen troublesome outcomes from gel implants. I really have not seen any breast implant illness or ALCL patients before the Panel today. My cosmetic and reconstructive patients might have contracture, rupture, or seromas that are treatable without grave long-term consequences.

I believe it is important to maintain availability of silicone gel breast implants and ADM for their acceptable safety profile. We need to continually monitor implants with registries in conjunction with the FDA. We need to inform and educate patients on true science, and we need to provide optimal aesthetic outcomes and recovery for our breast cancer patients.

Thank you.

DR. LEWIS: Ms. Carol Small.

MS. SMALL: Thank you for the chance to speak today. My name is Carol Small, and I traveled from North Carolina without compensation.

I am a reconstructed patient, and in 1999 I was implanted with one McGhan saline textured implant. All was well with me until it no longer was. I've shortened my litany of misdiagnoses. One oncologist, one plastic surgeon, two radiologists, and one urgent care for pain. My symptoms included pain, swelling, fluid, and looking really misshapen. Years

into my symptoms, I was finally diagnosed with BIA-ALCL plus CD30 after an incidental testing during an implant exchange. Two on your Panel suggested all tissue not go to pathology. My ALCL would have been missed.

Post-surgery, I was told by the oncological surgeon that he was unable to remove the entire capsule as it was stuck to my ribs. He said he could see rib nubs and I had to keep you safe, so I just closed you up. The ALCL ate my ribs.

Six cycles of CHOP chemotherapy followed because tissue was left behind on my ribs. Prior to chemo, my heart was healthy, as shown by an echo. After chemo and not feeling better, I am currently diagnosed with, and treated for, chemo-induced heart failure.

I wish to address the manufacturers and those women we heard from yesterday, telling us how wonderful implants are. Like myself, women with implants may love them until their implants cause this manmade cancer or breast implant illness. Please listen to us. Individually, we are underdiagnosed and make up a small fraction of those injured by implants. But we have suffered mightily, and the FDA, you have the power to stop other women from the same fate.

Please understand that my manmade cancer and subsequent heart failure could have been avoided if the following had taken place:

1. Had I been warned that the textured implants cause BIA-ALCL.
2. Had my oncologist been informed of my signs and symptoms that they were ALCL, that my cancer may have been avoided.

There are many requests from you. Ensure that all medical practitioners know and understand the disease and its presentation. Ensure that patients, these women, are properly informed and warned of the risks of ALCL. Remove textured implants from the market that has been done in over 30 other countries. ALCL is a devastating diagnosis, especially after breast cancer. It was mentioned yesterday that the statistic is 1 in 80,000.

We remind the Panel that the statistic in Australia is 1 in 1,000, and for those of us diagnosed, it is a very big deal. Earlier detection is important, but it isn't the same as saving a women from getting cancer. Breast cancer patients need to know what risks they are taking when they choose textured implants.

Thank you very much.

(Applause.)

DR. LEWIS: Ms. Varuna Srinivasan.

DR. SRINIVASAN: Good afternoon. I'm Dr. Varuna Srinivasan, a physician with an M.P.H. from Johns Hopkins, speaking on behalf of the members of the Patient, Consumer, and Public Health Coalition, a group of nonprofit organizations representing millions of Americans. We have no conflicts of interest.

FDA has been slow to recognize the full impact of BIA-ALCL and needs to do more to protect women from it. Scientists first reported the association between breast implants and ALCL in 2008, but patients didn't hear about it. It was another 3 years before FDA and the media first acknowledged the possible association between breast implants and ALCL. The link was strengthened in 2013 with the MD Anderson Cancer Center study of 60 women with BIA-ALCL. The next year, the NCCN released a worldwide oncology standard for physicians to test and diagnose BIA-ALCL.

In 2016 the World Health Organization added BIA-ALCL to its classification of lymphoid neoplasms. The FDA website did not acknowledge that implants sometimes cause ALCL until 2017. Before that, the vast majority of women considering breast implants were not informed about the risk of ALCL from implants, especially textured implants. We now know that BIA-ALCL is more common than we first believed. Australia's superior surveillance system has estimated it as high as 1 in 1,000 women with breast implants. The delayed intervention of the FDA and surgeons everywhere on this matter is too serious to

ignore. For those women who were barely informed of these severe risks, it has had terrible and sometimes fatal consequences.

What should FDA do to help protect women from ALCL? Research indicates that at least some textured implants should be banned because they are most likely to cause ALCL. FDA should conduct or require research to determine if the benefits outweigh the risks for any textured implant. FDA should require training for physicians and informed consent studies with breast implant patients to evaluate success in explaining the risks.

As a condition of approval, FDA should mandate that a two-page checklist explain all the local complications, adverse outcomes, and frequently reported symptoms associated with implants, in an unbiased manner, at least a week before surgery. This checklist should be written by ALCL patients, researchers, and plastic surgeons. Doctors should also monitor their patients regularly for signs of ALCL.

The ASPS registry should also include UDI numbers and to maximize useful information. The FDA should require UDIs to be printed on breast implants. In addition to reoperations and ALCL, registries should also include information about other adverse events provided by patients, oncologists, and other physicians.

Cancer patients and augmentation patients deserve to know the risks of breast implants, and the FDA needs to ensure that happens.

Thank you.

(Applause.)

DR. LEWIS: Ms. Madris Tomes.

MS. TOMES: Thank you. Okay, my name is Madris Tomes, and I have not had breast implants. I'm here today as a data advocate, and sometimes that data shows that I should also be a patient advocate. This is one of those times. I previously worked for the FDA as a UDI manager and as a MAUDE replacement manager, so that was on adverse event

reporting. I also spoke to the FDA panel on mesh just 3 weeks ago.

Breast implants are the single-most reported device from user facilities, which are mainly hospitals. Through February 2019, there have been over 51,000 adverse event reports for breast implants that have been made publicly viewable in MAUDE.

This is a chart that I put together to show how the data looks to somebody that's in the public trying to see the adverse event reports. You can see that there is a huge dip in the adverse event reporting that's available to the public because of the use of summary reports. This does look very different than the chart you saw yesterday, which I dropped in last night. I want you to notice the difference in what the public has been able to see. The difference would be that in 2017, they're showing 50,000 adverse event reports. Only 15,000 of those were viewable to the public.

An adverse event report comes in, and if it's a summary report, you will see a marker. It looks like this, for the most part, in public MAUDE. You can see here that a report that came in in 2017 actually originally came into the FDA in 2004.

Summary reporting should not be allowed by the FDA because it's not easily accessible. You don't know what you don't know.

Device registry data is also not necessarily a good idea. There are 120 device registries for breast implants worldwide. The data is not publicly available, and when outcomes are unexpected, the registry does not measure that outcome. Reporting to a registry does not replace adverse event reporting by physicians.

I'd like to ask the FDA today to speak with the Joint Commission and look into testing of seroma and tissue for explants where BII or ALCL is suspected. I'd also like to recommend a study that's not funded by industry, preferably through an organization like PCORI, the Patient-Centered Outcomes Research Institute, and I think that that would be a really good move to show the public that the FDA cares about this data and really should be

making all of it public.

(Applause.)

DR. LEWIS: Ms. Robyn Towt.

MS. TOWT: My name is Robyn Towt, and I'm a breast cancer survivor. I am here at my own expense today, and I have no conflicts of interest.

I was diagnosed with breast cancer in 2017, and I chose to have a double mastectomy, and I did reconstruction with tissue expanders and these Mentor silicone implants. These were mine, in my body. There are no leaks, there are no ruptures, they are perfect and pretty much just like our new caplets; they're brand new, and they made me horribly ill. I've had cancer three times in my life, and those breast implants were worse than all three of my cancers put together. Keep in mind, I want to let you know I did not have chemo, I did not have radiation. I felt great when I had breast cancer until I got breast implants and they took me down. And I worry for my breast cancer sisters because a lot of them blame their symptoms on chemo and radiation and I had neither. Yet, I explanted after only 4 months, and all of my symptoms disappeared within 1 week. Every single one of them.

So, we've heard a lot these last 2 days, doctors saying that all of their patients are completely happy with their implants. Those surgeons aren't seeing their patients. Their patients are seeing neurologists, endocrinologists, allergy specialists; they're not going back to their surgeons.

So, we're missing the mark here. The system has greatly failed us. The benefits do not outweigh the risks. The majority of the benefits are monetary benefits from the industry people and the surgeons. Not the patients.

We also heard earlier this morning from Dr. Sowder, who talked about social media being a group of women that are feeding off of each other. But our women get better after

their explants, and our women aren't making up bald spots on their head, skin rashes, puffy face and eyes. It's not a placebo effect. We get better after explant.

So, after I found about BII, I joined a group called Breast Implant Illness and Healing by Nicole. I'm also an admin on that group, and we have 70,000 women. So, as I stand here and talk to you, I want you to picture, please, behind me 70,000 women, and if that's hard for you to picture, it's about the size of a football stadium where a Super Bowl would take place.

So, I also believe that if everyone says that BII is rare and ALCL is rare, then maybe the industry should help pay for our explants. If there's not very many of them, then it shouldn't cost that much.

I work closely with the Arizona Society of Plastic Surgeons, and this was my patient information booklet that I never got. I didn't get this until 5 months after my explant, and my Arizona surgeons told me they only get a couple of these in each box with a whole shipment of implants. So, I also talked to a Mentor rep who told me they throw a few in with a whole shipment of implants, but the surgeon is welcome to ask for more and they would be happily provided.

There's a large disconnect. The patients haven't been protected. This has been going on for decades. It's time to do the right thing. You've heard all of our pleas today, the same pleas you've been hearing for the last 30-plus years. I don't even need to name them all; we all know what they are. Informed consent, a patient-doctor checklist. I created one; I have copies. Please see me after the meeting.

DR. LEWIS: Ms. Towt, please conclude. You're way over time.

MS. TOWT: And I will be available for anyone to talk to after the meeting. Thank you for having me today.

(Applause.)

DR. LEWIS: Ms. Caroline Turco.

MS. TURCO: So, my name is Carrie Turco. I traveled at my own expense from South Carolina. I've had breast implants for a total of 2½ years before having them removed. Prior to implants, I was 25 years old, and I was in the healthiest shape of my life. I was working out daily; I was on an organic plant-based feeding diet. At this time, I was also training for a pageant, which I later won, which put me in the running for a national pageant, Miss South Carolina, USA.

Within 2 weeks of getting breast implants, I began to see an overall decline in my health. It started with chronic UTIs, yeast infections, chronic fatigue, and then it rapidly moved into more serious health complications such as inflammation, food intolerances, gut issues, and major digestive problems. Within 5 days of removing my implants, I lost 8 pounds of inflammation. By Week 3, I virtually had all of my gut problems cured, and all of my digestive problems had cleared up.

My goal, as I stand before you, is to bring real change to women who have been negatively affected by these medical devices. Overall, I know there's a general lack of accountability and lack of compassion on behalf of the FDA and the manufacturers whereby these devices originated from. This insensitivity and borderline mockery of the grassroots approach that has been formed on behalf of desperate, sick women who are seeking answers for our health in various blogs, forums, and Facebook groups highlights the general lack of concern and lack of knowledge available to us as women.

I stand here today as the last line of defense between women getting breast implants and women getting sick. Because of the vocal stance I've taken on social media, women are reaching out to me in mass numbers via Instagram, Facebook, and other social media platforms asking me and advocates like myself, are these devices safe? Do they cause cancer? They don't know and they're coming to us. My question is why are these

women coming forward to me? Why are they asking me for health information? More importantly, why have they lost trust in the system, in the surgeons, in the implant manufacturers? Because of this platform, I have a reasonability to give honest and accurate answers to these women, but you've made it difficult to do so.

This is a crucial time in FDA history. You are losing credibility and trust from the American people, and this lack of credibility and trust is starting to transcend into issues that are bigger than breast implants. Sometimes I feel as though you have negligence and cover-ups and they take precedence over ethical practices.

In a lot of ways, you've failed the American people. Where you have failed us, we will pick up. Your refusal to acknowledge breast implant illness and the refusal to provide us with evidence-based information has impassioned us to do what we can do to inform the public and we do this via a grassroots approach, but we need your help. The time is up. We've been fighting this since the '90s, and it is time to stop.

