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UNITED STATES OF AMERICA

FOOD AND DRUG ADMINISTRATION

MEDICAL DEVICES ADVISORY COMMITTEE

GENERAL AND PLASTIC SURGERY DEVICES PANEL

GENERAL ISSUES PANEL

August 13, 2025

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Via Web Conference

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90 Church Street

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Good morning. I would like to call this meeting of the general and Plastic Surgery Devices panel to order. It is now 9:00 AM My name is Dr. Hobart Harris. I'm the chairperson of the panel. I'm also a professor in the Department of Surgery at the University of California San Francisco with research interest in wound healing and the host response to infection. I note for the record that the voting members present constitute a quorum as required by 21 CFR part 14. I'd also like to add that the panel members participating in today's meeting have received training in FDA device Law and regulations. Please be aware that this meeting is being recorded and will be accessible to the public, including the Zoom chat. For today's agenda, the committee will discuss a new indication for use for dermal filler devices in the décolletage area, and will make recommendations regarding risk associated with new indications for use, such as in the décolletage area, the potential impact of filler material on imaging studies and clinical exams (for example, breast cancer screening), pre-market and post-market study assessments for benefit and risk, removal of dermal filler implant material, and patient preference. Before we begin, I would like to ask our distinguished committee members and FDA representatives present virtually to introduce themselves. Committee members, please turn on your video monitors if you've not already done so and unmute your microphone before you speak. When I call your name, please state your area of expertise, your position, and your affiliation. So we'll begin with Dr. Alam.

Good morning. My name is Murad Alam. I am a vice chair and professor of dermatology at Northwestern University in Chicago and a voting member of this panel,

Dr. Galandiuk

Yeah. My name is Susan Galandiuk. I'm a Colonorectal surgeon from the University of Louisville and a panel member.

Dr. Hunt.

Hello, I'm Kelly Hunt. I'm professor and chair of the Department of Breast Surgical Oncology at the MD Anderson Cancer Center.

Dr. Sandler,

Sorry. I thought you were going alphabetical, maybe. I'm Howard Sandler. I'm the chair of Radiation oncology at Cedars Sinai in Los Angeles.

Thank you. Dr. Matarasso.

Hello, I'm Alan Matarasso. I'm professor of surgery at Hofstra Northwell and Systems Chief of Cosmetic Surgery and the current president of the Plastic Surgery Foundation.

Thank you, Dr. Shuffett.

Good morning. I'm Sandy Shuffett. I'm a full-time breast imager at Baptist Health Lexington, former faculty, School of Medicine, Emory University, also on the board of trustees at University of Kentucky for over six years. President of the Board of Medical Licensure in Kentucky as well as a member of the Board of Medical Licensure for four years. I'm presently a panel member.

Thank you, Dr. Ballman.

Hi, I'm Karla Ballman. I am a professor and the division chair of clinical trials and biostatistics at Mayo Clinic in Rochester, Minnesota, and I'm a panel member.

Thank you, Dr. Milburn.

Hi, I'm Meghan Millburn. I'm a breast surgical oncologist and also the program director of the Breast Surgical Oncology Fellowship at Luminis Health and I run the Medical Center in Annapolis.

Thank you. Dr. Spector.

My name is Myron Spector. I'm a biomedical engineer, professor emeritus at Harvard Medical School and affiliated at MIT working in the area of biomaterials and a long time ago, Chairman of this panel.

Thank you. Dr. Grimm.

Hi everyone. I'm Lars Grimm. I'm a breast radiologist and associate professor of Department of Radiology at Duke University Medical Center.

Ms. Pawelski,

Good morning, Lynn pawelski. I'm Vice President Global Regulatory Affairs and Country Quality and Regulatory for Baxter Healthcare in Deerfield, Illinois, and I'm the industry representative on the panel.

Thank you, Ms. Brummert.

Yeah, my screen did something weird. Good morning. My name is Rachel Brummert and I will be serving as the consumer representative today.

Thank you. Ms. McCall.

I'm Debbe McCall and I'm your patient representative for today.

Thank you. Ms. Chauhan, she's not with us. Okay, Ms. Vuniqi,

Good morning. I am Bleta Vuniqi. I'm a biomedical engineer, currently acting office director in Office of Health Technology four, which is the Office of Surgical and Infection Control Devices here at CDRH FDA.

Thank you. Dr. Chang.

Hello, I am Cynthia Chang. I am a biomedical engineer. I'm the acting division director for the Division of Plastic and Reconstructive Surgery Devices in the Office of Surgical and Infection Control devices in CDRH, FDA

Thank you and Ms. Washington.

Good morning. My name is Evella Washington and I'm the designated federal official for this meeting.

Thank you. So once again, I'd like to remind all attendees to mute their microphones until they're called upon to speak. If you have a question, please use your raise hand feature and unmute your microphone once I call on you. Ms. Evella Washington, the designated federal official for today's general and Plastic Surgery devices panel will now provide the conflict-of-interest statement and some introductory remarks.

Good morning. I will now read the conflict-of-interest statement. The Food and Drug Administration is convening today's meeting of the general and plastic surgery devices panel of the Medical Devices Advisory Committee under the authority of the Federal Advisory Committee Act (FACA) 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 at 18 USC subsection 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 USC subsection 208.

Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have financial conflicts when it is determined that the agency's need for particular individual services outweighs his or her potential financial conflict of interest. Related to the discussions 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 purposes of 18 USC subsection 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 committee will discuss a new indication for use for dermal filler devices in the Décolletage area and will make recommendations regarding risks associated with these indications for use such as in the Décolletage area, the potential impact of filler material on imaging studies and clinical exams such as breast cancer screening, pre-market and post-market study assessments for benefit and risk, removal of dermal filler implant material, and patient preference.

Based on the agenda for today's meeting and all financial interests reported by the committee members, no conflict-of-interest waivers under 18 USC subsection 208 have been issued in connection with this meeting. Lynn A. Pawelski of Baxter Healthcare is participating in this meeting as a non-voting industry representative acting on behalf of regulated industry. Consistent with Commissioner Makary's April 17th, 2025 statement. FDA is only including industry representatives and advisory committee meetings when required by statute. FDA is required to include any industry representative in today's meetings under 21 USC subsection 355(n)(3)(c). Industry representatives are not appointed as special government employees nor are they regular government employees. Industry representatives serve as non-voting members of the committee. Non-voting industry representatives represent all regulated industry and not any particular association, company, product, or ingredient and bring general industry perspective to the committee. Under FDA regulations, although a non-voting member serves in a representative capacity, the non-voting member shall exercise restraint in performing such functions and may not engage in unseemly advocacy or attempt to exert undue influence over the other members of the committee.

Today's meeting includes guest speakers who will give a presentation to the committee and respond to questions from the committee, but they will not

participate in the committee deliberations or render advice to FDA guest speakers are non-government employees or special government employees participating in a nonofficial non-governmental capacity who are not bound by conflict of interest laws and regulations and are not formally screened for conflicts of interest. However, in the interest of transparency, FDA asks that guest speakers address any personal financial involvement with the firm, product, or other entity affected by the committee's discussions. Guest speakers disclose such interest to allow the audience and the committee to objectively evaluate their presentation. Today's speakers have reported the following interest in relation to the matter before the committee: Dr. Glaberg has acknowledged that he has past and current consulting and speaking interest with Allergan Corporation, Solventum (3M) Healthcare Corp, Corza Medical (Quill), Guidepoint Global, and Gherson Lerhman Group, and reported Stock Holdings in Red Rock Holdings, Scar Guard and Evolus Inc.

Dr. Shridharani has acknowledged that he has past or current contract, Principal Investigator, Consulting, Stockholding, and speaker interests with Sofregen, Collplant, Allergan, Galderma, Prollenium, and Tiger Aesthetics. Doctors Council and Gutowski have reported no interest in relation to today's meeting. Disclosure of conflicts of interest for guest speakers follow applicable Federal Laws, regulations and FDA guidance. The guest speakers participating in this meeting are

presenting the views of their professional societies, not their personal views. FDA asks that all other participants, including the industry representative and open public hearing speakers advise the committee of any financial relationships that they have with any affected firms, its products, and if known, its direct competitors. We would like to remind the members that if the discussion involves any products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participant needs to inform the DFO and exclude themselves from the discussion and their exclusion will be noted for the record.

Thank you. We would like to remind the members and consultants that if the discussions involve 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 the other participants to advise the panel of any financial relationships they may have with any firms at issue. A copy of this statement will be available for review and will be included as part of the official transcript. Please be advised that all participants should turn on their cameras and mute their microphones. If you wish to speak, use the raise hand feature at the bottom of the zoom screen and wait to be acknowledged by the chair.

Once acknowledged, you should unmute your microphone. When you are done speaking, click the raise hand button again to lower the hand and mute yourself. If you need to step away from your computer, please send a direct message to Dr. Harris on the Zoom platform and be sure to turn your camera off and make sure your microphone is muted. Please unmute your microphone before you speak and mute it again when you are done. To assist the transcriber with identifying who is speaking, please be sure to identify yourself each time that you speak. For press inquiries, please contact the HHS press room at www.hhs.gov/press-room/index.html or call 202-690-6343. Thank you very much, Dr. Harris.

Thank you. I would now like to just invite two of our additional panel members to introduce themselves beginning with Dr. Minkis.

Hello, my name is Kira Minkis. I'm a Mohs and dermatologic surgeon and the head of that division at Weill Cornell in New York City. Thank you for having me on this panel.

Thank you, and Dr. Zuley.

Hi, I am Rita Zuley. I'm professor of radiology, vice Chair of Quality and Chief of Breast Imaging at the University of Pittsburgh.

Great, thank you. So, thank you also Ms. Washington for your conflict of interest presentation and remarks. At this time, I'd like to ask Ms. Bleta Vuniqi, the acting

office director for the Office of Surgical and Control devices who will provide some opening remarks. Then we will view FDA's presentation on today's meeting topic. I'd like to remind the public observers at this meeting that while this meeting is open for public observation, public attendees may not participate except at the specific request of the panel chair Ms. Vuniqi,

Good morning and welcome to the US Food and Drug Administration's Advisory Committee Panel meeting. My name is Bleta Vuniqi. I'm the acting Office director of the Office of Health Technology Four, the Office of Surgical and Infection Control devices within Office of Product Evaluation and Quality in the Center of Devices and Radiological Health. Our division of plastic and Reconstructive Surgery is responsible for the review and regulation of dermal filler devices. I would like to begin by recognizing and thanking the individuals of the FDA's Dermal filler team who have devoted commendable efforts in preparing for this meeting. The agenda for this meeting and the executive summary have been provided and they're also available online at FDA's website. To supplement the executive summary and the FDA presentations, we have invited external speakers to provide insights on specific topics. As we look forward to the discussion, there are certain aspects of the agenda I would like to highlight for you.

Dermal fillers are aesthetic devices, meaning that the decision to proceed with injection procedure is elective. The benefits are dependent to a great extent on the value assigned to them by the patients themselves. Likewise, the risks need to be weighed against the benefits by each patient in consultation with their healthcare providers. In 2021, our division held a general issues panel meeting on dermal fillers on the risk of intravascular injections and the role that patient preferences information plays in evaluating the benefit risk profile. This was motivated at that time by the abundance of new dermal filler submissions, both in the form of new formulations and devices as well as new indications and anatomical locations. The panel brought into practice new safety procedures including labeling updates to mitigate risk of vascular occlusion. Since the 2021 panel meeting, we have continued to see an expansion in new dermal filler approvals as well as ongoing interest in new indications for use such as the Décolletaage area.