Thank you.

(Applause.)

DR. LEWIS: Dr. Bruce Van Natta.

DR. VAN NATTA: Good afternoon. My name is Bruce Van Natta, and I'm a board-certified plastic surgeon in private practice in Indianapolis and a board member of the Aesthetic Surgery and Education Research Foundation. I'm a medical advisor to Galatea Medical, the distributor of P4HB surgical mesh, and receive advisory compensation. The FDA has requested information on the use of surgical mesh in mastopexy and reconstruction.

Throughout my 30-year career, a fundamental problem in mastopexy is that we're working with skin and soft tissues that have failed and simply can't support the weight of the breast. As a result, we can have recurrent ptosis and further surgeries, and for this

reason, plastic surgeons have sought out an answer and turned to a variety of products to support the weakened tissues.

There have been three different devices used for soft tissue support, including acellular dermal matrix that you heard about this morning, and Seri scaffolds. Seri was found to have a high level of adverse events and has all but been abandoned. ADMs, however, have proven quite effective in both breast reconstruction and revisional surgery.

I'm here to discuss my experience with the third option, poly-4-hydroxybutyrate. This is a synthetic mesh that's FDA approved, it's a monofilament, biologic material, and it's completely absorbed in 18 months. I've used this mesh in more than 400 patients. It acts as a temporary supportive scaffold while being replaced with Type I collagen, and then it's converted by hydrolysis and the CO_2 in water.

I want you to be aware, there has been published a Level 1 randomized study in complex hernia showing that P4HB mesh was superior to polypropylene, a permanent mesh, and ADM, with lower seroma rates and infections.

In addition, I co-authored a publication in the *Aesthetic Surgery Journal* in February of 2018 on a post-approval study for P4HB in mastopexy. This demonstrated the effectiveness of this mesh in maintaining correction of ptosis with very low adverse events and no interference with mammography.

In breast reconstruction, surgeons are currently combining both ADM and this mesh around an implant. This decreases postop pain, produces soft, natural results and low complication rates. And I'm here to tell you, the ability to have a nipple-sparing single-stage reconstruction with minimal complications and a superior result is a tremendous option for our mastectomy patients.

I want to have one point of clarification. This mesh that I'm talking to you about and the ADM are not the same as the permanent mesh that has been used in the treatment of

female incontinence with the associated problems.

In addition to addressing concerns about long-term follow-up, as you've heard, the Aesthetic Society has developed an electronic data collection system, called ANN, that will allow monitoring and data collection in these mesh patients.

In summary, the use of P4HB mesh in my practice has provided excellent soft tissue support. It's improved long-term patient outcomes and reduced revisions, all with minimal adverse events.

Thank you for your time.

DR. LEWIS: Ms. Roxane Vermeland.

MS. VERMELAND: Thank you for allowing me to speak today. My name is Roxane Vermeland, and I am from Illinois. I paid my own expenses to be here today.

I was diagnosed with breast cancer in 2012 and underwent chemotherapy. After having a bilateral mastectomy with textured expanders, I had smooth implants placed. Because my breasts were uneven, my plastic surgeon encouraged me, in 2015, to exchange my implant to the new state-of-the-art Allergan textured implants. I was not informed of any lymphoma risk, even though ALCL risks were already published before 2015.

For over 2 years I had major aching on my chest wall that no physician could explain. After 3 years, my implants swelled and was painful. I researched online and worried I might have lymphoma. My plastic surgeon laughed and said it's so rare, you do not have this. I think your implant just needs to be flipped over and I can flip it back. I screamed in pain as he attempted to flip it. I told him that I felt fluid, and he did an MRI. He did not believe me, but fortunately, he ordered it anyway. The MRI showed fluid and a seroma, so I needed a drain put in. I gave my plastic surgeon the guidelines to the tests for BIA-ALCL that I found online. I asked the radiologist if he had the correct orders to test my fluid because he had never heard of this lymphoma. I made him call my surgeon because I refused to let him

drain the fluid without the correct instructions.

Soon after my drain was removed, I had fevers, chills, and vomiting. The plastic surgeon said it was a virus. Call your primary. My primary said it's an infection. Call plastics back. Barely making it to the ER, I tested positive for sepsis. I was in critical condition and was transferred to the hospital. They had to remove my left implant, and I was in ICU for almost a week fighting for my life.

I went to the Mayo Clinic to have the other implant, both capsules, lymph nodes, and part of my ribs removed. My 3-month PET scan showed I had two more positive nodes that were behind my ribs and could not be surgically removed. I flew to MD Anderson seeking advice from Dr. Mark Clemens, but I eventually went to Mayo and became the first patient with BIA-ALCL to have cryoablation in order to avoid chemo just this January. Unfortunately, 3 weeks ago an ultrasound showed I had developed a mass on my chest wall.

Another PET scan showed activity in my nodes. Two recurrences in less than 8 months of being diagnosed. The thought of going through chemo a second time is terrifying to me. I cried every time I walked through those doors knowing what it was going to do to me.

After doing the research and finding out that the FDA and plastic surgeons knew, prior to the 2015 surgery, that textured implants could cause this lymphoma, I feel sad and angry. It's not fair to me that myself and other women have been kept in the dark over the risk of this horrible disease. Allergan offered me $7,500 towards cost of my surgery if I agreed to never speak about this again. I refused. Because I'm a breast cancer reconstruction patient, I have recently been informed that Allergan and Mentor have released smooth expanders. If textured implants are not a concern, then why have smooth expanders become a priority for the top two manufacturers in the industry? Patients need to be informed of the risks of textured implants. And what's inside those implants. Never

would I have put those in my body. It's tough enough to go through breast cancer, but to get another cancer caused by implants is unacceptable. Please, please make the right moral decision to ban these implants like the other 30-plus countries and hold Allergan accountable.

Thank you.

(Applause.)

DR. LEWIS: Dr. Robert Whitfield.

DR. WHITFIELD: My name is Robert Whitfield, and I'm a board-certified plastic surgeon and member of the Aesthetic Society. I'm the President Elect of the research arm of the society, also known as ASERF. And nothing to disclose.

In that capacity, I am working to identify evidence-based research to better understand breast implant illness and breast implant-associated ALCL. This research will then be used to educate the surgeons and benefit the patients associated. We are committed to sharing this data with healthcare stakeholders in real time.

The Aesthetic Research Foundation has already funded two studies regarding breast implant illness. The first is a qualitative pilot study which will use an Amazon Mechanical Turk to identify a group of women with the symptoms to assess the specific breast variables, and these folks will be asked to complete a symptom inventory, subscales of the BREAST-Q, a validated tool to measure quality of life, and patient satisfaction. The control group will be an age-matched cohort. A subset of these patients will be asked to participate in another qualitative set of interviews to be conducted by naive assessors to assess surgical and medical history, symptoms related to their illness, and treatment-seeking behaviors for this illness. Responses to those interviews will be coded and analyzed for relevant and common themes.

Then we have a second study funded by ASERF on breast implant illness. I'm leading

this study myself. This study is to be completed with an age-matched cohort as well. The patients will be required to complete a standardized preoperative survey and postoperative survey at different time intervals. The explanted specimens from their procedure will be sent for DNA, fungal, and bacterial analysis to determine the exact cause of any biofilm on the implants. Patient DNA analysis will be performed for genetic predisposition specific to things like MTHFR, CMT, and superoxide dismutase mutations.

Data collection for these two studies will be facilitated by the mobile application you've heard of today, the Aesthetic Neural Network, or ANN. This application provides survey tools for the members and the patients, device tracking as well as allowing for aggregating the data in a secure environment.

Breast implant-associated ALCL is a rare lymphoma that has been discussed here already. It consists of a problem with textured implants, biofilm, and genetic predisposition. Using ANN to follow patients being evaluated and treated for breast implant-associated ALCL will be an effective new way to capture and consolidate the data period. It also allows us to use workflows already instilled in the app to make sure that problems like we just heard don't develop. ANN will also allow for enhanced communication with its patients about breast implant-associated ALCL.

The Aesthetic Society's Research Foundation has funded the Aesthetic Neural Network because it is a novel user-friendly technology which will be used to gather and evaluate long-term data from physicians and patients to facilitate informed consent about breast implant benefit and risk.

Thank you.

DR. LEWIS: Ms. Laurie Wieder.

MS. WIEDER: Thank you. My name is Laurie Wieder, and I live in Prince William County, Virginia. I was diagnosed with breast cancer in 2018. I am here to speak for

continuing to make available the widest range of options to women as they face breast cancer.

Before 2018 I, like many people, knew women who had breast cancer but didn't realize the variety of diagnoses, treatments, and so-called solutions. I say so-called solutions because there are no perfect solutions. However, I'm glad I had multiple options, including reconstruction with smooth gel implants.

Receiving a diagnosis of breast cancer is traumatic. One day I was a healthy 63-year-old who enjoys walking and hiking and the next day I alternated between feelings of disbelief and deep grief. While I was fortunate to be diagnosed early, I learned that my physical appearance and perhaps my ability to be active would be forced to change. I was to have a bilateral mastectomy.

I investigated my breast reconstruction options with the help of my doctors, literature they provided, and even Dr. Google. I learned I could simply heal from my mastectomy with a different outward appearance. I could obtain prostheses which might limit my physical activity and my selection of clothing. I could have reconstruction following additional surgery on my abdomen, buttocks, or thighs. This was particularly abhorrent as I did not want surgery on other parts of my body. Finally, I could have reconstruction using saline or gel implants, both of which, I learned, do not come with a lifetime guarantee and, in some cases, have serious complications. In short, there was no perfect solution.

Because I value an active life, I did not want additional surgical trauma to other parts of my body and wanted to return as closely as possible to my pre-surgery appearance, I chose breast reconstruction with smooth gel implants. I understand I need to take responsibility for this decision. I will need regular doctor visits. I must be observant of my body. I understand my gel implants may not last forever. I made an informed decision among less than perfect options.

I do make one additional request. I understand that preventative monitoring, such as the MRIs and sonograms that have been discussed, can help identify problems with my gel implants. But those procedures or this preventative monitoring is not covered by health insurance. I ask that you would support public policy that requires coverage for this preventative monitoring when women have had reconstructive surgery following a mastectomy.

Thank you very much.

DR. LEWIS: Ms. Theresa Williams-Mott.

MS. WILLIAMS-MOTT: I traveled from Michigan, and I'm not being paid to be here and I have no conflict of interest. My name is Theresa Williams-Mott, and I'm known around Detroit as Tracy Barry. I flew in a news chopper reporting traffic and lots of breaking news and sometimes juggling nine things at once. Nine. Your head would explode if I sat here and told you what I had to handle up there. I was running the camera at the same time that I was reporting on a radio station, listening to cues on a TV station that I was holding their live shot for, and then waiting for them to come and take my shot and my report from me. I tell you this for a reason and I'm getting to it.

I had boundless energy, worked out all the time. I didn't have an ounce of fat on me. Loved to work out until 1998. I went and got McGhan textured saline implants. I loved them. Loved them. I was thrilled until I started getting depression, anxiety, chronic fatigue, muscle fatigue, I couldn't work out. Never connected it to the implants. This went on for 20 years and got progressively worse, to the point where I became suicidal. The depression got so bad, and I don't think you're hearing enough about the depression, and I think these reporters in here should really do a study and investigate how many women have committed suicide and had breast implants, because I'm one of them who almost committed suicide.

(Applause.)

MS. WILLIAMS-MOTT: And I'm postop a year, and I have had no depression, none. How did it vanish? Where did it go? Where did the anxiety go? Where did my microphone go? There it is.

(Laughter.)

MS. WILLIAMS-MOTT: My nickname became Dory at the television station I was working at on the morning show because I couldn't remember anything, from *Finding Nemo*. Where are we going again? What's your name? What are we doing? It was comical, but it's not funny now looking back. I was losing my brain.

A year ago, before I had surgery, I handed my husband a piece of paper in the kitchen and said here, put this in the office. He came back 2 seconds later, and I'm spinning around trying to find the piece of paper, and he said what are you looking for? I said I can't find the piece of paper I need you to put in the office. He said you just gave it to me. I stood there in shock and said what are you talking about? He said you just gave it to me. I just put it in there. I have no recollection of this, none. It was a total blackout. I was blacking out all the time. Wasn't drinking. What is happening?

People are not talking about how implants affect your brain. They affect you, they cause anxiety, depression, and they cause suicidal depression. And seriously, somebody needs to investigate this, and I think, shame on you, shame on you, this has been going on since the '90s. My roommate in the hotel on this trip has been fighting you since the '90s. What is going on? What is this? I mean, really, you're just sitting on your hands is what it looks like to me. You're just sitting here and ignoring us, and you're getting paid with our tax dollars.

(Applause.)

MS. WILLIAMS-MOTT: Do something, do your jobs. We're tired of it.

(Applause.)

DR. LEWIS: Dr. Sidney Wolfe.

DR. WOLFE: Thank you. I'm Sidney Wolfe. I'm a physician, and I'm the founder and senior advisor of Public Citizen Health Research Group.

Since the early days, we've been very concerned with the issue of implantable devices such as the breast implant, and in 1973, 3 years before the device law was passed, we testified at a House hearing which was considering new legislation. Our testimony was directed at the deficits of the legislation, which did not have any kind of requirement for premarket testing for all implanted devices or all life-sustaining devices, life-supporting devices, ionization-emitting devices.

Despite our testimony, there was a lot of pressure from the device industry not to have this because it costs more to actually test things before you put them on the market. And so the device industry, which had made a fortune, and we gave examples in the testimony of devices that had gotten people in trouble, killed, because they had not had premarket testing, they stood against it and it was never incorporated, and I'll get back to that later.

In 1989 we appeared before this Panel on the topic of autoimmune disease and cited, by then, some very good evidence as to how the immune system would be stimulated by silicone, Nir Kossovsky published a paper in 1983 on this, and we were very concerned such that a year and a half later we petitioned FDA to ban silicone gel breast implants. This was in November of '91. And there was a moratorium placed on them not too long after that.

Just moving forward, in 2011, a week after the FDA made their announcements about ALCL, a very angry plastic surgeon called me up and he said you won't believe what I'm going to tell you. So, I said what is it? I hear a lot of disbelief about things like that.

And he said there's just been a video conference sponsored by ASPS and ASAPS urging their members not to really admit what ALCL was, and I'll just read you a direct quote from the transcript that this guy sent us.

"Yes, it's a clinically malignant tumor, but it has such a benign course that when we're discussing ways to talk to the media, we decided that we would call this a condition. When we talk to the media, not a tumor, not a disease, and surely not malignancy." And they recommended the same thing be done to women. We got that letter sort of -- the whole thing stopped, and it tells you the other side of these organizations.

Today's conference -- I have about 30 seconds more. Today's conference raises the question by FDA of the fact that these postmarket studies are not being done reliably by some companies.

And I'll end with this statement, which is these post-approval studies to obtain information that should've been studied before, not after, approval remind us why much more extensive mandatory preapproval animal and human testing on such permanently implanted devices is necessary. Otherwise, women or in other cases, both genders --

DR. LEWIS: Dr. Wolfe, please --

DR. WOLFE: -- are too often serving as guinea pigs.

(Applause.)

DR. LEWIS: Ms. April Zimmerman.

MS. ZIMMERMAN: Thank you for listening to my testimony today. My name is April Zimmerman, and I have traveled from Kansas City, Missouri at my own expense.

In 2012 I was a healthy mother of three who had run two half-marathons and decided to undergo a breast augmentation. My board-certified plastic surgeon recommended smooth Mentor MemoryGel silicone breast implants. He said this was the safe new silicone that you could cut in half and it wouldn't bleed. He even showed me an

implant cut in half. The doctor requested a physical, stating I was in good health and we set my surgery date for June and I was very happy with my breast implants.

However, over the next 5 years, my health began to slowly deteriorate. Two thousand and thirteen brought severe cystic acne all over my body and frequent UTIs. By 2014 I noticed blood in my urine, heaviness in my limbs, extreme fatigue, and a strange metallic taste in my mouth. In May of 2015 I was diagnosed with lupus. I had a second opinion to confirm, as I led a very healthy lifestyle. In 2016 I experienced memory loss and my hair began falling out. I also developed frequent unexplained fevers. Even my ophthalmologist mentioned he could see a strange allergic reaction in my eyes.

By 2017 I could no longer run. I was having trouble functioning day to day. This illness was taking an enormous toll on me, my marriage, and my ability to be an active part of my children's lives. In May of that year I had an MRI. My doctor said that not only did I have a rupture, but my right implant shell was completely dissolved, and silicone had bled into the lymph nodes of my left axilla and chest wall. I explanted in June of 2017. My surgeon had to scrape silicone off my clavicle and my right ribcage.

After surgery, my lupus symptoms slowly began to improve. My ophthalmologist no longer saw the allergic reaction, and I started to run again. Over those 5 years I saw nine different doctors. I asked three of them if my breast implants could be the cause and they all said no, the FDA says breast implants are safe. I'm here today to tell you that what I experienced could've been avoided if I had been warned that breast implants can cause systemic symptoms, if I had been warned of silent ruptures and directed to get regular MRIs, if any, any of the doctors I saw had told me that my illnesses could be caused by my breast implants, and if breast implants were mandatorily tracked in a national registry that includes information about symptoms and not just reoperations. Over this time, my insurance has paid over 100,000 dollars in claims, which does not include the amount I paid

or the cost of my medications. Today I believe there are tens and thousands of women like me wandering from doctor to doctor not linking their systemic symptoms to their breast implants.

I ask that you stand up for women's health and require that all surgeons not only understand the signs and symptoms of BII, but thoroughly discuss the risks with their patients. They must report all possible adverse events regardless of whether they think they are related to implants or not. FDA, there is still a problem. I have silicone in my lymph nodes.

DR. LEWIS: Ms. Zimmerman, please conclude, you're way over time.

MS. ZIMMERMAN: And I have yet to find a doctor that can get it out. For something that is so inert, it's entirely cosmetic, and it still affects my daily life.

Thank you.

(Applause.)

DR. LEWIS: Dr. Diana Zuckerman.

DR. ZUCKERMAN: Thank you for the opportunity to speak this afternoon.

As I mentioned yesterday when I spoke, there have been many studies of breast implants, but most are so poorly designed or poorly conducted that they should never have been published and certainly not included in an Institute of Medicine or a Tufts review.

The studies conducted by the breast implant companies and submitted to the FDA stand out for a different reason. Most were very well designed, but then they lost track of most of the patients that were supposed to be in 10-year studies. Yesterday, FDA showed us slides of some of the studies where more than 80% of the patients were missing. Some of the patient groups, such as revision patients, had seven women. One study had only 12 women that were reconstruction patients. These are not data. These aren't even anecdotes. When you have so few people, not only can't you say anything generalizable

about them, but as Dr. Li mentioned, it's a problem when these studies include many different kinds of implants, and you don't know exactly which kind are causing problems and which ones aren't.

You can't draw any scientific conclusions, obviously, those of you who know statistics, you can't from a study that's missing 60% or 70% or 85% of the patients. And as we know from the patients who have spoken, some of the women tell us that they weren't unintentionally excluded, that at some point they were intentionally excluded by the people running the studies. They were in the studies, they reported problems, and suddenly they weren't in the studies anymore.

And yet one of the manufacturers, Ideal, tells us they have more than 90% of follow-up with 8 years of data, and I'd like to know how they did it, and I think everybody here should be asking, how did you do it? And I think FDA should be asking how they did it, and if these are accurate numbers and if the incentives were appropriate, I hope FDA will talk to the other implant manufacturers about doing as good a job of keeping people in the studies.

I also just want to clarify some of the things that have been mentioned about the study that I presented yesterday. Ninety percent of the women in our study showed improvement when they were explanted and the other numbers I heard from Dr. Tervaert were 50%, and he measured it differently, much more stringently.

So, this meeting has made one thing very clear. There is a disconnect between what the patients are saying and what the plastic surgeons are telling us. The plastic surgeons told us that they always warn their patients of the risks, but then at the same time they're telling us that they don't think that there are very many risks and that, in fact, most of their patients are very satisfied. So, it's that difference of perspective of the patients who are telling us they're not being told enough, not that they're being told too much, that they're

not being told enough and the plastic surgeons who think that they're telling their patients everything they need to know, and that's why informed consent really needs to be improved. The solution is not a 200-page patient booklet.

DR. LEWIS: Dr. Zuckerman, please conclude.

DR. ZUCKERMAN: Sure. I've got 30 seconds, thank you.

DR. LEWIS: No, you're over 30 seconds.

DR. ZUCKERMAN: Okay. A 200-page booklet by Mentor is too much, and a two-page checklist would be great.

(Microphone turned off.)

DR. LEWIS: You're done. Let's move.

Ms. Keri McElroy.

(Applause.)

MS. McELROY: My name is Keri McElroy. I traveled here from California at my own expense, so I have no conflict of interest. Thank you for letting me speak today.

I was augmented with Mentor smooth silicone gel cohesive implants in July of 2009 because I was very thin, and I had double A-cup breasts and I just wanted to feel like a woman. I was told they were safe, and the only risks involved were infection and capsular contracture. I'd like to add, I was extremely healthy. I had no allergies and no preexisting health issues.

Immediately after implanting, I began to catch frequent long-lasting colds and flus. By 2012, slow oncoming symptoms began, and I got tired very easily, developed gut issues, anxiety, my vision began to decline, I had chronic UTIs and yeast infections. Yet I absolutely loved my implants and I thought my ailments were due to being a single mom working two jobs and aging. By 2015 I started having severe fatigue where it was absolutely difficult to get up and take care of my children, and depression kicked in. By 2017 I had rashes all over

my face, brain fog, breast pain, muscle and joint pain, and at this point was when my friend referred to the online support group where I read hundreds of stories that were my story.

I returned to see my original plastic surgeon, who reassured me my implants were fine. I should not have listened to her. The next year, before my explant surgery, not only did I develop almost 50 debilitating symptoms, I was diagnosed with hyperthyroid, I had elevated cholesterol, Raynaud's syndrome, half of my hair fell out. I had an extreme choking sensation in my neck, and my face was covered in extreme rashes and bone dry. My anxiety and paranoia became so severe I was having constant panic attacks and contemplating suicide, because if this was my quality of life for the rest of my life, I didn't want to live anymore. I was a shell of the vibrant, outgoing woman I once was, and all my general practitioner wanted to do was send me to a psychiatrist.

I explanted my intact implants September 26th, 2018, exactly 6 months ago today, with a complete en-bloc explant. Most of my symptoms are gone or improved. By 4 months postop, my thyroid had healed itself without meds. My cholesterol dropped to normal levels by itself. My hair started growing back, my face completely cleared up, and my anxiety and depression disappeared.

For 8 years I thought my implants were the best decision I had ever made, and by 9 years I truly believed I was going to die. Of course, these women who have only had them for 1, 2, or maybe even 5 years think they have no issues and love them, but where are those women going to be in 10, 15, 20 years? Women need to be warned of all the risks involved when making the decision to augment or reconstruct. They need to be able to get that informed consent, and doctors need to recognize breast implants causing illness when women come looking for answers. For decades, hundreds of thousands of women have become ill with no idea what's wrong with them and just being told it's all in their head. Just because this isn't happening to the doctors or the surgeons doesn't mean it doesn't

exist.

Thank you.

(Applause.)

DR. LEWIS: Dr. Lalitha Jacob.

DR. JACOB: Good afternoon, I'm Dr. Lalitha Jacob from St. Petersburg, Florida. I'm actually an M.D., a physician, a neurologist. I was the picture of health until January 2007 when I had a smooth silicone breast implant put in. I was not informed about a single problem related to the implant. At that time, I had not seen my patients coming to me with MS-like syndrome and ALS-like syndrome. That happened only later.