This new indication presents additional specific risks that we will ask our advisory committee panel to discuss today in light of the aesthetic benefits that they offer to patients. For example, in the décolletage location, there's a potential for filler material to impact imaging procedures such as breast cancer screening as materials may be visible on imaging. In consideration of this and other potential risks, we will discuss what assessments and mitigation strategies may support the benefit

risk determination for Décolletage treatment. When the presence of dermal filler material presents a concern, there's the question of how to remove the implanted device. While removal methods have been reported in the literature, no products for removal have been approved by the FDA and there's still much that is unknown that warrants discussion. Finally, we will discuss how to enhance the informed decision process of patients considering these treatments through benefit risk assessments and patient preference information. We appreciate everyone's interest and work up to this point and look forward to the informative discussion over the course of the day. I would now like to introduce my colleague from FDA's Center for Devices and Radiological Health, Dr. Taili Mata who will be providing the clinical and regulatory overview of dermal fillers.

Good morning. My name is Taili Thula Mata and I'm a biomedical engineer and lead reviewer in the division of plastic and reconstructive surgery devices. Today I'm going to be providing an introductory clinical and regulatory overview of dermal fillers. For my talk, we'll be discussing some general background information about dermal fillers, the regulatory process followed by an overview of their indications for use, various considerations when using dermal fillers, their benefits and risk and their increasing and evolving use dermal fillers, also known as injectable implants are used to fill wrinkles and provide volume. Dermal fillers

are soft moldable products composed of a variety of materials ranging from synthetic material to material sourced from bacteria or animals. Some examples of these materials are crosslinked hyaluronic acid, calcium hydroxyapatite, and poly-L-lactic acid. The material properties and sourcing can impact the resorption profile and time to absorption of the product.

The resorption profile describes the complete pattern of how the dermal filler is absorbed from its dosage form over time. It focuses on the entire absorption process while the time to absorption refers to specific time points in the absorption process. Also, the diverse material properties of dermal fillers can significantly influence the effectiveness and accuracy of various imaging diagnostic tools, potentially affecting clinical interpretation and patient outcomes. In addition to the material components, some of the derma filler products regulated in CDRH contain analgesics, such as lidocaine or mepivacaine, in their formulation. These are drugs approved in the Center for Drug Evaluation and Research, or CDER, and therefore these dermal fillers are combination products. Dermal fillers are considered Class three medical devices. At FDA we classify devices best based upon risk. Class three devices represent those devices with the highest risk to patients. In the case of dermal fillers, they are high risk medical devices because they are considered implants, and they present a potential unreasonable risk of illness or injury.

There are two product codes associated with dermal filler products. LMH and PKY. LMH is used for products that are intended for use on the face, while PKY is used for products that are intended for use in the back of the hand. The review to determine marketing of a dermal filler product is conducted through the pre-market approval or PMA application process. The review focuses on the benefits and risks of the product, including substantive review of preclinical and clinical data and the product labeling. Any information relevant to the safety and effectiveness of the device must be provided and reviewed. For dermal fillers, both clinician and patient labeling are carefully reviewed by FDA.

Dermal fillers have been approved for various indications that include different anatomical areas on the face and the hands in adults over 21 years of age. FDA reviews and approves dermal fillers, not only for new formulations but also for new indications with the specific defined anatomic locations. The reason being that different anatomic sub regions such as nasolabial folds, lips, chin, et cetera, present risks specific to the underlying anatomy such as nerve, blood vessels, muscles, organs, and the function of that anatomic region. dermal filler products have received approval for 10 specific anatomic locations with intent to create smoother or fuller appearance in or adjacent to the injected area in addition to the lip, cheek,

peroral rhytids and nasolabial folds, other indications include infraorbital hollowing, jawline, and temple augmentation.

The benefits of dermal fillers include the correction of age-related deficit such as wrinkles or augmentation of body structures for aesthetic purposes. As with any device, there are risks associated with dermal filler use. The risks may occur shortly after injection or may occur later. Most injection related risk associated with dermal feathers such as swelling and bruising occur shortly after injection and typically resolve in a few days to weeks. In some cases, adverse events may emerge weeks, month or years later. Common risk of dermal fillers include swelling, pain or tenderness, firmness or induration, bruising, redness among others. Less common risks include granuloma, lumps or nodules, injection site infection, open or draining wounds, et cetera. Other less common, but potentially more serious adverse reactions include angioedema and anaphylaxis as well as adverse events involving inadvertent intravascular injection which may lead to irreversible damage including blindness. Note that based on preliminary review of published literature and medical device reports, the FDA has identified cases of bone resorption in the chin, jaw, midface, or forehead in patients who received hyaluronic acid dermal filler injections directly on the bone.

In some cases, adverse events associated with dermal filler injection led to the need to remove the device. Possible reasons for removal of dermal filler implant material include intravascular injection, visual disturbance, impending necrosis, nodule formation, overcorrection, an undesirable aesthetic result or other factors. Removal of the injectable filler depends on the composition of the product. There are no products approved by FDA for removal of any type of dermal filler device, but several management strategies have been proposed and tested in clinical use under the practice of medicine. With new indications and injection locations, unique risks may lead to additional reasons that device removal may be necessary. My colleague, Dr, Sung Yoon will discuss unique risks associated with the décolletage injection location in the next presentation and we look forward to the panel feedback on how the benefit risk profile for dermal fillers injected into the décolletageshould be evaluated considering the current removal options. In 2024, the use of dermal fillers continued to increase in the United States. Dermal fillers are the second most commonly performed minimally invasive aesthetic procedures with over 6.2 million dermal filler treatments performed in 2024. Since the 2021 general issues panel meeting on dermal fillers, there have been 12 dermal filler PMA approved for new products or new indications.

Also, with the growth of dermal filler usage, new indications for use are being proposed and new variations of devices are being designed. There has been increased interest in new injection locations for dermal fillers such as in the décolletage area, also referred to as the décolleté, the thighs, and other areas of the body other than the face. With regards to the décolletage region, given the proximity of the décolletage to breast tissue, there are unique risk and concerns associated with treatment of this anatomic location. We'll be discussing the benefits and risk of dermal filler injection in the décolletage area in the next presentation and look forward to panel feedback on these topics. I would like now to introduce my colleague, Dr. Sung Yoon, who will be giving the next presentation.

Thank you. Good morning. My name is Sung Yoon, and I'm a board certified plastic surgeon and a medical officer in the division of plastic and reconstructive surgery devices. Today I will be discussing the benefits and risks of dermal fillers with new indication for use in the décolletage. In this talk, we'll first discuss the treatment of the décolletage, which will include an overview of the anatomic region, consider the décolletage and its proximity to the breast, a brief discussion regarding screening for breast cancer, the risks specific to injection of dermal filler

into the décolletage and the agency's proposed strategies to address those risks. In addition, we will present the MDR analysis for the upper anatomic indications including neck, chest, décolletage, and breast.

The décolletage refers to the upper chest region, though there is no strict definition based upon universally accepted anatomic landmarks. As illustrated in this figure, the décolletage is typically represented as a triangular region. It extends superiorly to the clavicles. The lateral extent of the décolletage may vary and may extend as far as the lateral extent of the clavicle inferiorly. The décolletage extends to approximately the xiphoid process. Dermal fillers may be injected to treat lines and wrinkles which are typically oriented vertically in this region. The décolletage is in close proximity to the breast tissue and there is the potential for a considerable amount of overlap, which is patient dependent. The exact position and extent of breast tissue can vary between individuals. In general, the breast region extends horizontally from the sternum to the mid axillary line and can extend vertically from the clavicle to the rectus abdominis inferiorly.

As you can see in this figure, these anatomic regions may overlap considerably. Given the proximity of the breast and the potential for substantial overlap. It is important to also discuss breast cancer when considering injection into the décolletage. Breast cancer is the second leading cause of cancer death in women.

The lifetime risk of a woman in the US developing breast cancer is approximately 13%. Given this risk, the current recommendations for breast cancer screening typically include routine mammograms for all women at average risk. It is also important to note that patients receiving treatment for the décolletage are predominantly female.

For décolletage, the indication in general is for injection to treat lines and wrinkles within this region. Due to the overlap of the décolletage with breast region and given that most patients receiving treatment are female for whom routine breast cancer screening via mammography is widely recommended, there are new specific risks and concerns related to injection into this new anatomic location including imaging interference, impact on clinical exams, and impacts to the breastfeeding and the lymphatic system. With regards to risk that the agency has considered the first new specific risk of injection into the décolletage relates to the potential for dermal fillers to cause interference or other findings on breast cancer screening studies. The effects on these imaging studies from different dermal fillers of various chemical composition into décolletage is unclear. There is literature that has reported on the potential for dermal fillers to make a mask an underlying malignancy, though this was not specific to the décolletage region.

In addition, there is report of multiple patients who have had lymph node enlargement following complications from dermal fillers, which were injected many years prior to imaging studies where the lymph node enlargement was documented. Given this available body of knowledge regarding dermal fillers, there is concern that misdiagnosis via the screening test may result in additional unnecessary testing or procedure as well as delay diagnosis of these patients. The panel will be asked on additional risk to be considered for injection into the décolletage area as well as any sub populations to be excluded because the benefits may never outweigh the risks.

To address this risk for pre-market clinical study, we propose the collection of baseline imaging, mammograms, ultrasound or MRI, preferably within two years prior to injection and post-injection. These imaging should be evaluated by a committee comprised of subject matter experts. If the mammogram or imaging study was not performed pre-market, the information may be provided in a post-approval study. In addition, we propose inclusion of radiographic images of the implanted device being included in the labeling for the device. Second, new specific risk relates to potential for diagnostic error in clinical examinations. Dermal fillers have long been known in the literature and in MDR reports to cause

granulomas, lumps, bumps and nodules and filler material may also migrate. These adverse events have been described weeks to years after injection. These adverse events may lead to positive findings during clinical examination. More specifically, there are concerns that injection into the décolletage may result in positive findings during clinical breast examinations where palpable filler nodules or granulomas or mistaken for suspicious breast masses or conversely, interference where presence of filler material mask or obscure detection of breast pathology.

There is also the potential for misdiagnosis in patients who have received injection of dermal filler into their décolletage if a new suspicious mass is inaccurately diagnosed as a complication of the dermal filler. This will then lead to delayed diagnosis and treatment. To address this risk, we recommend device cards be provided to patients which may be included in patient records for dermal filler injection into the décolletage To help ensure that patients are aware that these dermal fillers injections should be considered relevant procedures when undergoing mammography or other breast imaging and that future healthcare providers are adequately informed, these device cards would include the name of the filler, the type of filler, and the date of injection. It may also include information related to the radiographic appearance of the filler. In addition, we recommend a post-approval study to evaluate late onset adverse events and their

effects, if any, on the clinical diagnosis of breast masses. The third new specific risk relates to the proximity of the breast tissue, which may then affect breastfeeding as well as the lymphatic drainage system of the breast. Information relates to this new risk is limited and input from the advisory panel is needed. The potential outcomes include negative impacts on breastfeeding and obstruction or other adverse impacts on the lymphatic drainage system.

To address this risk, we recommend premarket follow up until quiescence of the inflammatory response as well as post-approval studies to evaluate the presence of any impact on lactation or the lymphatic system, the panel will be asked on the mitigation strategies proposed as well as any additional assessments or mitigations that should be considered. Even though injection into the décolletage, breast, chest, or neck is not an approved indication for dermal fillers devices in the United States. Several MDR reports have been received for this off-label indication to evaluate the risks of injection to this anatomic location, an MDR analysis was performed by the agency for all dermal filler devices. From 2007 to 2024, there were 186 serious injury reports for dermal filler injections into the chest, breast, neck, and décolletage regions. The top reported code include nodule, swelling, pain, inflammation, and erythema. Of noted, there were also two reports of pulmonary embolism.

Although MDRs are a valuable source of information, this passive surveillance system has limitations including the potential submission of incomplete, inaccurate, untimely, unverified, duplicate, or biased data in the reports. In addition, the incidence or prevalence of an event cannot be determined from this reporting system alone due to potential under-reporting of events and lack of information about frequency of device use. This concludes the presentation of the benefits and risks of dermal filler injection into the décolletage. We welcome panel's consideration of these points when we discuss the questions later. Thank you very much. Next, Dr. Olafemi Babalola from the FDA will present on patient preference information.