So, I agreed to the procedure, and I ended up with severe systemic toxicity leading to lupus-like syndrome that almost killed me. With the 16 different complications, I had 16 different doctors taking care of me. It destroyed my marriage of 25 years 2 years later to a physician, a gastroenterologist. As of the beginning of last year I was forced to completely stop working at the peak of my career, and I have additional training in anesthesiology and psychiatry, also. This took me down professionally, personally, financially, health-wise, as well as in my appearance from one extreme to the other. If you don't believe, you just have to move your eyes from me to the photograph on the screen on the wall.

That is the way I looked just before my implantation surgery 12 years ago, and this is the picture taken actually just before the -- in 2006. The implant was placed the following year, January 2007. And I would like you to pay attention to my eyes because the first change of toxicity was seen in my eyes. This is the way I looked in 2008. Extreme swelling, discoloration, complete loss of eyelashes, eyebrow, I have no eyebrows now, it's all eyebrow pencil. My sclera has never been white since then, so always reddish. And before this, I always looked 30 years younger than my age, and this obviously made me look 20 years older.

And this is the life-threatening acute bacterial cellulitis that I developed, which was secondary to the lupus medications that were given to me by my three different rheumatologists, which compromised my immune system further, putting me at high risk for life-threatening complications. I was pushing IV antibiotics into myself and seeing patients with this infection going on. So, I had eight attacks of diverticulitis of the colon with rupture and the last one with a 4½ cm abscess in the abdomen, requiring emergency resection of one foot of colon. And you name it, every system was involved.

So, I would appreciate it if FDA can give me a chance to sit down with you and make my recommendations as to how we can prevent this problem happening to another human being, because in this day and age in America that claim to offer the best medical treatment in the world, it should not happen. And as an intelligent --

(Applause.)

DR. JACOB: Intelligent, highly educated woman, I should not be standing here telling you about my whole life, I lost my whole life because doctors approved the fact that to system we have in place to proving the problem is not being effective.

Thank you.

(Applause.)

DR. LEWIS: Dr. Kamakshi Zeidler.

DR. ZEIDLER: Thank you. I am Dr. Kamakshi Zeidler, a board-certified plastic surgeon practicing in Silicon Valley. As a clinical investigator for breast devices and author of peer-reviewed publications and an international educator of my surgical techniques, I am honored to share with you my real-world experiences. I am, at the core, a physician who cares deeply for my patients in a very personal way. I practice the full gamut of plastic surgery of the breast. I do cancer reconstruction, both implants based and complex microsurgical procedures. I do all forms of breast enhancement with and without breast

implants. I specialize in complex revisions of all types of breast surgery. I do breast implant removal with and without total capsulectomy for patients wanting a different aesthetic or for systemic symptoms that they attribute to breast implants. I have personally cared for a patient with breast implant-associated ALCL. And my beautiful sisters both carry a BRCA gene mutation and have been through implant-based reconstructions. Their experiences have given me a deep understanding for what patients need.

Compared to my business partner who practiced these procedures over the past 30 years, I'm grateful that I have so many tools to provide highly individualized results for my patients. When patients choose round or smooth implants, I prefer to place them under the muscle to decrease the risk for capsular contracture. When patients choose over-the-muscle placement for a more natural feel, I prefer a textured surface to prevent capsular contracture and anatomically shaped implants to maintain a natural look. When patients choose smooth implants over the muscle, I incorporate ADM to decrease the risk of capsular contracture, or a synthetic mesh to decrease the risk of malposition and future operations.

In patients having post-mastectomy radiation, oftentimes they prefer a smooth implant because they slide and move and create a more natural feel. In patients with recurrent capsular contracture, I prefer a textured implant, sometimes an ADM. And when it comes to textured implants, I'm very selective about which type of texture I recommend, as it is clear that different types of texture are associated with very different risks.

Acellular dermal matrix and synthetic mesh are a mainstay of many of these procedures. They add thickness and support to weak tissues and especially when implants are placed over the muscle. Prepectoral reconstruction has become a mainstay and virtually eliminated the severe animation deformity that many patients experience after breast reconstruction, and our literature has not caught up with the benefits of this

technique. I also use fat transfer to thicken tissue, correct radiation fibrosis, and provide an option for volume enhancement in patients not wanting implants or wanting their implants removed.

In summary, there are choices and options, risks and benefits that vary based on each patient's unique anatomy and lifestyle. Every patient should have an opportunity to choose which procedure, which recovery process, which devices, and which risks are worth the benefits of their desired result.

I look forward to hearing the responsible decisions from the FDA that allow me to deliver the same kind of quality of life that I give to all of my patients today, and the quality of life that I'm so happy my sisters were afforded.

Thank you.

(Applause.)

DR. LEWIS: Dr. Steven Teitelbaum. And we only have three speakers following Dr. Teitelbaum before we have to conclude.

MS. WILBURN: My name is Sarah Wilburn, and I am speaking on behalf of Dr. Steven Teitelbaum. The following is his testimony.

"My name is Steve Teitelbaum. I'm a board-certified plastic surgeon. I am a Clinical Professor of Plastic Surgery at UCLA, and past president of the Aesthetic Surgery Education and Research Foundation. I have no financial disclosures.

"I have listened intensely to the discussion at this meeting and have one important item for the Panel to consider. The Panel should recommend that breast implant manufacturers limit the use of breast implants to physicians board-certified by the American Board of Plastic Surgery.

"The airline industry does not allow new drone pilots to fly commercial jets. Yet many physicians with no formal surgical training are using breast implants. The FDA

restricts the sale and use of other drugs and devices to physicians with appropriate training and it should do the same with breast implants.

"We know surgical technique is the key. Any suggestion otherwise is unproven and not evidence based. And I am happy to clarify any questions the Panel has on this. Refined surgical technique reduces complications, capsular contracture, reoperations, ALCL, and possibly BII. The FDA should require that breast implant manufacturers limit the use of breast implants to physicians board-certified by the American Board of Plastic Surgery.

"On behalf of my specialty, I thank you all so much for your time and to create a safer world for patients."

(Applause.)

DR. LEWIS: Dr. Michelle Managhan.

DR. MANAGHAN: I'm Dr. Michelle Managhan, and I'm an American Board of Plastic Surgery certified plastic surgeon at Johns Hopkins. I'm the past Patient Safety Committee chair and a current Health Policy Committee chair for the American Society of Plastic Surgeons. I have no industry conflicts, and I treat reconstructive and aesthetic patients on both sides of the implant debate. Today I'll highlight the informed consent process, essentially how I talk to patients, how I educate patients and myself.

You've heard diverse perspectives, and this is absolutely what plastic surgeons hear in clinic. I hope you'll see plastic surgeons are perfectly positioned to blend knowledge of the cutting-edge scientific literature with clinical experience to guide each individual patient in the decision-making process. Individuality is important. Every patient is unique, every patient receives unique treatment, so every conversation is just a little different. I've heard the testimony here. I have heard the discussion in clinic. I believe informed consent is not just a signature; it's a rich process that occurs over time, and I exist to ensure that my patients understand what we know as well as what we don't know and what we're working

to learn more about, what they hear on social media, as well as what's published in the scientific literature, what to expect for their surgeries, as well as what we can predict but for which we would still prepare.

My patients and I discuss the risks, benefits, alternatives, and timings of their choices. We talk about history, mesh, MRI screening, insurance issues, pros and cons of devices like saline, silicone, smooth, textured, round or anatomic. We discuss the feel of implants to touch through the skin. What does soft mean? What does capsular contracture look like? We talk about implants not lasting forever, how each patient's breast size, shape, position, and composition affect implant choices, what happens if a patient chooses to change or remove their implants, and changes to the body and breasts as we age with or without implants. We discuss the potential for serious complications. And I share general stories from patients who have been unhappy with implants, too.

Conversation. I hear are implants safe? Will I get cancer? Will I need more surgery? What will I look like? What implant should I choose? What if I change my mind? I ask, what are your goals? What led you to the clinic today? What are you looking for in the future?

I value how individual surgeon feedback coalesces to a voice to shape the future. The American Society of Plastic Surgeons communications, informed consent information, and meetings have all helped members stay current on the BIA-ALCL and BII evolution. I've listened, and I've heard, for years. I and other plastic surgeons care. Please, let's continue to come together, let's strengthen the patient-doctor relationship, let's continue to allow plastic surgeons to protect and serve their patients and continue to allow plastic surgeons to deliver excellence when patients choose to consider breast implant surgery. I'm honored to be here. Thank you.

DR. LEWIS: Dr. Akash Chandawarkar.

DR. CHANDAWARKAR: My name is Dr. Akash Chandawarkar. I'm a resident physician in plastic and reconstructive surgery at Johns Hopkins, meaning I'm training to become a board-certified plastic surgeon. I'm not paid to be here, and I'm actually here at the expense of my co-residents who are covering my shifts because they also feel that this is important.

I spend over 80 hours a week learning the ins and outs of plastic and reconstructive surgery, not because it is fun or easy but because I care about patient safety. I'm asking the FDA to consider limiting sale of breast implants to only board-certified plastic surgeons.

It is apparent that technique is critically important to outcomes after breast implantation, including complications, reoperation, capsular contracture, BIA-ALCL and potentially, breast implant illness. Therefore, an important variable to consider in your analyses is who is putting in breast implants and managing the patients after.

In my 6-year training program, I primarily learn how to operate and take care of patients safely. I'm only given board certification at the end if I can prove that I can operate and take care of patients safely.

Other organizations, such as the American Board of Cosmetic Surgery, are not accredited by the American Board of Medical Specialties, which means there's no oversight in training of these non-plastic surgeons in patient safety. Informed consent requires an informed surgeon.

I want patients to know that the current generation of board-certified plastic surgeons find it critically important to teach the next generation, me, about the safety of placement of implants and management of BIA-ALCL. The proof is in the pudding. We have multiple questions on our annual and cumulative board exams about diagnosis and treatment of ALCL. I want the Panel and the FDA to know that some implant companies have made the choice to sell to only board-certified plastic surgeons, while others have not.

I believe this to be a key factor for patient safety.

I urge the Panel and the FDA to investigate whether or not problems related to breast implants may be confounded by who is putting them in and taking care of them afterwards.

ASPS and ASAPS are professional organizations that only accept board-certified plastic surgeons, and I commend them for teaching us future plastic surgeons that patient safety comes first.

Thank you.

(Applause.)

DR. LEWIS: Ms. Laurie Casas.

DR. CASAS: Thank you. My name is Dr. Laurie Casas. I'm a board-certified plastic surgeon in clinical academic practice for 29 years. I'm also a Clinical Professor of Surgery at the University of Chicago and a board member of the Aesthetic Society. I have no financial disclosures to report. Thank you for the opportunity to discuss how I have arrived at best practices for breast implant informed consent discussions.

Unlike many surgeries, informed consent does not end at the time of breast implant surgery. We need to share decision making with our patients to determine a path of long-term care and periodic monitoring for the lifetime of that implant.

As new patient-specific and implant-specific data are identified, we need to communicate this information to our patients in a timely manner, sometimes in person, but oftentimes electronically. Clearly, we need new technologies to collect patient-centric and implant-specific data at the time of implant surgery and longitudinally. Relying on data from industry post-approval studies has not been enough.

I applaud the creation of the FDA's National Evaluation System for health Technology, or NEST, and its goals to link and evaluate information from many sources to

improve collection and evaluation of post-approval real-world data.

It is also vital that the Aesthetic Neural Network, or ANN, in conjunction with the Aesthetic Society, add critical data to the existing National Breast Implant Registry at the time of implant surgery and on an ongoing basis.

Our collective goal is to quickly identify, communicate, and act on implant device safety concerns. Over the past 2 days I'm hearing that we need a structured educational checklist for informed consent. I agree, and the Aesthetic Society hears you. The Aesthetic Neural Network, or ANN, will have a breast implant informed consent checklist that will be updated as new safety information becomes available.

First and foremost, I'm an advocate for breast implant patients. My goal will always be patient safety and a better informed patient, through transparent and informed dialogue at the time of implant surgery and throughout the lifetime of each implanted device. Inadequate data collection must stop today.

Thank you.

DR. LEWIS: I thank all of the presenters for the information and for their sacrifices in coming here at their own expense to present to us. The Panel is very grateful to you, as is the FDA, for taking time and effort to do this.