I am Olufemi Babalola the health Economist within the division of Patient-Centered Development in the Office of Strategic Partnerships and Technology Innovation at the Center for Devices and Radiological Health. For over a decade, CDRH has been committed to bringing the patient's perspective and experience into our regulatory efforts. In 2016, FDA issued a guidance document on the role that voluntary patient preference information can play in regulatory decisions. PPI is defined in our guidance as qualitative or quantitative assessments of the relative desirability or acceptability to patients of specified alternatives or choices among outcomes or other attributes that differ among alternative health interventions.

Patient preference information is not the same as clinical trial data information. The patient preference information study does not replace such clinical data, but instead assesses the relative value that patients place on the medical products profile or its alternatives. Patient preferences can help evaluate how patients view trade-offs between benefits and risk of various treatment options.

The FDA has published guidance regarding what factors may be considered in benefit risk determinations. CDRH recognizes patient preference information can supplement the assessment of benefits and risks. Patient preference information studies can help inform how options will be considered by reasonable patients as they consider their health choices. Patient preference information assessments consider both the patient's willingness and unwillingness to accept the benefits and risk of the device relative to alternatives. PPI can be useful during FDA's benefit risk assessment for certain devices in several major ways, including to help identify the most important benefits and risks of a device for a particular indication for use from a patient's perspective and to help clarify how patients think about the trade-offs of these benefits and risks. To be included in FDA's benefits risk assessment, patient preference information studies need to be designed, conducted, and analyzed in a way that allows for useful evidence to be generated. The PPI guidance lays out features that can assist in the determination of whether a study is

of high quality to generate valid scientific evidence, well-designed and conducted patient preference studies include features such as the use of established good research practices, effective communication of the benefits and risks, features or attributes relative relevant to the treatment options.

An important step in the development of a PPI study includes the identification of key features or attributes that characterize the benefit risk profile for a given device and indication of use. Such attributes of a device include demonstrated measures of effectiveness, safety, and other device characteristics that may impact benefit risk considerations, including but not limited to benefits, risks, duration of effect, and frequency of use. Established good research practice in the development of PPI studies recommend not more than nine attributes in PPI studies attributes should be of clinical and regulatory relevance and salient to patients. The panel will be asked to provide input on which key risks the panel will recommend for incorporating into a patient preference information study to estimate the maximum risk that patients will be willing to accept. In other words, are there specific risks that the panel is most concerned about given the potential benefit for this new indication?

Thank you.

Thank You to Presenters in the FDA. Now, are there any panel members that have brief clarifying questions for the agency? So remember, please use your raised hand function. Dr. Alam.

Hello, Murad Alam. Thank you for that nice presentation. You mentioned, I believe FDA mentioned that they're relying primarily on MDR reports. Does FDA have any data from any source pertaining to the incidence of general or specific complications related to injection of dermal fillers into the décolletage?

Hi, this is Cynthia Chang. Maybe I can get started on that. I believe the FDA has looked at MDR data for these specific anatomical regions and turn it over to Dr. Taili Mata regarding the adverse event reports specific

To décolletage.

Good morning, Taili Thula Mata. Thank you, Cynthia. Yes, we have received MDR reports specific to décolletage area. For those MDR reports, the top problem codes that we have received include swelling, pain, inflammation, skin irritation, erythema, edema, urticaria, dysphasia, granuloma, and nodule formation. That's the yes.

Would you have any idea about the incidence? What number of these complaints there are relative to the number of injections being done in the area?

Well, as we only get what is reported and this being off label use, we have received, we, from the MDR analysis we have performed, we have received 20 MDRs specific to the area, the décolletage area.

Dr. Ballman,

Has there been any reports of missed breast cancers or misdiagnosis of breast cancer when there wasn't due to the injection in this area?

Thank you for the question. I'd like to invite Dr. Sung Yoon the address that question.

Hi, this is Sung Yoon from the FDA. I think your question was just for clarification, is your question for the MDR or is your question in general for literature?

Well, either, I mean any sort of indication either from the literature or from MDR or is the FDA aware of any such occurrence?

For the MDR question, I can defer that to Dr. Taili Mata, but in terms of actual, and as Dr. Mata had stated earlier, MDR is a passive collection of information, so to state that if it wasn't reported in MDR, it did not exist,that's something we cannot state. However, we are not aware of specific reports where breast cancer was missed, but again, the reporting for the MDR is passive, so as you know Dr.

Ballman, it's difficult to state whether that has never happened. And one more additional detail is that as you know, the indication for décolletage has not been approved or there are no devices, so that could also underestimate the number of reports that may or may not have been reported to MDR.

Thank you,

Dr. Zuley, you have a question?

Yeah. Thank you. So one of the things that I didn't see in review of the packet that was sent was a comment around the timeframes of these different symptoms. So it appears that inflammation and erythema swelling are acute, but is there any evidence or documentation from currently approved fillers of how long that phase lasts and when one would expect to see granuloma and lumps form following the injection?

This is Cynthia Chang, so I believe from the MDR data there can be a variety of timeframes which are represented. However, I'd like to turn it over to my medical officer colleagues to address more detail regarding the timeframes of when these various events might occur. I'll start with Dr. Yoon.

Dr. Zuley, thank you for your question. And this I believe was already stated in our executive summary, but as you know, injection site reactions are common and the ones you mentioned about the inflammation or pain, those are usually immediate

or what we called acute and which can be immediately after injection, and that may last for days. As for the nodules that you had asked about, it really depends on the filler and as you know, every filler is different composition wise, and so it depends on the filler and it also depends on the patient. So the nodules, which are considered foreign body reactions, it can occur months, weeks, months later. That's what we have seen in the approved devices that have been that we've seen at the FDA.

Thank you. Dr. Specter. Oh, sorry, was there. This

This is Cynthia Chang. Perhaps Dr. Mata could also comment on the timeframes in the MDRs that have been.

Yes, as Dr. Yoon mentioned, it will depend on the dermal filler, but we have received MDRs where these long-term adverse events have occured, stayed after three months, but as long as three years or six years after the treatment.

Okay. Dr. Specter,

Yeah, it relates to the nodules and the MDRs. You just mentioned the nodules. Dr. Yoon could foreign body reactions, but is there any fibrotic component to a nodule? I'm just trying to get the definition, histological definition of what a nodule is because it's the highest incidence in the MDR.

Well, I'd like to invite Dr. Sung Yoon back to address the question.

Sorry, I was having audio trouble. Thank you for the question. Yes, nodule is the highest, and again, there are, it depends on the filler type. As for the histology, I can't really state whether the nodules are only from foreign body by reaction. It could be from inflammatory reactions as well, but I don't think I can speak about the histology of the nodule, but it is our understanding that it is an inflammatory process and that it is a part of the, it may be part of the foreign body reactions to the dermal filler material.

Dr. Matarasso,

Thank you. This is Alan Matarassaso from New York Plastic Surgeon. I have two questions and comments. I'd like to circle back to my esteemed colleague, Dr. Alam's question about the incidents. If this product were to be approved and sold specifically for the décolletage area, are we able to get an incidence of what is reported in terms of complications? That's my first question.

Thank you for that question. I can start and I'll ask Dr. Taili Mata to join if she has any additional comments. The expectation is that any adverse events are reported to the agency via the medical device reporting system. So the expectation would be that any reportable events that may cause injury or potential to cause injury are reported to the agency at this time, due to the fact that the injection in the décolletage area has not been approved, although we're seeing some reportable

events, we believe that that number is quite low in comparison to if the devices were to approve and it will be used in potentially larger amounts than it is today.

Specifically, for example, we have fillers that are approved for the angle of the mandible and so on. Can the manufacturer be compelled to report how many times they've sold it for the décolletage area so that when we find out there are 20 MDR events that we actually can calculate the incidents? Is that feasible?

This is Cynthia Chang. I believe it's always a question of interest what the incidents of these various adverse events may be. It is challenging to develop a denominator for any of our medical device reporting adverse events. Sales information may be proprietary, and in addition, it's also I think, challenging to even for the manufacturers to determine what is being used for what indication, as that would often lie with the practitioners in terms of how they're using the devices, we do receive information from manufacturers via annual reports for our pre-market approval class three devices from which we can understand the numbers of units sold from the FDA perspective. However, there's certainly a gap between the numbers sold and used and of course the number of patients actually treated in specific anatomical regions. So definitely a great question. There are certainly challenges with being able to calculate a specific incident.

I appreciate that. And may I just to conclude with one additional question with regards to the breast, do we have any reports specifically with masses appearing in the breast or difficulty with radiographic interpretation based on injections that were done in that anatomic area?

Perhaps I'll turn to Dr. MaaMata to comment on any specific reports in the breast. Thank you.

Yes, we have received very few MDRs on dermal fillers being used for the breast or the nipple augmentation. In terms of imaging impact, we do not have that information. That was not reported in the MDRs. There were other complications reported.

Thank you. Okay, Dr. Alam.

Thank you. Murad Alam, follow on questions. I think what Dr. Ballman was asking related specifically however to the issue of breastfeeding, have there been reports where people were having, women were having difficulty with breastfeeding because of prior injections of dermal fillers at the site? Thank you.

I'll start and then I'll invite Dr. Taili Mata to address the question in more specifics. Due to the fact that injections in the D décolletage area have not been approved by the agency at this point, there's limited post-market data that we have available to really make a good judgment or a risk-based decision. Hence the reason that we

really look for your guidance and input during the panel today. But I'd like to turn it over to Dr. T if there's anything specific that you'd like to add.

Thank you. Yes. I mean we have not received is limited. The information that we have received, we have not received any information in the MDRs related to breastfeeding. When we do get some reports is that the patient has received the dermal filler and they're pregnant, and that's as far as we get. There is no follow up on those reports.

Dr. Minkis?

Right. Minkis. I wanted to know if there was any precedence for obscuring imaging or delays in diagnosis of any tumors in other locations such as in approved locations on the face where I presume you probably have quite a bit of data due to duration of approval in various locations on the face.

Thank you for the question. I'd like to invite back Dr. Taili Mata in addition, Dr. Jackie Francis may be able to add additional contact to that question.

Thank you. Thank you for the question. In relation to the MDR reports, when we did an analysis on different other locations and image impact, most of the reports when they use imaging, what it was reported was for the removal and how the efficacy of that. We have a few reports where they could see the dermal filler, they could see an obstruction, they didn't know what it was and they had to do a biopsy

to remove it. But those are very, very few incidents and again, just a reminder that this is a passive surveillance tool that we have. Thank you,

Dr. Galandiuk.

I apologize. I've had horrible computer problems and now I'm on my laptop, so hopefully everything will be smooth from now. And because of that, I apologize if my questions have been asked previously by other people, but just from looking at the materials we were provided previously, I had two questions and again, apologize if these have been covered, but one was there was a reference in the materials we were provided previously that there was a higher rate of granulomatous mastitis in individuals that were Hispanic. And also there was a thought with dermal fillers that there was a higher rate of post-inflammatory hyperpigmentation in individuals that were of Fitzpatrick skin type of four to six. And with that, is there any evidence either in the marketing post-marketing reports of any kind of higher rate of granuloma formation in individuals of darker skin pigmentation, specifically granulomas or anything like that that might interfere with imaging, breast imaging in individuals of darker skin types? And the second question would be, it seems to me in looking at some of these reports that certain of these products are more likely to interfere with imaging. And specifically, and I may be wrong in this, but it seemed to me like that the calcium hydroxyapatite and

the methyl methacrylate were more likely to interfere with imaging. And I may be wrong on that, but I'd love some clarification. Please. Thank you so much.

Thank you for the question. This is Cynthia Chang. Perhaps we'll start with the first question regarding increased rates of various adverse events in patients with darker skin types. I think it may be difficult to get specific numbers. Perhaps I can turn to Dr. Jacqueline Francis, one of our medical officers, to address some of the general trends and concerns that we've seen based on our review of the available clinical evidence. Dr. Francis

Is my video on it. Oh, okay. So regarding your specific question about the rates of adverse events, to clarify, are you talking in general, are you talking about the décolletage.

In the décolletage area. Because if there's a higher rate of post inflammation associated hyperpigmentation, you would wonder if there would be a higher rate of granulomas associated with inflammation if that would be used in the décolletage and if that would then interfere with imaging because both would be associated with inflammation,

Correct? Do not believe, and I'm more familiar with one in-house application than the other, so I don't have specific information on the other. For the one application that I was more intimately involved in, there was not a difference in those kind of

rates between Fitzpatrick skin types, but I would have to do research on the other one that I did not lead on to be able to answer that question for the other one.

And if I could add to that, as we mentioned previously, due to the fact that injections in the décolletage area have not been yet approved by the agency, there's limited information that we have available to really address your question, but we look forward to your comments and guidance pertaining to the risks or potential risks of injections in the décolletage area.

Okay, we're going to take these last three questions, Dr. Grimm.

Hey, good morning everyone. One of the things that I haven't seen, discussed or mentioned is age, which is important. When we talk about these potential complications both for imaging and breastfeeding, do we have any information about the proposed age over which these injections are planned to be used, either from patient interest surveys or from industry or just any information whatsoever? Because that really changes kind of the risk benefit calculation for some of these proposed concerns that we're discussing?

I can start on that. Regarding the age of the patient's, we're definitely interested in the panel's comments on the impact of a range of ages and the differences in benefits and risks for different patients of different ages. In some of the studies that we tend to see for general dermal filler indications, often the patients maybe

middle age, maybe forties to sixties or seventies in general. However, there may be younger or older subjects. Of course in clinical practice and in literature, there may be a wider range of ages in which we see reports of these products being used. But we're certainly interested in any comments on age. And I will also turn the mic over to Dr. Jacqueline Francis to address additional considerations regarding the age of patient.

Could you please repeat that question because I was still trying to look and to answer the other question to make sure that I had that response correct.

Yeah, I was asking if we have any indication of the proposed ages that this procedure will be used for because that impacts the different potential side effects or negative outcomes that we're talking if we're going to approve this.

Generally speaking, our devices for these indications are for ages 22 and older. For those enrolled in the study in particular, I believe they were mostly over 40. Again, I would need to confirm that especially for the other study. But generally speaking, this is still in house and we're still in the process of reviewing this. So is your question really what data had been submitted or is your question what regard?

No, it's rather what the proposed, if we had to get, if we have some idea of what the kind of median or average age of patients who would be getting this procedure

done in the future if it was approved. Are we talking typically women in their thirties, forties, fifties, sixties? Because those risks shift over the age profile.

True. So by the day that, by what we would anticipate, I would say that would likely be to your actually to what you said, maybe in the thirties to forties, more like forties. Unfortunately, I think I might be, I'm somewhat speculating that because I would, again, would have to be discussed and agreed upon with the team.

Great, thank you.

Yeah, I'd like to add to that one of the questions that we have for the panel is consideration of certain population that may maybe at higher risk and that would include potentially an age group. So we do look forward to your comments as it pertains to age or subpopulation that may be at higher risk if they were to receive the injection in the décolletage area.

Dr. Zuley, you have a question?

Thank you. So I have two questions if I could ask. The first is relative to the loss of bone, that was noted in the pre-meeting materials because the ribs overly or underlie the décolletage and we are speaking about a population of primarily women who may have osteoporosis or osteopenia, and oftentimes there's not a lot of space between skin and bone in this same region. How is FDA considering risk factors for cohort of women who have known bone loss prior to this procedure?

That's my first question. And my second question relates to inadvertent vascular injection. So there could be, or I'm wondering about any sort of data that would be available that is not something as serious as loss of vision, however, skin necrosis, skin discolorations, retraction of the skin, all of which are also signs of breast cancer. The question that I'm asking is, is there any incidents data or timeframe data that we would have available in order to be able to better understand when such events may be occurring? And the reason that's important for imaging radiologists is these people will come to us and we would want to avoid unnecessary procedures if we believe it's due to an injection. Thank you.

This is Cynthia Chang. I can begin to address those questions. I think they're excellent points to bring up. And regarding the bone loss and bone resorption adverse events, we are certainly interested in the panel's feedback on how to consider those risks in relation to other risks and any potential mitigation strategies. And so that's certainly something that we're looking to the panelists to provide feedback on. I'll turn it over to Dr. Sung Yoon to address the questions.

Dr. Zuley, thank you for your question. Just kind of going in order, I think your first question about was about the bone resorption that we had presented in the executive summary, and I think that is a great question about patients who may have osteopenia. The bone resorption that we described in our executive summary

was for the face for the supra periosteal injections with the use of the hyaluronic acid,HA , fillers, and that those have been reported in literature as stated in our executive summary. As how that translates into potential patients who have osteopenia or for at risk for bone loss, we think that's an excellent question and we would certainly seek your input and your expertise on that. But you are correct, as we described in our presentation, the décolletage, the breast and the chest area, there's such an overlap and it's not just the breast, totally agreed.

There are ribs underneath. So I think that your input and your insight will be very helpful for us. As for incidents for when the events may be occurring, again, that really depends on the fillers, but also I say fillers, but I think there are multiple, it's multiple meaning it's the volume, it's the injection, it's the plane of injection, it's the patient and the unique anatomy each person has. So it's multifactorial, but certainly would also seek all of your expertise on input on that. I do want to mention, there was a question, I don't remember which of the panelists. It was about the imaging and the fillers and about detecting. So I just want to say there is a filler, it's Radiesse, calcium hydroxyapatite that has been approved for the hand. And if you look at the labeling for it, one of its concerns that FDA had was because it's calcium hydroxyapatite, its potential to show up on x-rays or imaging. And so that is something also that was studied further in a post-approval study. So in terms of

whether imaging, whether any of the fillers can show up on imaging, yes, that is true, they can, but I wanted to point that out and address that question, which I think went unanswered earlier. But if you have any other questions, please let us know.

Thank you. We're going to get one final question. I know some of the panelists have some additional questions, but I'm going to ask that we save those into our afternoon opportunity to once again reengage with the agency. So just write those questions down and keep them in mind and we will get to them a little later. So our final question, Dr. Shuffett,

I was just going to comment just on the imaging, we do a review of our radiology literature, mainly from people who are injected in foreign countries with a host of these materials. There is obscuration on mammography and that brings up a concern for some of how we're going to evaluate this. For example, giving ages. In the United States, most women don't get a mammogram until they're 40 years old. And if we were to start to inject younger individuals, they wouldn't be normally qualify to get a mammogram unless they were high risk. I guess as a breast imager, my focus is to find a cancer as small as possible, and that is my concern with the fillers potentially obscuring a cancer on a mammogram until it grows larger and then it requires more serious treatment. So I think that for me is the most

concerning in any of the injectables into the décolletage and the potential or not knowing how to remove the filler satisfactorily, potentially a reading ahead with hyaluronidase, we don't know what the imaging, after you've injected a person with hyaluronidase to get rid of a nodule, for example, what would its imaging appearance be?

So that's mainly my concern at this point.

Dr. Yoon, do you have a comment?

I just want to say thank you, Dr. Shuffett, for your comment. I think that's really helpful. I think that as for age, as we had stated, dermal fillers are approved for anyone 22 and over. So the concerns about imaging applies not only to those women potentially at 40 and above who may be recommended to have breast cancer screening, but even younger women, as you know, they may be due to family history or just medical history that they are maybe at high risk. So I think that for us, our concern is for imaging it for women for all age. But certainly, we look forward to your comments in the afternoon session.

Thank the panel members for your very thoughtful questions and the responses from the agency. This point we'd like to move on to the external speakers, we'll begin with a presentation from Dr. Natalie Curcio. All the speakers have been granted 12 minutes to make their presentations. So Dr. Curcio, you may begin.

Can you see the screen? Yes,

We see it.

Okay.

Yes.

So good morning. My name is Natalie Curcio and I'm a board certified dermatologist and Mohs surgeon. I own my own dermatology practice in Nashville, Tennessee, and I'm an adjunct professor of health policy at the Vanderbilt University. School of Medicine. I'm here to present on behalf of the American Academy of Dermatology Association or AADA. Thank you for the opportunity to speak this topic. Here you can see my relevant disclosures for your reference. First, I'd like to briefly highlight the role of the AADA in dermatology and explain why this topic falls within our scope of expertise. The AADA is the leading society in dermatologic care representing more than 17,500 dermatologists nationwide. We are committed to excellence in the medical and surgical treatment of skin disease, advocating for high standards in clinical practice, education and research in dermatology and dermatopathology, and promoting ongoing advancements in patient care to ensure individuals receive the highest standards of dermatologic treatment, including the use of dermatologic fillers while patients

considering dermal fillers should be informed of potential risks. Minimizing these risks also requires ongoing physician training, enhanced patient education and continuous improvement of informed consent.

Here I've provided an off-label disclaimer to underscore that there are no currently FDA approved indications for fillers in the neck and décolletage. Dermal fillers are trending. The demand for noninvasive cosmetic procedures has steadily grown over the past seven years. In 2024, hyaluronic acid or HA fillers were one of the most popular minimally invasive offerings with over 5 million patients opting to enhance their features with HA fillers and for non-hyaluronic acid fillers, there were more than 900,000 procedures performed. With this rise of popularity and fillers comes the continued importance of safety in dermatologic procedures, the AADA consistently underscores the need for these treatments to be performed by qualified experienced physicians such as board certified dermatologists and plastic surgeons or by non physicians who are directly supervised by them.

The most common fillers used in the neck and décolletage include hyaluronic acid or HA, calcium hydroxyapatite or CaHa, and polylactic acid or PLLA. Most commonly in this area, hyaluronic acid fillers with the low G prime or low viscosity are those used to improve wrinkles and textures in the neck and décolletage. HA fillers typically come as a prefilled one cc syringe most commonly

mixed with lidocaine. Calcium hydroxyapatite comes up as a prefilled 1.5 cc syringe. To make hyper dilute CaHa, which is most commonly used in this area. Bacteriastatic saline is added as indicated for skin tightening and wrinkles in the neck and décolletage. Polylactic acid packaged as lyophilized powder is reconstituted with sufficient sterile water hours prior to the procedure to create hyper dilute PLLA with often lidocaine being added right before injection to improve skin tightening and wrinkles in the neck and décolletage.

These all serve different purposes depending on the area being treated and the patient's specific needs. Protocols can vary based on age, level of correction needed, and the patient's response to treatment. Studies have demonstrated the clinical safety of dermal fillers and the neck and décolletage. Dermal fillers are used in this area to improve skin texture, crepiness, skin thickness, fine lines and wrinkles, and skin tightening. Common minimal adverse events include redness, swelling, pain, minor bruising, and lumpiness post-injection. These are usually mild and transient. While intravascular complications are always a possibility, they're less frequent with superficial injections in the neck and décolletage, many of which may be intradermal or subdermal in the superficial cutaneous plane. Depending on the filler, the proper technique and physician training are critical to reduce these risks. Additional long-term studies are recommended to further

evaluate their efficacy in order to reinforce safety data and refine treatment protocols.

While major adverse events such as intravascular complication are extremely rare, additional long-term studies are recommended to further assess their safety. With current reports indicating either no adverse events or only mild transient reaction in these areas, for example, delayed onset nodules, which are less common risks, can often be reduced preemptively by massaging the area after injecting either the HA fillers or hyper diluted filler material. These techniques when combined appropriately support both safe and successful rejuvenation outcomes. Specialized physicians like dermatologists should utilize continuing medical education opportunities offered by physician societies and other organizations to assist in the reduction of these events. The AADA, for example, provides comprehensive courses including workshops in dermal fillers that feature hands-on training and injection techniques and provide guidance on patient assessment and treatment planning to help optimize cosmetic outcomes.