We will now move directly to the final Panel session regarding recommendations and deal with Questions 6 and 7. Question 6 is the Panel will be asked to discuss MRI screening recommendations for silent silicone gel-filled breast implant rupture. The first discussant will be Dr. Howard Sandler, and the second will be Ms. Rachel Brummert.

Dr. Sandler.

DR. SANDLER: Thank you.

So we're asked to relook at a recommendation that was made a number of years ago when silicone gel implants were approved for use with MRI beginning 3 years after

implantation and then every 2 years afterwards, and maybe we can have just some clarification on this during our discussion, but I think the assumption is that it's important for patients to have silent rupture detected as early as possible so that therapy, including explantation, be performed.

What I haven't seen today is whether that's absolutely true or not. Is it absolutely true that silent rupture needs to be treated early and completely or can it be managed more conservatively? So, I feel slightly uninformed about the consequences of silent rupture at this point. But if, in fact, it's important to be detected and treated right away, then yes, some kind of monitoring program should be in place. We saw from FDA summarizing the industry reports that the incidence of silent rupture -- or first of all, that most of the ruptures that occur are silent and intracapsular and also, importantly, they don't really occur very often before 4 or 5 years. So, while the recommendation that MRI screening begin at 3 years is not too far off, one could imagine that that date could be pushed down the road a couple of years if one wanted to recommend a monitoring program, for example, starting at 5 years.

What I would say is that while this MRI schedule was well intentioned, it's clearly been a failure because it's just been too challenging for individuals to have routine MRIs when they're feeling well and there's issues with expense and insurance coverage, etc., so it's been impossible to have this schedule followed rigorously. So even though it was well intentioned, I don't think it can stand without modification. It doesn't make any sense. So I would say that one alternative would be to say that if silent ruptures can be managed conservatively, then one option might be to just be extremely conservative and have no imaging with either ultrasound or MRI, or alternatively, one might offer patients the option of beginning monitoring, say, at 5 years after implant with either MRI or some other appropriate form of imaging such as ultrasound. And so that's my thoughts on the

discussion we've had today.

DR. LEWIS: Ms. Brummert.

MS. BRUMMERT: I echo that, and I understand that there needs to be some sort of surveillance on silent rupture, and obviously, I think that it needs to be caught as early as possible. The big concern that I have, and that a lot of people seem to have, is that MRI is not covered by insurance or it's a lot of money out of pocket. So, I'm not a physician, so I don't know what some of the alternatives would be, whether ultrasound is a better way to try to detect it, but I do think that early detection is the key to keeping people from getting sick from the ruptures.

DR. LEWIS: Thank you.

Comments from the Panel? Dr. Leitch.

DR. LEITCH: Like a lot of us, I think providing patients a choice -- so I think what we're seeing from the data is that the rupture rate starts to increase at 5 years and so it's reasonable to wait until then to do a screening for silent rupture but still, you know, most people won't be ruptured at 5 years, and so a person could make a decision, as patients often do. If there's an 80 to 90% chance everything is okay, they may choose not to make the investment in screening, but other people may say it's worth it to me to be screened, and then to give them the option of the MRI which is the best tool that we have for detection of rupture and then as sort of a second best, the ultrasound, although I think it's important that the ultrasound and even the MRI be done at a center with highly qualified people to be able to detect that because ultrasound is a very operator-dependent test.

You know, so I think setting it up from the outset when a person gets breast implants, for that to be in part of the informed consent about the options, not just to say, well, the FDA says to do it at 3 years, but to say, you know, there are some options, these are the risks of silent rupture, and then have the patient be able to participate in that

decision making about what they -- you know, what they want to do.

DR. LEWIS: Dr. Lippman.

DR. LIPPMAN: I'd like to, first of all, say I agree with Dr. Sandler completely. I'm not sure that I understand what the point about early detection of asymptomatic leakage is yet. Because I take care of breast cancer patients, I have dozens of patients in whom asymptomatic leaks have been detected who have done nothing about it and nothing has happened. So, I'm a little bit at sea about that critical issue. We also heard wonderful comments from women who said based on, I assume, imaging that their implants were intact when they developed their symptoms. So, I'm not sure I see the exact relationship for that. The point I might make, and it's been made before by people interested in what's in these implants, is that there's a brand new era of metabolomics and looking by mass spec at almost infinitesimally small amounts of things that circulate, and people don't have silicone in their bodies unless they have silicone in their implants, and I would be wondering whether or not there would be a readily developable straightforward blood test to detect leaks by detecting some of the leakage products in the circulation, either in blood or urine. I think this is something, if it hasn't been explored, should be.

DR. LEWIS: Dr. Chevray.

DR. CHEVRAY: Right now, when I and, I think, most plastic surgeons place the silicone gel-filled breast implant in a patient, among many things we tell them, or I tell them, that the FDA has recommended that they have a screening MRI at 3 years after implantation and I tell them that's the recommendation, but the reality is that very few patients have that done, for reasons we've discussed.

When I see a patient that is sent to me because they or their physician feels or is suspicious that they have a ruptured implant and I ask them -- I order an MRI, that is generally covered by their insurance company even if the implant was placed for cosmetic

reasons. If the same patient doesn't have a suspicion of rupture and they try to get an MRI for screening reasons, it's generally not covered.

Okay, if I see a patient that has -- comes with an MRI that confirms they have an implant rupture, I ask them how they know, do they have any symptoms? And if they do not have any symptoms, I tell them the FDA recommends that we remove the breast implant and either replace it or not replace it, is your decision, but I would also give you the option of doing nothing because, as far as I know and as far as we've heard today, there is no evidence that a ruptured implant is any worse than an intact implant for causing ALCL or BII or other diseases or conditions. Sorry, for an intracapsular rupture. If it's an extracapsular rupture, then I recommend removing the implant, the capsule, and all of the silicone material that I can possibly remove. Because of all of that, personally, I think the recommendation for having the screening MRIs at 3 years and 2 years -- every 2 years after, that is -- it's nice academically and in the setting of a clinical trial, that would be nice because you'd like to know when an implant ruptured, if the patient subsequently develops issues, if you're studying this, you know, you'd like to know that, but that's not the situation with the general population of patients who are getting implants for cosmetic reasons.

Dr. Lewis, our Chairman, has suggested that in place of MRI maybe we recommend ultrasound, not necessarily high definition, which is not generally available, but regular ultrasound is cheaper, it carries less risk to the patient, is easier to obtain for screening purposes perhaps at 5 years when implants are more likely to be ruptured, to consider that. To consider that.

DR. LEWIS: It seems, in view of the information provided by Dr. Destounis, that high-resolution ultrasound, which has been suggested repeatedly from the audience, is actually not practically available at this point in time. Perhaps it will be some years hence. But we've also heard from her that traditional ultrasound, in fact, works fairly well as a

screening procedure. I guess, in thinking about all we've heard, it seems that the MRI recommendation should be dropped, as suggested by the American College of Radiology, for two reasons.

Number one, it's probably too early to pick up a significant number of ruptures given the data we've seen about the onset of that, typically around Year 6, 8, or 10. In addition, the compliance rate of patients who have to pay for that themselves, we've been shown, is somewhere around 5% or less. So, it's effectively a useless recommendation. Ultrasound is far easier, quicker, and cheaper for patients. So, I guess my suggestion, given all we know at the moment, is that we recommend that screening ultrasound be conducted at 5 or 6 years post-implantation. Again, we're talking now about asymptomatic patients. Symptomatic patients should, I believe, always go to MRI, but asymptomatic patients would have a screening ultrasound at 5 or 6 years with repeats at either 2- or 3-year intervals and for any equivocal ultrasound, an MRI would be done in backup. But if it were completely negative and if the patient were asymptomatic, that would be the ongoing recommendation and that seems to be a feasible and workable solution that would detect rupture and allow the patient to make a decision in regard to explantation. So, I would actually suggest that we adopt that as a policy, unless people have a better idea and want to alter it.

Yes, Dr. Leitch.

DR. LEITCH: And I think I agree with you that we should get rid of this 3-year MRI, but I think also, again, in response to what we hear in the testimony of, you know, people having the complaint and then no one addressing it, I mean, that's -- I think that's what is really frustrating to patients is, you know, they have these -- you know, their breast is swollen, you know, they have a specific complaint and yet it's not addressed. So, I think emphasizing response to symptoms, however far out the person is from the implant placement, you know, is obligatory and the screening is a more optional approach.

DR. LEWIS: It's been repeated, we haven't heard of any evidence that a delay in addressing rupture has any -- has yet shown consequences, but we also have been shown that 97% of women, when notified of that, want the implant removed. So, I think that's an obvious reason for having the screening procedure.

Dr. Portis.

DR. PORTIS: A couple things. I think it makes sense to delay the screening. Two things come to mind, and I will try to be articulate about this at the late part of the day. But what we've heard from women is a lot of women don't initially link their symptoms to their implants and so having screening, maybe not at 3 years, also signals to women early on that this may be an issue, and this is one way to think about it, and then we're following up and maybe then women start to make that linkage, also. Does that make sense?

DR. LEWIS: Dr. Burke.

DR. BURKE: But also, Dr. Destounis pointed out that a mammogram might be also good, it is a good way of screening, and that is not as technician dependent.

DR. PORTIS: So, the issue with mammography, even though I know sometimes if you have reconstruction, you're not having mammography on your reconstructed breast, not typically. Maybe the physicians can speak to that.

UNIDENTIFIED SPEAKER: Correct. That's correct.

DR. CHEVRAY: Right. Once you've had a mastectomy, you don't get screening mammograms subsequently, but that doesn't preclude you from getting a mammogram. If the FDA decides that a screening mammogram should be done at 5 years, that's okay. It's okay if you have a reconstructed breast. So, this would be screening for implant rupture, not screening for breast cancer.

DR. LEITCH: I don't think we heard that a mammogram is the best tool for screening.

DR. CHEVRAY: No, mammogram is a poor modality for detecting a ruptured implant.

DR. LEITCH: Yeah, yeah.

DR. LEWIS: If there's no other disagreement, is the Panel comfortable with that recommendation?

UNIDENTIFIED SPEAKER: Yes.

DR. LEWIS: Dr. Ashar, are you comfortable with that?

DR. ASHAR: Thank you.

DR. LEWIS: We'll move now to Question 7. The Panel will be asked to discuss the role and responsibility of all stakeholders for communicating breast implant-related risks and benefits to patients. Dr. Karen Burke will lead the discussion on this, followed by Dr. Colleen Gallagher and Ms. Lynn Pawelski.

DR. BURKE: All right. I think a very impressive part of this hearing were all the testimonials, and there is no doubt that these patients feel that the informed consent failed them, that they were not aware of the risks of breast implants. So, the question is should the FDA mandate a standard checklist for a consent? And I think, through our discussions, I would classify the checklist to be kind of three parts. The first one would be that patients should know that possibly they will need a revision, that just having an implant is not necessarily for life and in fact, that having a breast implant is a lifetime commitment, that they have to be aware, longitudinally, even if they have no symptoms. So, we've just talked about a screening maybe starting at 6 years and maybe being every 2 or 3 years after that.

The second category, I would think, that should be in a standard checklist are that there may be predisposing factors and we don't know them yet. We would explain we don't know them, but certainly, as was pointed out, if a patient had a past medical history of many allergies or connective tissue disease or immune deficiencies, if they have a family history of connective tissue disease or immune deficiencies.

And the third thing is there are some genetic predispositions that have been

mentioned in the literature. There are papers. I can't validate how important these correlations are, but at some point, we may make some genetic tests that could be done.

The third category is, of course, the diseases we've talked to, talked about, the breast implant illness with so many varied symptoms. Patients should be aware that this is a possibility and that if they have any new and different symptom, that they should immediately contact the surgeon that placed the implant. And going with this, we should make other specialties, especially rheumatologists and thyroid doctors, aware of this possibility.

And then the final thing, that they must be aware of this very rare complication of ALCL. Even though it's rare, if you get it, it's terrible. So perhaps the FDA should consider a black box label so that it's emphasized that this is a possibility, and patients, I think that once they've had surgery, they almost forget that they've had -- after you've lived with your implant, 10 years later you almost forget that you have an implant and if you're asymptomatic. So, again, the longitudinal vigilance is important even if patients are asymptomatic.