A combination approach often produces the most optimal outcomes for the patient seeking neck or décolletage rejuvenation. However, additional long-term studies may be needed for combination procedures. Maintaining high safety standards, including proper product selection and proper injection technique are key to safely

administering approved high quality dermal fillers in combination with other procedures. The skin in the neck and chest is typically thinner and more prone to atrophy with age, emphasizing the importance of patient exams and assessment when choosing the correct filler and or procedure for the right patient. As previously stated, currently no dermal fillers have an FDA approved indication specifically for the neck or décolletage. However, several consensus recommendations support the use of calcium hydroxyapatite and polylactic acid as biostimulatory agents for body rejuvenation including the neck and chest. Several smaller studies have been done to support the safe use of hyaluronic acid fillers in this area. Additional clinical research is needed to further establish evidence for best treatment practices and long-term outcomes. To reduce adverse events, dermal fillers should be administered by or under direct supervision of an experienced physician given the importance of anatomy expertise and injection technique and dilution if indicated, proper patient selection, and ongoing assessment and long-term monitoring after filler administration. For example, the chest skin atrophies or thins over time due to intrinsic factors such as aging and extrinsic factors, including behaviors like exposure to UV, infrared and visible light pollution, smoking and poor nutrition.

When it comes to removal, fillers can be dissolved with hyaluronidase, which is an off-label use of the enzyme. CaHA and PLLA, however cannot be dissolved and must break down naturally over time. To treat overcorrection, superficial HA placement, or migration, hyaluronidase is delivered to the skin and subcutaneous tissue in low doses by direct infiltration of the visible or palpable mass of HA. Massage is recommended to mechanically mix the enzyme with HA and promote the filler degradation. In rare cases of vascular occlusion by HA, high doses of hyaluronidase should be promptly injected into the ischemic tissue. It is imperative to keep multiple vials of hyaluronidase in office in case of emergency and have detailed protocols on product usage. Patients should be fully informed about the short-term common and more uncommon, mysterious side effects of all fillers. Given the popularity of cosmetic dermatologic treatments such as fillers, physicians should inform their patients of the availability of hyaluronidase for dissolving HA fillers versus the inability to dissolve other fillers such as CaHA or PLLA.

The AADA maintains that removal of filler injections should be performed by appropriately trained physicians or non-physician personnel under the direct supervision of physicians understanding anatomy. Proper patient selection and expert technique are vital for reducing complications. Physicians and supervised

non-physicians have the training and expertise to minimize the risk of severe complications, identify pending complications, and manage them promptly and effectively. For the safety of the public, do-it-yourself administration of fillers by laypersons or by non-physician providers without direct physician supervision should not be permitted. The AADA offers comprehensive dermal filler resources and frequently asked questions on our website. We encourage patients to make informed decisions and we provide accessible information to the public. We also appreciate the FDA's frequently asked questions on dermal fillers and their off-label use as these resources help educate patients about the appropriate applications and potential risks associated with these procedures.

Dermatologists, plastic surgeons, and other specialty physicians have the specialized training needed to safely perform these minimally invasive dermal filler injection procedures. Studies show lower complication rates when injections are done by qualified professionals. Ensuring patient safety with dermal fillers and the neck and chest relies on clear and informed decision making by doctors and patients, physician oversight, and adherence to evidence-based protocols. Additional studies are needed to further validate the use of fillers in the neck and décolletage as their benefits significantly outweigh the risks. Furthermore, approving the use of hyaluronidase for dissolving HA fillers would enhance

transparency and support, improving training and education around managing related complications. The AADA welcomes the opportunity to collaborate with the FDA to ensure dermal fillers are safely administered to patients and remain under the supervision of qualified physicians who can appropriately oversee other medical personnel. Thank you again for the opportunity to speak on this critical issue. If you have any further questions, please feel free to contact the AADA at the email provided on the slide.

Thank you, Dr. Curcio, Dr. Curcio. Thank you. We will now review the remaining prerecorded presentations from our external speakers.

Good morning. My name is Karol Gutowski and I want to thank you for letting me present on behalf of the American Society of Plastic Surgeons at this FDA Dermal Filler Panel. As a board certified plastic surgeon, I have 25 years of experience with injectable products in different clinical situations. I've taught numerous courses to other plastic surgeons on the proper use of these products and injection techniques, and I'm also a member of various American Society of Plastic Surgeons Committees, including those which focus on emerging trends such as dermal fillers, patient safety and quality, as well as evidence-based initiatives. I do not have any financial disclosures and currently do not have any ties with any dermal filler companies. ASPS feels strongly that all educational material must

include training in the safe and appropriate use of dermal fillers. This requires a proper understanding of the anatomy and the treatment area as well as understanding of the various physical properties, differences in viscosity, longevity and tissue integration between these products, and clear safety protocols for managing any sort of filler related complications. Specifically things like intravascular injections and tissue loss including vision loss. Practitioners should know that there are ways of reversing some of the fillers including off-label hyaluronidase for hyaluronic acid-based fillers and all injectors should have an emergency toolkit, sort of a crash cart, which has the appropriate products on there in case of a significant adverse event.

Any injectable dermal filler

Product may have an impact on radiographic imaging and cancer screenings. This is particularly true if the product is used off-label and away from the face where most of these are used. Although uncommon fillers may migrate or move beyond the injection area, which could theoretically mean a filler could move to the breast parenchyma, although this was very unlikely it is and it is hard to find any reports of this happening. Theoretically that could be a concern In some cases, dermal fillers have been used for nipple reconstruction and these radiographic images have been visible in patients who've had breast cancer. However, in most cases they can

be identified as a filler product. There were cases of a non FDA approved hyaluronic acid filler interfering with breast cancer detection, but this filler was not available in the US. There is also a report of lymph nodes being enlarged near the dermal filler treatment area, so this potentially could interfere with cancer imaging.

Also, in some cases, injectable fillers have been used to enhance nipple projection both for cosmetic and reconstructive reasons. However, this should be easy to identify and the patient should be able to report a history of this happening in case there is any concern on imaging. It's difficult to estimate how often dermal fillers are used off-label, such as in the neck or the decolletage. However, social media influence may affect the frequency of these injections as well as the popularity of the new weight loss medications as patients may seek the biostimulatory effects to improve the skin rippling in the chest.

Therefore, if off-label use is to be expanded, those who do these injections need to be aware of the potential implications on imaging and cancer detection. Also, researchers and manufacturers who deal with these products should study the impacts of these fillers in areas such as the chest because the potential risks of imaging abnormalities in cancer detection, possibly a pre and post-market approval assessment should be done when these products are used in the chest, neck and decolletage area. It would be important to know what imaging looks like before

and after injection and if there's any effect on the regional lymph nodes. Thank you again for allowing me to present on this topic on behalf of the American Society of Plastic Surgeons,

Good morning. My name is Dr. Scott Glassberg and I'm a private practice plastic surgeon in New York City, and I'll be speaking to you on behalf of the American Society of Plastic Surgeons about further considerations in dermal filler safety. I'm a past president of the American Society of Plastic Surgeons and immediate past president of the Plastic Surgery Foundation and involved in numerous aspects of injectable filler care through the society's numerous committees. These are my financial disclosures. When it comes to dermal fillers, we feel that it's important for patient education informed consent to be key aspects of the care of patients. ASPS advises all of our members to obtain informed consent for all dermal filler procedures, which is an essential opportunity to discuss the risks and benefits of the procedures. This includes the type of the procedure and product being considered, options for dissolution of the filler if needed or desires such as with hyaluronidase or through direct excision, location of the injection, and discussion of on and off-label uses. If injecting in the neck, chest, or breast area such as we've talked about this morning, discussion of the impact on cancer screenings is essential.

These include the breast area, the head and neck area, the thyroid area. Depending upon the types of radiologic examinations, it's important to remind patients to inform the relevant physicians that are treating them about injections they have had recently or even in the distant past and the type of product and the areas with which they were placed. Setting realistic expectations is key, including the range of outcomes that can be expected with the use of these filler products and/or alternative or combination treatments. When it comes to new indications for derma fillers, it's important to talk about off-label use such as the decolletage that we're speaking about this morning, and these should be clarified in the informed consent process.

Anatomy and the downstream impacts vary, which each new type of indication of use, and so these new usage should be probably evaluated for their risks and benefits and these items should be discussed with the patient. Migration since this is a real possibility, should also be part of the discussion. As fillers injected in one area can easily migrate to other areas. When it comes to the decolletage, clearly this migration can be, for example, towards the breast area. Human or animal fat tissue-derived dermal and subcutaneous filler products may offer an alternative to patients for some indications. That's because these regenerative products tend not

to interfere with imaging as they tend to become integrated into the tissues. Potential interference with imaging will be different based on each type of filler and patients should be aware of the type of material that's being injected.

We also feel it's important for the incorporation of patient preference research into the data and discussions. Patient preference studies collect data on which treatments aspects matter most to patients, including the trade-offs they're willing to make. Patients may risk risks differently than physicians and researchers and therefore it's important for patient insights be incorporated to help drive relevant study endpoints. This is one example of a recent paper in the breast implant area, which was authored by multiple members of CDRH at FDA and is a good and great first step into patient preference research. Incorporation of the patient preference research is valuable in evaluating importance of needs for patients. Some examples are - exploring the preferences of women with dense breast tissue are elevated risk of breast cancer into their decision making. Would patients accept a trade off of uncertainty related to breast screens against the benefits of a decolletage skin rejuvenation? That decision may be very different between what the surgeon decides and what the patient decides. A ASPS hope companies in this space will voluntarily explore and consider patient preference research and consider patient preference as a part of ongoing regulatory submissions to the

FDA. ASPS urges the panel to consider appropriate times when patient preference research can best support indication expansion and updates to the labeling.

I thank you very much for the time this morning and your consideration.

Hello, my name is Sachin Shridharani. I'm a board certified plastic surgeon in New York City. I'm the founder of Lux Surgery, the confluence of luxury and aesthetic surgery, and also associate clinical professor of plastic surgery at Wash U School of Medicine in St. Louis, Missouri. And finally, I'm representing the Aesthetic Society as a board member at large and I'm incredibly honored to be able to speak to you about the dermal fillers for this FDA panel. Dermal fillers are the world's second most frequently performed cosmetic procedure. They are only second to neuromodulator treatments. Millions of patients undergo these treatments on various anatomical areas per annum, and here you can see that over the course of the last several years we see a significant uptick in their overall utilization for a whole myriad of different reasons, but really we saw steady growth pretty consistently from ’06 to 2020 and then started to see tremendous amounts of increased utilization for once again a host of different reasons which we can discuss.

There also seems to be non hyaluronic acid dermal filler procedures that have seen a tremendous amount of increased demand for biostimulatory components because of the neocollagenesis and overall improvement to texture and quality of the skin. For the most part, hyaluronic acid dermal fillers dominate the landscape. If we look at what is currently available in the anatomic areas, you can see the distribution of the number of products that are approved for these various indications, and there are approximately 24 dermal fillers that are currently FDA approved in the United States with the nasolabial fold being the most frequent area treated. The future of dermal filler landscape though here you can see involves decolletage ,body, and neck lines. There's a tremendous amount of interest and an unmet need for areas outside of the historical regions being able to have aesthetic improvements in these various areas that are already shown to have an improvement with fillers that we currently have can only be mirrored and hopefully be supplemented by being able to get global improvements aesthetically in these other various regions. And if we look at the new dermal fillers that are projected to enter the market over the next decade, you see that we have approximately 40 HA and nine non-HA.

The growing demand has led to a tremendous amount of increased research and scientific publications and if you look at areas being treated basically below the clavicle, meaning the body, there is a lot of interest in popularity. We've seem to be

able to have mastered many of the various areas on the face, but patients want to have an improvement in other areas as well. And the decolletage is a continued area that is seeming to have a lot of growth because patients have a concern secondary to the aging process extending into this region beyond just the neck. And if we look at over the last 10 years, we've seen a lot of increase up to six X of publications in the decolletage region that you can see now approximately 36 publications between 2015 and 2025. Now, I mentioned an unmet need earlier and really that includes deeper wrinkles in the decolletage area.

Historically, we've been able to treat fine lines and pigmentation and we've been doing that basically with topicals and chemical peels, laser treatments. Now these three elements in general seem to improve texture and quality of the skin, but many patients have deeper edge treatments and it really requires a multidisciplinary type approach and multimodality rather than multidisciplinary approach to be able to see an overall improvement in this region that patients are seeking. And the dermal fillers address that unmet need because of the aging pathology that occurs in this region, which includes substantial dermal thinning and also deeper wrinkles and creases.

Anatomic considerations in the decolletage are very important, and again, we understand that our goal is to treat the wrinkles. We're not interested in treating breast tissue. Investigational studies really often require the palpation and assessment of this region so that there are distinct boundaries and avoidance of treating breast tissue. One of the things that gives us a lot of confidence is there's a pretty low risk of vascular compromise in this area because there's no terminal circulation, there's not large caliber vessels coursing through the dermis here with that terminal circulation or end response, so a VO or vascular occlusion that can prove to be devastating in areas of the face leading to either necrosis or stroke, even reports of death and of course even blindness,that is not really a tremendous concern here because again, there's no terminal circulation. And there's also tremendously low risk of any type of thoracic cavity penetration. The needles that are being used here range from 32 to typically 33 gauge for the most part with very low G prime and less viscous types of HA fillers and the target area is intradermal. We want to be treating more superficially in the decolletage for correction of those wrinkles, so we're not doing deep injections where we have concerns of using large caliber needles that are deeper and longer in nature and can actually perforate or penetrate the thoracic cavity. So we have a lot of confidence for safety optimization in this area.

When we think about the types of actual products that are historically used, which are hyaluronic acid CaHA or calcium hydroxyl apatite and then polylactic acid, they all function a little bit differently. So dermal fillers are readily identified on various imaging modalities and they definitely are not known to compromise signaling integrity and recall that these are not permanent implants and these signals go away over time as the product is actually metabolized. So for example, whether we're talking about MRIs, x-ray/CT or ultrasound, HA in many of these looks to be either low density, opaque or very similar to water or has sort of anecoic or hypoechoic areas based on what we're looking for. Calcium hydroxyl apatite you can see has high intensity microcalcifications on two of these modalities, and then poly-L-lactic acid, which is biostimulatory in nature purely has soft spots of surrounding fat or subtle soft tissue foci.

So we really have again, ability to distinguish quite readily and easily these various biocompatible products. With any type of injection. Adverse events and complications are possible, and that is definitely something that we see with dermal fillers. Migration are one of the concerns that one could see potentially in the decolletage. Now to date, there's not one literature, excuse me, not one case in the literature to support any migration in the decolletage region. There's less risk of

migration because again, there's not a lot of mechanical movement in this area. We don't have a tremendous amount of muscle motion in this region, which creates any type of migration. Also, the fact that it's more superficial in the decolletage doesn't allow for migration into deeper areas of the skin, especially like breast tissue. Typically, fillers are going to go towards the path of least resistance such your needle track.

Well, here we're talking about using a very small gauge, superficial small length needle. Also, the smaller volumes are used in each injection area and they're done with typically low pressure, so it's these tiny micro droplets, superficial techniques that give us, again, confidence that we're likely not going to have any type of migration. Microparticles of CaHA and PLLA don't migrate because of just their overall properties. In one case of breast augmentation, so not decolletage, but actually trying to inject the breast, there's a case of HA migrating into lymph node after a BA and as was after a lot of volume used. And migration though has reported in facial treatments and that's again secondary to the depth of injection, the proximity to certain larger caliber vessels and lymphatics.So the actual potential complications can be nodules, inflammatory reactions or granulomas. We do see this with HA fillers, CaHA or even PLLA, and these are uncommon, but these adverse events can in fact occur, but they're typically temporary and self-

limited or if they're causing any types of symptoms, they often can be treated without any type of major surgical intervention.

These complications are typically acute and they are relatively easy to distinguish, so they don't again look or behave like any type of breast disease or malignancy that we're accustomed to seeing when we talk about actual breast cancer or even non-cancerous issues in general. So we have, again, confidence to be able to really distinguish between any type of true pathologic condition versus an adverse event that can in fact occur from an HA. When we think about the overall paradigm of being able to treat in the decolletage as a plastic surgeon and someone who does train thousands of individuals around the globe per year on the safe use of non-surgical aesthetic interventions and injectables, we know that there are going to be important considerations to get good outcomes and optimize patient journeys. Firstly, the anatomy is going to be key and the onus will be on us to make sure that we are able to distinguish the areas of treatment versus the surrounding breast tissue.

And of course, a physical exam is paramount to making sure that we only identify and treat the appropriate areas and again prior to injection that physical exam would be necessary. Correct injection technique. This is something that gets distilled down as a correct time. For the most part, we want to be using a

superficial droplet type technique, micro droplet placed intradermally, and again, this should lead to decreased overall risk. Certain types of retrograde fanning intradermally could also be used to optimize if we're going perpendicular to the actual lines, but tangential within the dermis itself. And then again, one could also make sure that they're able to identify adverse events. We've discussed nodules and granulomas which can occur filler migration, less common, less likely to occur in this area, and again, vascular occlusion is something that we're not as concerned about. Certainly a patient informed consent is important and imaging will help differentiate and discern between a filler and actual pathologic elements that can occur in this region, and then of course following the label will be key with guidance from the FDA and looking at how to best partner so that we can optimize again, improvement in this area.

So I think that there is a tremendous opportunity to treat and to create solutions for an unmet need that currently exists in this aesthetic anatomic location. You very much for the opportunity to present and happy to field any questions. Thank you.

Hello, and thank you for the opportunity to speak with you today. I'm M. Laurin Council, current president of the American Society for Dermatologic Surgery. In addition, I've done some consulting and research for Regeneron and Castle Biosciences and I'm a full-time employee at an academic medical center,

Washington University in St. Louis. The reason why today's conversation is so important is we are seeing an increase in filler demand in the United States. At the time of our most recent ASDS procedure survey dermatologists performed over 1.6 million filler injections in the year prior to the survey. This does not include fillers that are injected by other non-physician injectors and other non dermatologists, so this number is likely even larger than that. We know that adverse events can happen with dermal fillers. These can be small adverse events such as local tissue reactions, infections, but also more serious adverse events such as embolization of the filler into the arterial system causing vascular occlusion, tissue necrosis, and even blindness or stroke.

There are certain anatomic locations that are at higher risk. These are things such as the midline of the face or nasal area, and that's why knowledge of vascular anatomy is so essential for all filler injectors. The American Society for Dermatologic Surgery believes that dermatologist, plastic surgeons, oculoplastic surgeons and facial plastic surgeons are those with the most education in this and therefore the most highly qualified to perform these filler injections. The ASDS convened a multidisciplinary soft tissue fillers evidence-based task force. The task force consisted of eight board certified dermatologists, who were all ASDSA members, a plastic surgeon, a facial plastic and reconstructive surgeon, an

oculoplastic surgeon, two patient representatives and a methodologist. The ASDS fillers guideline task force determined that the topic of preventing and treating adverse events of injectable fillers requires the development of evidence-based practical guidelines to support decision-makingin daily practice. The task force recommends the strategies to prevent vascular occlusion, including if an injector sees vascular regurgitation during the process, he or she should immediately stop the injection and consider hyaluronidase at the site, and patients who develop vascular occlusion, the ASDS recommends that high-dose hyaluronidase should be injected promptly into the scan at the side of the occlusion and any areas of ischemia on the immediate periphery.

In addition, ASDS recommends that all adverse events that are serious in nature should be reported immediately both to the device manufacturer and to the Food and Drug administration. Filler adverse events are likely under-reported and they're increasing in frequency as the popularity of injectable fillers increases. Physician offices are more likely to report these adverse events than those in med spas and out in the community. The ASDSA in conjunction with Northwestern University developed the cutaneous procedures Adverse Events Reporting Registry, and this is a voluntary reporting database of adverse events that occur during these surgical procedures. Data are used to monitor and identify practice and or educational gaps

and to identify any potential risk factors that should be noted and mitigated. Today we're asked to consider a new treatment area the decolletage. We have very limited data on the safety of injections into this region, but we have similar studies in the medical literature reported on the use of hyaluronic acid directly into the breast.

These are a little bit different technique. Hyaluronic acid into the breast has historically been very large volume injections larger than what would consider for injection into the decolletage, but similarly, we do know that these hyaluronic acid injections can be seen on radiological studies and therefore may interfere with breast cancer screening imaging. Other injectable materials, poly acrylamide gel and calcium hydroxyapatite are more radio opaque and would have even more interference in this location. In addition, hyaluronic acid injections directly into the breast, there have been reports of these being uptake into the lymphatic system showing also on radiological studies and mimicking lymphoma, so that should be taken into consideration. There are very few studies evaluating the safety of dermal fillers into the decolletage. The medical literature focuses mainly on technique and does not have reports of adverse events in this location. Because of that, it is potentially a more safe procedure than injection into the breast, but it will be visible in radiological studies and as these injections increase, we are more likely to encounter these safety events that should definitely be monitored. The ASDSA

supports the informed decision process where patients are allowed to consider the risk and benefits and therefore make the appropriate choice for themselves given the current lack of evidence. Thank you.

Good day everyone. I am Juan Daccach, VP of Global Product Safety at Merz Aesthetics. Today I'll be presenting an overview of Radiesse injectable implant and its use in the decollete region. This presentation is part of the advisory committee meeting focused on

Dermal fillers. Before we begin, this is my financial disclosure statement.

Here's what we'll cover today. General trends in dermal filler use an introduction to Radiesse , its treatment paradigm for decollete wrinkles, clinical trial experience, post-market safety data, ongoing surveillance and risk mitigation. And finally, our conclusions. Please note that radiesse is not currently approved by the US FDA for use in the decollete. If you focus your attention to the left side of the screen, you can see that fillers offer a non-invasive surgical alternative to achieve enhancing and rejuvenative improvements. Procedures generally offer a lower cost alternative to patients with limited to no recovery time. It has been estimated globally that from 2019 that over 15 million filler treatments were performed. The total number of derma filler treatments globally surpassed 20 million by 2024. In 2023, there were approximately 5.5 million dermal filler procedures performed globally,

representing a 29% increase from the previous year with a 4% increase in the US alone.

Fillers are consistently ranked among the most common nonsurgical aesthetic procedures performed in the United States. If you focus your attention to the top right, you see a bar chart that depicts the number of global radiesse treatments performed by plastic surgeons, and you can see an increase starting from 2020 and continuing until 2023 and beyond. Publications on decollete treatment depicted in the graph in your bottom right of the screen show a constant increase starting from the year 2000 radiesse is an opaque white derma filler made up of calcium hydroxyapatite or CaHA microspheres in a water-based gel radiesse is biodegradable non-animal based and free from animal protein. Radiesse injectable implant diluted one to two with a 0.9% sterile saline solution is intended for the treatment of wrinkles of the decollete. Please note that radius has not been approved by the US FDA for its use in the decollete, but it did obtain the CE mark under EU MDR in 2024.

as we will see shortly. The safety profile of radiesse has been established and proven in short and long-term clinical trials and confirmed in almost 200 publications. If you focus your attention to the timeline at the bottom of the screen, you see that in 2002, the commercialization and the radiesse CE mark in Europe

for soft tissue augmentation of facial area was obtained. In 2006 FDA PMA approval for radiesse was obtained for the correction of moderate to severe facial wrinkles and folds such as the nasal labial folds, as well as correction of signs of facial fat loss for patients with HIV. In 2015 FDA radiesse was granted approval as an indication expansion for the correction of the volume loss in the dorsum of the hands, and in January of 2024, radius decollete indication was granted the CE mark under the EU MDR.

If you focus your attention to the image in the center of this slide, you can see that the decollete treatment region compromises approximately 100 square centimeters and is delineated superiorly by the sternoclavicular notch, laterally by the midclavicular line on both sides and inferiorly by the superior point of the inter mammary cleft. Radiesse injections are not intended for the area overlying or including breast tissue. They are performed at the dermal subdermal junction. According to Van Longen, the risk of damaging mammary tissue is negligible as the mammary glands are located underneath the superficial layers of the breast, which should be beyond the reach of a cannula and or needle.