I think that the question now does consent -- Dr. Wilkins pointed out that you don't want to have a 75-page booklet, and you don't want to have a one-page checklist with five items. So there has to be a balance in informing the patient, and certainly, the 75-page booklet with lots of references is great, and the doctor should say do look at this before you make this life-changing decision, but certainly there is something in between, we want something that doesn't take 2 hours to read and is comprehensible.

And I think that if patients -- it's fine to look at the internet. The patients should not depend on social media for their information. They should depend on their physician. The social media is more negative overall, probably, than positive and may not truly represent what we know now of the science of the complications.

So, I think that it's just -- it's actually compelling that the physicians must be aware, we must make physicians in other specialties aware and have this part of everybody's past medical history. I have a list of symptoms, I have a two-page medical history, and I don't have "did you ever have an implant" on my list of just things that I routinely ask. So, I mean, there's just no doubt that we need a consent and that we need everything I've just said. Thank you.

DR. LEWIS: Thank you.

Dr. Gallagher.

DR. GALLAGHER: So, I think one of the major issues is who's responsible for informed consent? A company can put together a very nice booklet having all the mandated information in it, but that doesn't mean that that takes care of it. So if we really want to follow some of what Dr. Green talked about in terms of informed consent being a shared decision-making process that includes the doctor and the patient and whomever else the patient may want to include, not forgetting that there are often other people involved, family members, you know, things like that that might want to be involved, so that they can have a conversation about what happens. One of the problems with big things like this, it looks nice and neat and small, but it's 76 pages.

Another one of the companies said theirs was 80 pages. Another one said -- and I looked at this not just -- I just looked at it when I first sat down earlier today, and I went no one's going to read this. No patient at MD Anderson is going to be handed this, as far as I'm concerned, because it doesn't have white space, it doesn't -- which is what we call -- that's the space you leave on a page for someone to think. It's crammed with words and whatever. There's lots of wonderful data points in it, I mean, in terms of graphs and charts and those kind of things, but they're small print.

They're written for people who are used to looking at that information. Most of the

patients are not used to looking at that kind of medical information. The other tricky part is that we depend on evidence. Today's medicine is practiced on evidence-based medicine, and the number of times that I sat here these last 2 days listening to we don't have the data, we don't have information, we don't know the answer, that's problematic.

(Applause.)

DR. GALLAGHER: So I think that the informed consent, we need to highlight that it is that shared decision-making process between doctor and patient and whomever the patient wants to include, that it should have some kind of checklist, not a checklist that looks like the one that's in this kind of document that says the doctor gave me time to think about this and ask questions. That's supposed to be an automatic, that doesn't let anybody off the hook. I think it needs to be a checklist such as what Dr. Burke was talking about that groups things into the big important questions and that it requires a very specific type of visit with the doctor. I know for myself, I do not have breast implants, that was not my thing, but I had to go to the doctor for something, and they gave me, and I'm not joking, 7 minutes to do an informed consent process, and the doctor got mad when I said excuse me, I have four more questions and he said, well, I have to go. Well, when are we scheduling my appointment to get my four questions answered? So, I think that we also have to recognize that physicians have to put into their time template the time for an informed consent conversation that many of them do, but I think the patients don't know the questions to ask. So maybe patient education documents that actually help patients figure out what questions they should ask because they won't know otherwise.

(Applause.)

DR. GALLAGHER: The other thing that I think is part of informed consent, because this is putting a foreign object into the body, you know, when someone goes and gets their knee replaced, they're often told this is made of titanium, this is made of whatever, it's kind

of a mini ingredient list. There is not an ingredient list, and I think many of the patients asked for that.

(Applause.)

DR. GALLAGHER: And since they've asked, I think that we have an obligation to respond to that specific request.

DR. LEWIS: Ms. Pawelski, you're the Industry Representative here on the Panel, would you want to comment and additionally tell us what role you think industry should take in this whole thing?

MS. PAWELSKI: Sure. That's part of my response. So, you know, what we've heard from all the public speakers are various things. First, that there are potential gaps in information, there's no information or there's too much information. So, I think we do have to focus on how we're informing and how we're having discussions. You know, FDA approves, and manufacturers produce and distribute these detailed patient brochures that already address many of the information gaps we've heard from patients over the past few days, but it's clear from the Open Public Hearing speakers that they're not getting that information or they're not having the time to read it. So, you know, first I think yes, the brochures are large. We need to make sure that the patients get them.

We need to make sure that they have the opportunity to take them home, digest them before the procedure and then use them and perhaps we can put a toolkit into the brochure or something where it helps them provide a checklist to go back with questions to their physician to then have a more proactive dialogue in the 7 minutes or in the short time that they're allocated. It is a lot of information, but this is not something that anyone enters into lightly. These are life-changing decisions, and it's not a decision that happens overnight.

You know, other than labeling and some of the things, I think FDA's a little bit limited

in some of their tools at their disposal, but at the same time I've seen opportunities where FDA has been able to work through consortiums and things with industry and other interested parties, so physician groups and things like that. There was an acetaminophen awareness coalition about 8 or 9 years ago where manufacturers and industry and FDA came together, and really, it's around coordinated communication efforts in multiple forums. So perhaps FDA's Office of Women's Health could help coordinate that. And I think really, you know, the focus from what we've heard and discussed, it has to be a collaborative effort. You know, surgeons, they play a critical role on the importance of a complete discussion, you know, they have to actually -- or their office has to give the patient the brochure and execute the informed consent or whatever it is we agree. Patients need to know to ask for a brochure, they need to know what's available to them, so how are we getting information so that, you know, patients can pull the information, potentially? Then they need to take it home and have time to read it, you know, before they consent to the procedure. We talked about a checklist for patient-physician interactions or an informed consent of sorts. We've seen some short two-page, and on the Allergan website as well, some abbreviated information that focuses on some key areas potentially.

And then I think the last thing we heard is how -- and maybe it's through a consortium with industry and some of the other groups, is how do we get to primary care and OB/GYN doctors and things, who are seeing the patients on a more regular basis with the information about some of the emerging data and some of the things we see?

DR. LEWIS: Thank you very much.

Let's turn now to 7a, which you can all see on the screens. The specific question: What additional steps can FDA take to ensure that patients are better informed about the risks of breast implants?

Dr. Chevray.

DR. CHEVRAY: I believe that it's the physician, the surgeon's responsibility to inform the patient. That's the bottom line of what I'd like to say in a minute or two here. All patients, almost all of them that testified here, I'm sure, went to see a plastic surgeon. They didn't know, when they walked into the surgeon's office, that there was something called ALCL or BII. They didn't even know to think there might be something like that, right? They're thinking about breast cancer or getting their breast augmentation. So even if the FDA mandates that there is a checklist that's used, just like there's this booklet that's available, this booklet is available in physical form in my office and in probably every plastic surgeon's office, it's available online, there are similar booklets that are available online at plastic surgery organization websites like ASPS but if the physician, if the surgeon, doesn't tell the patient about this booklet or about ALCL or doesn't use the checklist that the FDA has mandated, it's not going to help. It's the physician's responsibility, it's this relationship between the physician and the patient that the physician has to be responsible for obtaining informed consent for the procedure, the surgeries, the implants they put in.

I don't know that any mandates or laws, so to speak, by the FDA or others is going to help that because there are already all of these things, these tools, available for physicians and if the physician doesn't give them the brochure, doesn't tell them to go look on the website or doesn't tell them in person or have their own checklist, I don't know that additional layers of mandates is going to make that better.

DR. LEWIS: Dr. Portis.

DR. PORTIS: Well, a question for you, Dr. Chevray. So how do we do that? Because I really appreciate your points. When I talk to patients and we hear from people, your point is very good, what most people don't know to ask. When Dr. Gallagher talks about her experience, most people don't know to say, well, when can I talk about this? I tell patients

all the time, you know, tell the doctor you have more questions, but the average patient doesn't have the wherewithal to stand in front of the door and say I'm sorry, I need more time. So how do we get physicians to do what you're saying, because it's clearly not happening.

DR. CHEVRAY: So, it's education of the physicians. Professional societies have stood here and told us they're working hard to try and educate physicians, the plastic surgery societies say they're trying to educate plastic surgeons. Yeah, for something like ALCL, it took a while to identify it and then to disseminate the information. Nowadays, I would think that almost all board-certified plastic surgeons know about ALCL and have for some years now. We talk about it all the time in meetings internally in our hospital and our division of plastic surgery. I think this is not really the -- my opinion is that this is not -- that is, informed consent is not the responsibility or the purview of the FDA. It's a patient-physician relationship issue. It's about training doctors well. It's about finding a good doctor. You know, for example, if someone goes to see a radiation oncologist, there's not a black box warning on the outside of the radiation oncologist's door that if you get radiation, you could get angiosarcoma 30 years later, or if you get it in your head and neck, you may not be able to speak or swallow.

The radiation oncologist has got to tell them that. The patient doesn't even know that that's a possibility. When we hear patients here, they're talking to us after the fact. It's much different when they've walked -- just walked into the patient's office -- the doctor's office before they've gotten their breast implant. Their point of view is a lot different than after they've had the implant and after they've got the symptoms and after they've had all the problems. Now they know about all of this. They had no idea before. The physician has got to tell them.

DR. LEWIS: Yes, Dr. Brummert.

MS. BRUMMERT: I think it's everybody's responsibility in terms of informed consent and what I think is that the FDA should mandate a checklist, but I think it needs to be done with the FDA, with physicians and with patients, because there's a disconnect somewhere and it's been bothering me this entire hearing and I think if we do it that way, I think there will be less of a disconnect.

DR. LEWIS: Should the FDA go beyond a checklist and work with industry and patients and the societies to, in fact, develop a standardized consent form really across all of the types of --

MS. BRUMMERT: Yes.

DR. LEWIS: And it seems to me that the --

(Applause.)

DR. LEWIS: That what is needed, actually, is two versions. In the material we were presented there were patient brochures from the four manufacturers, three of them ran to 40-some pages and one to 72 pages, and they were not constructed really to inform patients in the best possible way. They were instructed to provide legal protection in regard to having covered all of the possibilities.

(Applause.)

DR. LEWIS: So, it's really essential that something be written with a different format that will inform patients accurately about risks and it needs to be shorter than 40 pages. But there does need to be a detailed list and there also needs to be a concise list that will list -- because when you really look at it, there are these three groups of things. There are the mechanical complications, which are actually quite predictable, of contracture, displacement, etc., and those over a 10-year period ran to 20-25%. So, the message also, I think, needs to be conveyed that breast implants should not be regarded as a permanent fix that you can forget about and never expect problems with.

The expectation should be set, in my opinion, for patients so that they don't have false beliefs about what's going to happen, that they have some realistic expectation. So, you have the mechanical complications that are very predictable and differ among the implants. You have BII, which has some frequency we don't know, probably between 1 and 10%, and you have ALCL, which is much rarer and perhaps can be addressed by what we've heard about, differing surface textures, to actually lessen the incidence significantly by modifications going forward. But those things, I think, could be discussed in a two- or three-page document, perhaps outline form, perhaps a checklist, with reference to a much more detailed document. It seems to me the FDA might be able to work with industry, with the two plastic surgical societies who clearly are very sincerely interested in educational efforts. And while the FDA doesn't have any direct jurisdiction over medical practice, it seems that you could establish working relationships with the two societies who obviously sincerely are interested in them and let them do the implementation in regard to plastic surgeons, themselves. But I think something needs to be prepared for patients that would be generally available and would guarantee that the principal risks are discussed in understandable form for them.

DR. CHEVRAY: I have a question for the FDA. Is there a precedent for this? Are there other implanted devices like a gastric banding device or an orthopedic implant that -- where the FDA has recommended or mandated a specific consent document?

DR. ASHAR: You know, I'm not -- my familiarity with some of those other devices that you listed is limited, but FDA does have a lot of experience as being a convener of various stakeholders to get work accomplished. So, convening these various groups would definitely be something that we could do and is an excellent recommendation.