Radiesse is safe and effective for treating decollete wrinkles in clinical trials. To the left, you see an investigator initiated trial titled Prospective Clinical Trial evaluating the long-term Safety and efficacy of Calcium Hydroxy Radiesse for

chest rejuvenation by Fabi and collaborators. In this IIT 20 female subjects showed improvement in the dynamic and resting appearance of decollete wrinkles at 6 12, 26 and 52 weeks after injection using the merz decollete scale. Subject satisfaction scores improved over the year using a seven point scale. No serious adverse events were reported. To the right of the screen,you see the results of two merz aesthetic sponsored clinical trials with over 265 female patients enrolled in the US and the EU with a combined follow-up between 52 and 84 weeks. Two, pivotal prospective multicenter evaluator blinded randomized studies of diluted calcium hydroxyapatite radiesse to treat decollete wrinkles. We found that over 70% of subjects showed at least a one point improvement according to the Merz aesthetic scale for decollete wrinkles, patients with severe baseline wrinkles showed the highest response. A high percentage of investigators and subjects were satisfied with the results. There were no treatment related serious adverse events reported, and the adverse events were mostly mild and localized. For example, injection site hematoma, pain and erythema discoloration and swelling.

Our ongoing safety surveillance is very important to us. Merz Aesthetics complies with FDA regulations requiring routine device surveillance and ongoing adverse event reporting. Specifically MERZ reviews any reports received included but not limited to clinical trials or spontaneous reports. Within the clinical trials, all

adverse events with special focus on serious adverse events from company-sponsored clinical trials offer insights from a controlled setting where intense training and monitoring occur and where clinical event details and outcomes can be verified. From the spontaneous reporting branch of our ongoing safety surveillance adverse events or cases from solicited and unsolicited sources, including spontaneous literature and non companies sponsored clinical trials or studies are reviewed. These offer insights from a usual care or real world setting. Such reports are made voluntarily and often lack medical details, clinical details, diagnosis and outcomes. Our radiesse post-market surveillance data for the decollete includes a search period from July, 2018 until May of 2025.

We used the mesh terms and search filters that you see above, and we found that post-market surveillance got 44 hits for the anatomical region, decollete, the zero cases reporting migration and or radiological interference. Less than 10 cases with therapy site decollete per year since 2018. Our risk management and mitigation is a continual process and we take this very seriously. From left to right, you see where we incorporate this. R and d clinical trials, our safety monitoring, and our post-market education. Within our r and d clinical trials, we have a strict clinical program and study design,we have input from investigators and key opinion leaders. We have and choose our appropriate patient population. We include

informed consent. We make a risk benefit assessment. We mitigate our risk with injection paradigm and indication specific safety assessments, and we carry out investigator injection training. Within safety monitoring we carry out clinical trial safety monitoring and reporting. We look for global spontaneous report assessment and monitoring. We look into global literature trending and signal detection instruction for use creation review and updates and investigator initiated trial study review. To the far right in post-marketing education we continue our risk management and mitigation with key opinion leader collaboration publication summarizing safety information and adverse event management, provision of global medical information, healthcare provider training, continual medical education, healthcare provider communication, and subject websites and additional information.

So the benefits to patients with radiesse are the ones you can see in this slide. For facial areas, patient satisfaction went up to 98%. For patient reported facial aesthetic improvement, it went up to 89%. Investigator reported improvement, 92%.In non-fatal areas inclusive of the chest,patient satisfaction went up to 90%. Also in non-fatal areas inclusive of the chest, patient reported improvement was of 94%. Investigator reported improvement in non-fatal areas, inclusive of the chest went up to 95%, and patients that were more pleased with appearance, 96% and

that feel more attractive and 80%. So to conclude, radisse has been commercially approved for use since 2002 and was approved for decollete wrinkles in Europe in January of 2024. The safety of radisse is established and has been proven in short and long-term trials and confirmed within the literature giving the characteristics of the product and with proper injection technique, which should be away from the breast and in the subdermal plane migration is unlikely. No reports of migration or interference in decollete have been received. Our global post-market data for radiesse does not show any signals or trends of potential concerns. There's a high percentage of beneficial patient outcomes after the use of radiesse and MERZ is committed to training activities and continuous monitoring of adverse events. With this, and on behalf of all merz aesthetics, I would like to thank you.

Hi, my name's Scott Hollenbeck and I'm here representing in InSoma Bio. It's a biotech startup company and I act as the lead medical advisor for that group. I'm also a professor and chair of the Department of Plastic Surgery at the University of Virginia in Charlottesville, and I'm also currently serving as the president of the American Society of Plastic Surgeons. It's my pleasure to be here, share my thoughts and input and opinion again representing InSoma Bio. So we have a scalable recombinant protein inspired by human tropo elastin, and it's temperature sensitive. Has a phase change that goes from a liquid to a solid. When it's room

temperatures, liquid body temperature is solid. The diagram is showing a representation of that and how that would feel. This occurs through a fractal networking. We can also adjust how long this stays and is degradable sometimes lasting up to a year and other instances. In fact, the form we're working on is degraded over the first three to six months. So that's the material we're working on.

But the real question is what is the decolletage? And if you look on different online sources, you can see is this the skin from the neck to the cleavage area? Is it the area from the neck to the shoulders to the chest, including the upper breast? That would be shown here. That definition. Both these definitions can be found online fairly easily. And so for that reason, I think there's some question here that needs to be clarified. But if you look on the market out there and what people are advertising both in the US and in Europe and other areas are treatments for rejuvenation, the decolletage, those fall into two areas, noninvasive and then minimally invasive. In the noninvasive realm, we're talking about lasers, microneedling, and topical creams. In the invasive, minimally invasive area, we're about filler injections, which are shown here as an option for this upper breast sort of lower chest area.

And you can see those being advertised as options, and that's what we're here to talk about. So one concern would be intravascular injections. You can see from this MRI, the breast and upper chest area has some sizable blood vessels, at least for the skin, and they typically originate from the internal mammary vessels and they perforate through the skin and muscle layers and can be two to three millimeters in size. And so from this cartoon drawing, you can see that these an inadvertent intra arterial injection could in theory cause tissue necrosis while an inadvertent venous injection could cause distribution of material through the systemic circulation. If you look down at that advertisement, you can see the lines drawn there presumably are showing where the injections to occur, and that definitely would cross over these regions where the internal memory perforators exist. And one way to detect that a rather easy way is using ultrasound with doppler feature and you can see the blood flow in these vessels and you could avoid those rather straightforward using ultrasound.

Another potential complication is needle puncture pneumothorax where the needle enters the lung and causes air to leak out of the lung, creating a dangerous situation known as pneumothorax. This can be avoided by not putting the needle into the chest cavity. And this study here showed that in many patients the average chest wall thickness is going to be around that four centimeter area, and that includes this

upper chest area where the great vessels are taking off. You can see the pec major pec minor muscles, and in there you'd have to go pretty deep to enter the chest cavity, but that in theory could happen. One way to avoid that is the use of ultrasound. Again, in this case, this is a doppler ultrasound showing a couple ribs there you can see, and then the internal mammary vessels flowing below that. And then you can see actually the lung cavity below that.

And so using ultrasound, you could avoid entering the lung space. Also, knowledge of anatomy would be helpful. Speaking of anatomy, we need to distinguish this area that includes the breast itself. The breast gland is the area where breast cancers can form, and so monitoring occurs there with mammography and self exam, and you can see that it's not always clearly distinguishable area from the top of the breast with the breast gland to this lower chest region. So that's an important consideration and you can see there if you extend and include those areas as the decolletage, you might get close in terms of injecting material around the breast gland itself, as many of you know, breast implants are most commonly used to enhance the upper portion of the breast as well as the overall breast size. You can see examples of a silicone or saline breast implant for that purpose there. But if you look online, you can find advertisements and case examples of breast augmentation performed with filler material. And you can see this patient

presumably has had filler material injected into the breast and upper pole, so that is something that is out there and can be found on the internet.

This is an issue when filler materials injected in the breast. This is an example of free silicone that's been injected. You can see it's obscuring mammography. There's a surgical photo of removal of that material. There's also case reports of a poly acrylamide gel filler breast augmentation, again, obscuring mammography and causing leaking of this material out during surgery. We do perform treatments now to address this kind of upper breast area using fat, I would say most commonly fat grafting. This is a post mastectomy patient who has tissue expanders in place, and you can see there's wrinkling or what we call rippling in the upper breast, and this is treated somewhat effectively with fat injections. This is a patient's own fat harvested and then injected into this area. There is no breast tissue there anymore, and so this can occur. Here's an example of a patient that's undergone that effectively to deal with the rippling in this upper breast area, and I've been able to write a couple papers on that related to the safety of fat grafting in this area and also monitoring post fat grafting.

But the real question I think is what is the decolletage as it pertains to filler injections? The problem is that poorly defined area and the term decolletage does not appear in most human anatomy textbooks. It does not include the breast or does

it include the breast? A little bit unclear, and I think that needs to be defined better if we're going to ask clinicians to do things the right way and use anatomical landmarks and terms. We should also use anatomical terms as opposed to this poorly defined term decolletage. So recommendations from my perspective. Again, as I said, define this term in this anatomical location. Use ultrasound guidance for injections. This can prevent a vascular injection, prevent pneumothorax and prevent injection into the breast gland inadvertently. As it pertains to breast fillers, I think these need to be considered separately. That would need to be something that is biocompatible, something that does not interfere with imaging as I showed you examples of how that can be problematic. So thank you again for your time and listening to my input. My email is included there and I'm happy to help in any way I can. Again, thank you for including me.

Thank you for those presentations. Now we're going to ask whether the panel has any brief questions for any of the speakers, and I'd like to take the chair's prerogative and begin the questioning. Is Dr. Hollenbeck back with us? I know he had to go to the operating room.

He's not,

No. Okay, so I'll save my question for later. Any other panel members? Dr. Alam, you have a question?

Yes, sir. I had a question for Dr. Daccash from Merz specifically. I was wondering whether since the their radiesse has been approved CE since 2024, if he could characterize what adverse events they've seen specifically in the decolletage and post-marketing surveillance and what actions, if any, they've taken to mitigate those. Thank you.

Hopefully you can hear me now. Thank you, Dr. Alam. For post-market surveillance on decolletage, we have not seen anything out of the ordinary as you would see in any other filler treatments. Inflammatory response, erythema, swelling, pain, nothing out of the common adverse events you would get from injecting a filler in the body.

Dr. Grimm,

Thank you. This is actually a question for any of the practitioners who do this. It's a little confusing me. I feel like I got a little bit of mixed information from the presentations about two things. One, the volume of injection at these sites. At one point it was referred to as micro droplets, but I kind of would like a little bit of a better sense of the volume as well as the anatomic target. Is this really just in the cutaneous tissues themselves, the subcutaneous layer? How deep is the potential

injection sites? So the volume at individual sites and the targeted depth of injection?

Sure. I'm happy to help weigh in on a component of this. This is Sachin Shridharani. Let me start my video here. Forgive me. Hi. So basically from a micro droplet type technique, often we use hyaluronic acid with a very low, what we call G prime resistance to deformation, smaller particle size, lower concentration of HA, and the volume is typically 0.01 mls. So you're talking about a 10th of an ml basically. So 0.01 MLS delivered intradermally. So relatively superficial papillary or the reticular layer, the dermis, we're not really interested in volumizing this area, so we're not injecting into the sub dermis or subcutaneous space typically because really the goal here is the fine lines creases and wrinkles. So we are staying in a superficial plane with a small volume spaced apart with a and material with HA that we could relatively spread quite easily when talking about HA as a practitioner, if you use other types of products that are more biostimulatory in nature, the target is still intra dermally and it's going to be in kind of a fanning type technique. So the goal is not to be subdermal. No one really wants increased bulk or volume in the décolletage. That's not the typical desired aesthetic outcome. It's improvement of tissue quality, which is why lasers, chemical peels, et cetera, have been the typical treatment paradigm because the goal is to improve the texture and

quality of the dermis, not to create bulk or volume or be volumizing the sub dermis.