DR. CHEVRAY: So, for example, the ASPS, the American Society of Plastic Surgeons, has consent forms that plastic surgeons can use, already created for -- there are many

procedures, including breast augmentation. So, the society has already done that.

DR. LEWIS: Were there other comments regarding 7a?

Yes, Dr. Lippman.

DR. LIPPMAN: I think, in some sense, this is trickier, I think, than we're letting on. I'm all in favor of informed consent, who wouldn't be, but I'm looking at this multipage document from Mentor that was distributed. It says it very clearly. I mean, if you read this, it's there. It's not the least bit hidden. I mean, it says exactly very high rates of replacement. It's there. And this tension of a quick informed consent versus a long one, we may be trying to invent this wheel around breast implants, but I use chemotherapy. I assure you, to my great regret, chemotherapy kills a lot more patients in a year than have ever been killed by an implant, forever. It's a terribly toxic treatment. It works in some cases wonderfully and we take those risks but informing patients about that is the most egregiously difficult thing. Most patients don't want to read the informed consents. We present them in Creole, in Spanish, in French, and in English in my institution. I'm not making this up.

And it's almost impossible, on an individual person, to have them fully assess these things and there's got to be some level of personal responsibility once the information is out there. Withholding information is completely unacceptable, no argument about that, ever. But at some level, I mean, you can't force-feed this, and I think we're going to go crazy if we sit here and say how many pages, how many checklists? I mean, there's a checklist in this. I'm not holding this out. I don't work for Mentor, I have no idea but, I mean, it's not like people aren't trying to do this.

DR. LEWIS: Well, I think Dr. Chevray's earlier point is relevant. I mean, the primary obligation is to the surgeon, but we clearly also have a patient population which is quite interested in being able to inform themselves. And so, while not everybody is going to be

interested in reading it and it's not going to be 100 percent effective, for those who want it, we need to ensure that it's available.

DR. CHEVRAY: The problem is those patients didn't know this is what they wanted to see. They didn't know about ALCL or BII when they went to the doctor's office.

(Applause.)

DR. CHEVRAY: So, it was available, but they didn't even know what they were looking for or that they were even looking for anything.

DR. LEWIS: But I think we're saying that that is a role that the FDA could ensure, that in fact, that would be provided.

(Applause.)

DR. CHEVRAY: But my medical school, my residency, my professional association, they also are trying to ensure that I do that, they've been trying for years to ensure that I and other surgeons do that. So, if I fail, I don't know that another mandate by the FDA is going to -- would have changed me failing to do that. So, some of these -- many of these patients say they don't remember, or they weren't told about certain risks. Some of them, I'm sure, were told and forgot. Some of them probably were not told. I don't know if there was a mandate by the FDA that they would have been told because there's already all these other avenues or booklets and online websites and societies trying to educate these same surgeons. I'm not sure that --

DR. LEWIS: No, but again, I'm not supposing that the FDA can mandate that the doctor tells the patient, but I think the FDA can work with the societies and the societies indeed do have influence over the doctors. The FDA, on the other hand, can ensure that objective information is available to patients, one way or the other, in a standardized way.

Yes, Dr. Burke.

DR. BURKE: Well, maybe that is the reason that a black box label, just because it

emphasizes it, even though that ALCL is a very rare complication, just to emphasize that, makes people aware.

(Applause.)

DR. CHEVRAY: I thought about the black box and thought it was a good idea, except that the box, the box for a breast implant gets discarded in the operating, right? So where are you going to put this black box, on this or on a website that, again, the patient doesn't know to go look for it? So, again, you're relying on the surgeon to tell the patient about this black box. The patient doesn't see the box. The box is in the operating room and gets thrown out.

DR. LEWIS: Okay.

Dr. Leitch.

DR. LEITCH: I think the other thing about informed consent which we do for clinical trials is when you're talking about complications, group them into, you know, common, less common and rare, to make it again easy for the patient to kind of work through the different things and rather than, you know, 100 things without any, you know, parsing out the differences between those complications.

DR. LEWIS: Yes, Dr. Gallagher.

DR. GALLAGHER: So, I'm aware that, you know, when I watch TV there are direct-to-consumer advertisements made for different drugs and things. Often, they'll have a comment something like "and such and such lymphoma has also occurred." Okay. And I always feel like okay, that's like a compromise statement, but it occurs but we don't know if it is caused by this, so we'll just say this. So, I think, though, that kind of information should be put in as an expectation in the advertisements and things like that that the companies come out with because I think that would be helpful.

(Applause.)

DR. LEWIS: Yes, Dr. Jaffe.

DR. JAFFE: So I think one issue is also, as was mentioned, that a lot of the symptoms that patients may develop they may not attribute to their implant, particularly for the breast-associated illness, and I wonder if having some sort of a wallet card that the patient would carry, you know, like if you're a diabetic and you carry a card, you know. You know, I'm a diabetic and this is a warning, and that having some sort of card that they could present to any physician when they encounter new symptoms or unexpected illness might be a concise way of communicating some of this information beyond the immediate patient and the original plastic surgeon, because I'm concerned that patients see other physicians and they may not even raise the point that they have an implant.

MS. PAWELSKI: I think implant cards do exist already with the products, right? So --

(Off microphone comment.)

MS. PAWELSKI: But the doctor has to give it to the patient, right.

(Off microphone comment.)

MS. PAWELSKI: Well, it's a card that talks about the implant, I mean, and then gives detailed information about the implant, so like the UDI is on the card, right?

(Off microphone response.)

MS. PAWELSKI: Yeah, the UDI would be on the card. I mean, this is just an anecdote. My mom just had her hip replaced, and I happened to be at the hospital when she got discharged, and when I met her back up at home later, I'm like, well, what hip do you have, where's your card, and she's like, I don't know. And it was just like, you know, the discharge nurse just -- I found it, it was in with all her stuff, but she would have found it like 5 years from now because she would've just taken the whole bunch of papers and just thrown it into a file cabinet somewhere. So, I just think, you know, there's these critical steps that may need to be focused.

DR. LEWIS: Let's move to 7b. 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 implant surgery and longitudinally, which is really an extension of what we've been talking about.

Dr. Gallagher.

DR. JAFFE: Can you change the screen, please? Whoever's operating the computer.

UNIDENTIFIED SPEAKER: We're on (b).

DR. JAFFE: Oh, (b). Oh, (b). Oh, I thought we --

DR. LEWIS: (b).

DR. GALLAGHER: So, I'm an avid reader of women's magazines, and I don't see stories about this. So, I'm wondering if the societies, along with patients, might want to write some stories and make sure that they try to get them into the women's journals and magazines and things like that. They need to be balanced articles, not like let me scare you, but I think balanced articles where they work together, something like that might be helpful to people.

(Applause.)

DR. LEWIS: Others? We've talked about several of these things already.

(No response.)

DR. LEWIS: Okay, people are happy.

All right, we'll go to 7c. Breast implant patient labeling contains information on the risks and benefits of 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.

Dr. Portis.

DR. PORTIS: You know, going back to -- I'm not a big fan of direct-to-consumer

advertising, but what if there were ads about these things on TV, essentially PSAs. You know, we've seen that the cigarette companies have had to put these very stark ads out about risk, you know, and informing of risk.

(Applause.)

DR. PORTIS: So, what if industry was required to do it or FDA was required to do it to say if you're considering implant surgery or you have had it, these are things that -- you know, did you request this information? Are you aware of these things? It doesn't necessarily even have to go into the whole list of risks, but somehow putting it in front of lots of people in a very clear way that you should be thinking about this, you should ask your doctor for that brochure.

(Applause.)

DR. LEWIS: Other comments?

(No response.)

DR. LEWIS: Dr. Ashar, do you have any questions about the direction we're going here?

DR. ASHAR: No, I think that this is great, and really, the question was aimed at trying to think of new and innovative ways to collectively take the patient voice and the providers and the manufacturers and bring them together. So, any other creative ideas that you have are welcome.

DR. LEWIS: The next two questions, (d) and (e), one is about BIA-ALCL, the other is about BII, but they really are the same questions in terms of how to inform patients and what we've been talking about here all along was a more comprehensive way of informing patients, including those two things. So, I think what we've talked about actually covers that already.

Dr. Jaffe.

DR. JAFFE: I just had a question about communication with education of surgeons and when I was on -- at the RAND panel a couple of years ago, which led to a publication about breast implant-associated ALCL, some of the surgeons at the panel said that most surgeons, if a patient comes into the office with a seroma, they aspirate the fluid and discard it and we strongly recommended against that and felt that, you know, any time a seroma fluid is aspirated, that has to be examined cytologically, you should go for a flow cytometry, and I've seen a number of cases in which there was delay of diagnosis because the original seroma fluid was not examined. So, has that practice changed among surgeons in the plastic surgery community?

DR. CHEVRAY: I know it's only been in the last, probably, 5 years that we, as plastic surgeons, have learned that one of the presenting symptoms of ALCL is a unilateral late seroma. And so, before that, if we saw a unilateral late seroma, we just aspirated it and discarded the fluid, but now I know to aspirate it, send it for CD30 flow cytometry, but that's only because I go to national meetings for CME and I learned. I mean, if you have -- let me just give you one anecdote.

So, my mother sees a 70-something-year-old primary care physician for decades. That physician didn't tell her about the vaccine for shingles. My mom got shingles and is disabled from post-herpetic neuralgia. Whose fault is that? I don't know, I wish the physician had kept up to date and told my mom to go get a shingles vaccine, but it didn't happen that way.

DR. LEWIS: Yes. Turn on your microphone, please.

DR. LIPPMAN: Dr. Ashar was thinking about other things that are innovative and I think that one thing I sense from the breast cancer experience, which I have a great deal of, is there sometimes -- sometimes there has been historically a bit of an adversarial relationship between advocacy and physicians and that, in breast cancer, has gone away

almost completely with the incorporation of advocates into grants and into review boards. It's a very happy relationship now.

I'm wondering whether or not the plastic surgery associations, possibly even the FDA, might consider a different kind of partnership where perhaps, as a simple idea, a position paper about ALCL or something like that was given so that it could be posted on these various sites. I'm not aware that that occurs and if I'm just simply repeating something that's already happened, I apologize. But it seems to me it would be a way to embrace a group that's captured some of the women who most want to get attention and information and they don't quite know where to go, so why not bring it directly to them rather than some brochure or something like that?

DR. CHEVRAY: So, the American Society of Plastic Surgeons has come out with a statement about BIA-ALCL, and I'm sure it must be on their website somewhere.

DR. LIPPMAN: Is it? I have no idea.

DR. CHEVRAY: I'm almost positive, although I haven't looked at it myself. I know it's published the society's publication arm, the journal *Plastic and Reconstructive Surgery*. The problem is that the women who have breast implants don't know that they need to look for something called ALCL. It's only after they get it that they know and then they go out and find it with no problem because they look everywhere online and it's easy to find if you know what you're looking for. But when they go in for a breast implant or a breast reconstruction, they have no idea what is -- what bad things could possibly happen.

DR. LEWIS: Dr. Burke.

DR. CHEVRAY: So, the surgeon's got to tell them.

DR. BURKE: I have two statements. One is that the American Academy of Dermatology did come out and say -- talk about HPV vaccines and we're looking -- and herpes vaccines were exhaustive. So, in other words, even though that's not -- they're

certainly diseases that we care for, but at least the society made a big point of kind of advertising to all dermatologists the necessity for that.

And I think that perhaps the cross-communication, we all have national meetings and we all have keynote speakers, some days there are five major speakers, and what I would suggest is that the plastic surgery and the aesthetic plastic surgery societies actively go out -- I mean, I would love to arrange that you give a speech, a half-hour speech, at our main symposium at our national meeting that talks about this. And, in fact, I'm now going to try to do that sometime in the academy instead of talking about my own research. But I think that if you go to different academies and even dental academies, I mean, we saw one case of dental implants causing something similar to some of these symptoms. But I think if you get your top speakers to speak as keynote speakers at national meetings of other societies, especially rheumatology, immunology, even lymphoma meetings, I mean, just to state everything that we know and what we don't know and what we're investigating, and I think that would really promote all of this because it would be in their journals, in their meetings, and the daily news brief we get from our national meetings, it could be a headline story but everybody will read it.

DR. LEWIS: Dr. Pawelski.

MS. PAWELSKI: So, it's directly related to Question (d) and then, Dr. Chevray, it does -- it is in the labeling right now for consumers. And so, when we talk about how it should be communicated, if you look at page 31, and this is class so everybody, it's going to be in all product labeling, I believe, the same way. But it talks about very small but increased risks, rare cases of death, how and when they were diagnosed, how long after the transplant, if you -- what symptoms patients should look for, how do they monitor them, they can help FDA understand the disease and the effectiveness, go to MedWatch and report it.

The profile information is in here. And it may not have a lot of white space, but it's

done in a half-a-page way and in a pretty easy to read way. So, I would just disagree, I think now, at least for the last few years and I think this change is probably a couple years old, it is in the information and it is in the brief summary to talk about it and call it out. So, you know, I don't know what else you can do to improve it because we looked at it here and other than white space and some other things, it's pretty thorough, relative to what we had talked about here.

DR. CHEVRAY: Right. And this is readily available online, on the internet.

MS. PAWELSKI: That's correct.

DR. CHEVRAY: So, patients aren't reading it because they either -- they got it and they don't want to read it, or they didn't know that it was that important.

MS. PAWELSKI: Right.

DR. CHEVRAY: Right?

MS. PAWELSKI: Yeah.

DR. CHEVRAY: It's there.

MS. PAWELSKI: Because then you can even look at ALCL in the index and it will take you to -- it's on two pages in here. So, it's there. I don't know how much better it could get, I mean, maybe some of the techniques Dr. Gallagher talked about.

DR. LEWIS: Okay, we're ready to move to (f). Are there opportunities to leverage existing social media platforms and other technologies to communicate benefits and risks associated with implants when deciding to obtain implants, and to stay informed on breast implant safety after receiving implants?

Dr. Portis.

DR. PORTIS: I don't know how this technology works, but I know if I go online and I search for something, the next time I go online I get an ad about something from that store. How do we, you know, when we're talking about social media, patients are searching for

things, are there ways that then -- again, that something pops up, that something comes that is a simple statement about things that they should be informed about or questions they should ask their doctor, and that that will prompt people because --

DR. LEWIS: Well, the patients that we've heard from clearly have a very active social media presence and they use it actively to maintain information among themselves, it seems to me, so I'm not sure if we need to worry about that. The question is how do we convey anything from existing institutions to that media?

DR. PORTIS: Well, part of what I'm talking about, though, we have a group of very informed people who are here and who are banded together. But I think, going back to the comments that Dr. Chevray and many others are talking about is patients, at the outset, when they're first starting to think about these things, when they're first starting to meet with their doctors, back to this point that they're not getting that brochure, they're not asking those questions, so very far back in the process because there are lots of patients who are not here today who don't know about these things, who aren't informed, that didn't even know, again, to ask the questions or who they should the ask the questions. And so, I appreciate what Dr. Chevray and others are saying, that it's on the surgeon and how can we also prompt patients early on in the process to be a better partner so that they know to ask the questions.

DR. LEWIS: Are there other comments from the Panel?

Dr. Gallagher.

DR. GALLAGHER: So, I'm wondering if asking the societies and including some of the women and their groups to make things available so that if someone does search for something that it can pop up because it's not going to be there if somebody doesn't create it. And I know when it comes to things like signing up for Medicare and for the insurance and all of those kind of things, HHS does some of that. A little of it, but some of it.

So I'm just wondering if FDA can't do it, does HHS do it, is there some other way that government officials can take some of this information and help people say here's what you should be asking of your doctor whenever, without saying, you know, don't do this or do -- other than to say these are some good questions you can ask or something like that to prompt them.

DR. LEWIS: Dr. Ashar, do you think you have enough to work with here?

DR. ASHAR: Yes, I do. Thank you very much for this discussion.

DR. LEWIS: In closing, I'd like to go around the table, we'll begin with Dr. Portis, and ask each panelist to comment on whether there are any additional actions not otherwise raised over the last two days that the FDA should consider, taking in regard to any aspect of these questions that we've had, not just the last question we were dealing with, but any of the other things that have occurred, if you feel there are things we haven't adequately covered.

Dr. Portis.

DR. PORTIS: Well, I'd like to thank the Panel for a robust discussion and for all the people who traveled here today to present and speak with us, I appreciate that. And I can't think of anything additionally, but I would like to echo this idea of both the surgical societies and FDA partnering with patients and patient advocates to be having these conversations about how to produce these things and I think that getting all of the groups together would be really important.

MS. PAWELSKI: I don't have anything to add. I just want to thank Dr. Lewis for keeping us on time and thank the Panel and then all the participants of the meeting, industry, and all the open public comment folks, I was honored to be part of this discussion. Thank you.

DR. LI: Just to comment, I want to -- my hope is actually that -- Dr. Lippman actually

mentioned it, but he stepped away, that there seems to be an adversarial relationship between some of the advocacy groups and either industry or perhaps even the FDA or us sitting here on the Panel, whereby though are not paid, and -- but I think that we're all here actually to try to do the right thing and I know many of the women, I believe your stories, you probably have been wronged or misdiagnosed or misled and I don't really dispute any of that and it's awful that those have happened, but that is not the intention and I think we're all here actually to try to improve that situation. And if we can somehow keep our passion but work on the same side, I think we'd get along a lot faster. Thank you.

(Applause.)

DR. SANDLER: I'd like to thank the FDA for inviting me to participate in the Panel discussion, it's been very interesting. And I'd like to echo the comments about dialogue between FDA and the patient community. I think that could only help.

DR. LEWIS: Dr. Gallagher.

DR. GALLAGHER: So we heard a little bit about it, but I don't think enough, in terms of suggestions, but one of the concerns that I have is that BII is still so undefined that we really need to work to define it so that it can be declared an illness because when someone gets an illness because they already had a surgery, the insurance should still cover that because the person got sick. That's the difference between, oh, I'm electing to do something and so I need to pay for that.

(Applause.)

DR. GALLAGHER: If someone gets sick, that's an illness, so we need to do something to get that declared as an illness with some level of definition or a syndrome or something so that insurance carriers can do it. Thanks.

(Applause.)

DR. LEWIS: Dr. Chevray.

DR. CHEVRAY: I'd like to make a comment that I just did not yesterday and that is there is one particular type of texturing, the salt loss method, that clearly has -- well, I shouldn't say clearly, but appears to have a substantially higher risk or is substantially more highly associated with BIA-ALCL and that texturing has been, I'll say, banned in we were told 38 other countries, and I think that should be considered by the FDA in this country.

(Applause.)

DR. CHEVRAY: So that one particular type of texturing has been identified as being just so much higher at risk of being associated with the lymphoma that it's striking, actually. The other one that was identified is polyurethane coating, which to my knowledge is not available anymore.

DR. ASHAR: I don't think it's ever been available in the U.S.

DR. CHEVRAY: Okay, I've seen patients -- okay, okay. I'm almost positive --

MS. PAWELSKI: If I could just clarify.

DR. CHEVRAY: -- it was.

MS. PAWELSKI: If I could just clarify or do you want to -- I mean, the -- it's not been banned in that many countries. So, there was one country, France, that asked for the product to be removed and the other is an issue with the renewal process. So, there's not a ban and I think that was presented to us yesterday.

DR. CHEVRAY: The presentation said Europe, Japan -- Europe kind of as a whole, Japan, Israel, and 30-something other countries.

MS. PAWELSKI: I didn't -- I wasn't -- okay.

(Off microphone comments.)

DR. LEWIS: Okay, Dr. Jaffe, did you make closing comments?

(Off microphone response.)

DR. LEWIS: Do you have any closing comments of things you think the FDA should

address?

DR. JAFFE: Well, I mean, one point that was brought up peripherally by a number of the public speakers was that surgeons, other than accredited plastic surgeons, doing breast implant surgery have a higher risk of complications, but no data was really presented on that. I don't know if you need to collect data on that point or if there are data, but the claim was made without any supporting data and I would just be curious about that.

DR. LEWIS: Dr. White.

DR. WHITE: I just want to endorse all the recommendations of other Panel members and Dr. Gallagher took my specific recommendation, so I specifically endorse that one.

(Applause.)

DR. LEWIS: Dr. Burke.

DR. BURKE: Well, first I want to thank the FDA very much for inviting me, and I'm certainly going to spread the news to the dermatologists and the rheumatologists that I speak to. And, first, it's an honor to be with all of the erudite experienced physicians that are on this Panel, and I especially thank all the patients that gave their testimonials. I think the fact that you came here and talked to us, I think we should just applaud you because, I mean, it's wonderful that you all came and could explain in detail what you've suffered.

But I still think that it's so important, we are researchers in the 21st century and we -- I mean, we just believe in evidence-based medicine and I think we can get the data. I think, in the retrospect, I think retrospectively in the registries, somewhere the data exists as a sticker in every single patient's chart about what implant they had.

So I'd ask every patient here to just get the stickers for every sequential surgery you had because that will add to the data, and we should -- and I think, on your networks of communication, just ask every patient to get their medical records and get that number and the sticker in the chart for every kind of implant that they've had, and I think that

retrospective data could be very meaningful. And the other important thing, I think, is to biopsy everything that -- every explant should be biopsied, all the serous fluid should be analyzed, it should be run through a cytometer to see the CD30.

(Applause.)

DR. BURKE: And we can do extraordinary -- if we knew -- I think the companies should tell us everything in that implant, I mean if there -- what could leak.

(Applause.)

DR. BURKE: And then that could be looked for. I mean, I think that chemistry is certainly available, and I think that that's a very important thing to emphasize to everyone removing an implant. So, I mean, those are my kind of final comments.

DR. LEWIS: Dr. Leitch.

DR. LEITCH: So, I think, you know, emphasizing patient choice. You know, one thing I worry about is that if we, as a general principle, leave breast implants as so maligned that people are afraid to have that type of reconstruction when they have breast cancer, we're going to have a real issue and, you know, people not being able to be reconstructed because there are a number of patients who can't have autologous tissue for one reason or another and do need implant-type reconstruction.

So while we need to be figuring out what is the best way that implants can be used and the best type and, you know, the use of the AlloDerm type, the ADMs, how that can best be used, but realize that we need to have choices available and then also the choice about how people are followed, you know, that they can make decisions about -- they know that they need to think about that and then make a decision about how they want to pursue it.

And whenever we try to do clinical trials to better understand the problems in breast implants, we do need the compliance of the patients to participate and, you know, that's

how we make progress in cancer research and so I think, in this arena, too, we have to have, you know, people who go into those studies to be willing to do the long-haul participation so we get the long-term data that we need, and the companies need to facilitate that participation, as well, and make it easy for the patients to participate in the long term.

DR. LEWIS: Dr. Ashar, do you have any final comments?

DR. ASHAR: I'd just like to thank everybody that took these 2 days out and all the months of preparation in advance of this meeting to come, the patients, caregivers, providers, professional societies, the manufacturers, all the FDA staff, and this Committee. It's been very helpful, and we appreciate your input.

DR. LEWIS: I'd like to thank the panelists for their efforts and contributions, as well as all the speakers who have provided the expert advice and data for us through this. I appreciate all of them who have come. I appreciate the people in the audience who have come and obviously made a major investment of time and money and coming here to present and make their case known, it's been immensely helpful to the Panel in understanding all of this. And I would sort of like to compliment Dr. Ashar, Commander Garcia, and their staff for the extraordinarily well-organized forum here. The audiovisual stuff has worked incredibly well, there have been no hitches whatsoever, and I think it's really been exemplary the way your staff has carried this off and I really thank you for all of that.

And with that, I close this session of the General and Plastic Surgery advisory board. Thank you.

(Whereupon, at 5:50 p.m., the meeting was adjourned.)

C E R T I F I C A T E

This is to certify that the attached proceedings in the matter of:

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were held as herein appears, and that this is the original transcription thereof for the files of the Food and Drug Administration, Center for Devices and Radiological Health, Medical Devices Advisory Committee.

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