Thanks, that's really helpful. Do any of the other practitioners have any different opinion or technique? Okay, thank you very much.

Ms. Brummert.

Rachel Brummert. I'm the consumer representative. I have a question for Dr. Curicio. Is she available? Yes. Hi. You mentioned that fillers are trending, and I was wondering what the age ranges are for people seeking fillers in your practice?

In my practice specifically, I would say in general, the majority of people would probably be forties to sixties, but I would say I have people in their thirties all the way up through their eighties. Thank you,

Ma'am.

Next question. Ms. McCall.

Debbie McCall, patient rep, and I believe my question is mostly based on Dr. Shridharani's recent presentation with younger women having more cardiac issues, they are involved. My questions are directly related to internal and external cardiac monitors as well as oral anticoagulants. There are specific external cardiac monitors that either go right along the sternum, right at the manubrium or right over the top of the breast, again close to the sternum. And then there are internal

ones that are subcutaneous again, right at the top of the breast. So I'm concerned about where does this fall into issues, particularly for the younger women that have these and then also those that are on long-term oral anticoagulants. What considerations are there for them?

Sure. Thank you so much Ms. McCall for those questions. So the first one, typically when we think about the aging or the maturing aesthetic pathology in this region, we're not typically seeing younger patients coming in for this, at least we have the age range in our practice, very similar to what my other colleague mentioned. But the actual indication when we're treating in this area are definitely individuals that have had a tremendous amount of overall kind of aging pathology in this region. So you're seeing folks, and they also have a lot of environmental lower Fitzpatrick skin types. So FSTs one, twos threes a lot of solar elastosis or solar damage. And so a lot of lines, creases and wrinkles. I don't recall the last time I injected a patient, twenties, thirties, or even relatively early forties with this, but it is going to be someone that you're seeing in a little bit of a later stage.

So that hopefully helps alleviate the question of the younger patient. As far as tissue depth though, with those patients that may have these monitoring devices, I think some of those might be relative contraindications if they're over the manubrium and superficial, a subcutaneous pocket or a placement of a pacemaker

in that subcutaneous plane is still definitely several tissue depths away from the target tissue. And if a patient was in my clinic requesting to get treated had a pacemaker, I would certainly circle the area and be superficial over it. But the other thing also is that most times those pacemakers are placed a little bit more laterally and even out of the zone, they're not typically placed in those.Plastic and reconstructive surgeon, if we have to replace that pacemaker and placed in a subpectoral pocket or places somewhere else, they're much more lateral. Whereas the target area here, if you look at the clavicle into the manubrium over the sternum, that is not an area where people typically place a subcutaneous pacemaker. So I think from an age, tissue depth, and location of pacemaker, we're typically able to safely inject in those regions. As far as your, does that help answer the first question?

I would like to clarify, and this is my fault, I should have clarified that. I was talking about internal loop recorders or internal cardiac monitors that tend to be more medial, not

Lateral,

But again in the similar area and they're also subcutaneous.

Sure. So again, with it being subcutaneous, because this is a very superficial intradermal injection, typically being injected with a 30,32 gauge needle that's only a few millimeters deep, we're targeting two to four millimeters. So we are, again, so many tissue layers away from it, but that could be a relative contraindication if necessary, but I don't think it would preclude any type of treatment as long as it's careful injection technique. And as far as the oral anticoagulants that you mentioned, that once again would be something where a patient would just be at increased risk of bruising. This is, again, in a very superficial injection. I think, as I mentioned from my lecture, there's no terminal vasculature here. So there's not a large caliber vessel coursing in this region that if you had a vascular occlusion would lead to a catastrophic blindness or stroke or end organ response or ischemic type event or necrosis because we're injecting with such small volumes superficially. So if a patient was on oral anticoagulants, I tell 'em there's a high likelihood that you're going to have prolonged bruising, but there's not something where I'm concerned about a hemorrhage in that lens.

And you wouldn't want to stop your anticoagulant hold a dose?

Depending on what the patient's condition was. If they had a tolerance for the fact that they might be bruised and they had an issue where they wouldn't be wise to stop the oral anticoagulation, then you're just proceed with it. If they could stop

their oral anticoagulants, all you're going to do is just increase their overall recovery, so to speak, from a social standpoint where if they wanted to wear something that was going to expose the decollete, they'd be able to without the risk of or less risk of a bruise, but you wouldn't have to stop it because you're not concerned about a large vessel that's going to bleed and create an actual hematoma or hemorrhage.

Great. Thank you very much.

Of course. Thank you for the questions.

Okay. Unfortunately, our time is running a little over, so we're going to get back to the questions you all have now, but we're going to open the public hearing and do the questions afterwards. So public attendees are given the opportunity to address the panel to present Data, information, or views relevant to the meeting agenda, Ms. Washington will read the open public hearing disclosure process statement. Ms. Washington,

Both the Food and Drug Administration, FDA ,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 for your travel, lodging, or other expenses related to your attendance at this 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, Ms. Washington. Thank you. FDA has received four requests for open public hearing portion of the meeting. Our first two presenters will be speaking live, the first of which is Dr. Diana Zuckerman. You have eight minutes.

Thank you very much. I'm Dr. Diana Zuckerman, president of the National Center for Health Research, a nonprofit think tank. We do not accept funding from entities that have a financial interest in our work, so we have no conflicts of interest. Thank you for the chance to share my perspective as a scientist who has looked at the data on dermal fillers for many years. Dermal fillers are very popular despite numerous well-known risks. As PMA products, those risks should be quantified with meaningful statistical data on the short -term and long-term risks rather than

merely listing adverse events as either common or rare. And unfortunately, statistics on risks haven't been available. As FDA considers whether these same dermal fillers or new versions of them should be approved for use in the décolletage area. I urge the FDA to improve the information available to patients about dermal fillers. FDA should require well-designed controlled clinical trials so that patients have the information they need to make informed decisions. That should require data describing clearly defined short-term and long-term risks. Because when the benefit is cosmetic, even short-term, mild or moderate adverse events, such as weeks long or months long pain, swelling, rash, or bruising, matters to patients. Specific information about the frequency and impact of migration also needs to be specified.

We agree with the FDA that the use of dermal fillers injected in this area has additional risks, such as potential interference with imaging and screening methods for cancer, and that could result in false negative or false positive cancer diagnosis. The agency gives several good examples to back up that concern. And as FDA points out, potential harm to the vascular and or lymphatic systems is a great concern for dermal fillers used in the décolletage area. It has come to our attention that some major manufacturers of dermal fillers have stopped reporting vascular system impairment and instead are categorizing those adverse events as obstruction

and occlusion. And this clearly is intended to make their products seem safer than they are, and not to come to the attention of the FDA in a negative way. And that's the kind of misleading reporting that makes it difficult to trust the data that some major companies are providing.

And as a result of manipulative data, patients are unable to compare which products are safer or to make informed decisions about what risks they are willing to take for these cosmetic improvements. We're glad that the FDA is talking about studies to evaluate which risks are most important to patients. Unfortunately, merely listing possible risks on a label or a patient booklet is not enough. We've talked to thousands of patients who've told us that they never saw the label or the patient booklet that they were supposed to be given and that was supposed to be required to be given. Not all physicians are as transparent as the experts here today. And of course, a lot of people doing these procedures are not physicians and in some states they're not even health professionals. But even if patients read and understood the information, there's a couple of problems. Number one, what physicians tell patients is much more influential than anything provided in writing.

Some physicians and their staff are unrealistically reassuring when they're in person. The written informed consent protects those people from legal liability if they make any overly optimistic assurances when talking to patients. And number

two, research and clinical experience both tell us that patients tend to underestimate risk when they want something. Don't we all do that? Vague statements about cosmetic complications that are quote short -term or transient may be misunderstood, and those complications may last much longer than the patients expected. Most patients assume that any risks that are referred to as uncommon or rare won't happen to them, and so they're willing to take the risk. But if they experience those rare complications, they feel betrayed and devastated. And that's especially true for serious complications, but also for cosmetic problems. And for these PMA products, patients do not have the legal recourse of compensation that they would have with an unsafe prescription drug or 510 K device.

We strongly agree with the FDA that we have little information about the impact of repeated use dermal fillers over a period of years. And since some fillers are already being used off-label for the décolletage area, FDA should analyze de-identified data from a registry. However, the FDA needs access to registry data to analyze it, but most registries in the US are owned by medical societies that do not currently make all safety data available to the FDA or the public. So the registries can help with their long-term data, but the FDA needs access to those data. FDA notes that subpopulations of patients may be at higher risk for some potential

adverse events. But again, research is lacking. So informed consent isn't possible for those patients in those groups. The FDA states that nearly every filler type has been associated with a severe complication leading to stroke. And I wonder,um, how many patients are aware of that.

As you know, there are unique risks to the décolletage area in addition to skin necrosis, anaphylaxis, abscesses, migration, granulomas, and the risk of intravascular injection, which FDA describes as inherent to treatment with dermal filler anywhere involved. So those unique concerns have to do with in addition to cancer diagnosis, also breastfeeding and a few others. The FDA noted a newly recognized adverse event, bone resorption, which as some of you have mentioned today, is of particular interest and concern for this particular area of the body. And although the total number MDR serious injury reports were less than 18,000 as of last fall, we all know this is a voluntary reporting system and that very few health professionals or technicians want to spend their valuable time reporting these adverse events, especially if they're already supposedly known. But because of that, you don't get a good sense of the quantity and frequency. And most health professionals don't have an incentive to report problems experienced by their patients, especially those physicians that might be considered responsible for those adverse events.

So the bottom line is , MDR data are not helpful for quantifying risks. In conclusion, PMA devices deserve good research for patients to understand the risks. When the benefits are cosmetic, the risks should not conflict with those cosmetic benefits. When the benefits are not lifesaving, the risks should not be lifesaving, and that's why it's so important to require scientific evidence that the benefits outweigh the risks so women can make informed decisions and understand exactly what those risks are, both in terms of the serious ones and the cosmetic ones. Thank you very much for the opportunity to speak today.

Thank you. Our next open public hearing speaker is Dr. Z. Paul. Lorenc.

Hello, this is Paul Lorenc. Let me just share my screen. Just good morning. My name is Paul Lorenc. I'm plastic Surgeon, Board certified in New York City in Manhattan. I'd like to thank the FDA and the panel for allowing me to speak.

Trying to get it. Here we go. So again, I think the FDA and the panel for allowing you to speak on 30 years of experience of breast surgery and close to 20 years of experience of using injectables biostimulatory agents as well in the area of the décollete. My disclosures are as listed as you can see. So I'd like to address the area specifically that has been discussed before and specifically when it comes to biostimulatory agents. And there are really three on the markets right now,

calcium, hydroxyapatite, poly L lactic acid and PMMA. These agents we use clinically, I have extensive clinical experience with using them in this particular anatomical area. I typically use them in a very hyperdilute or dilute manner, and this is to distribute and stimulate collagen production and elastin production. So this is a little bit different than what you've heard before as far as the injection of that area, this is an injection that is a subcutaneous, injection using a cannula and spreading a dilute amount of material to stimulate collagen and elastin.

And I'll like to share with you some of the science behind it. So calcium hydroxyapatite is really a component of human bone. It creates stimulus collagen production. It's suspended at CMC, which gives the initial volume. PLLA, polylactic acid long history over 40 years of use in surgery. It's particles lyophilized powder that's reconstituted, stimulates collagen and mostly collagen type one. As you can see in this slide, whether it's CaHA, PLLA or PMMA, really the ultimate goal is to stimulate collagen type one, which is what we call the younger collagen. And there are different mechanisms, but the point that I want to make is that this is locally concentrated. There are no systemic effects. There's data, recent data that no inflammatory reaction really happens with CaHA injection and with PLLA, it's a very mild subclinical reaction. And to this point and to the point of diluting the product, what we do is we dilute the products to really spread

the area or saturate the area with microparticles, microspheres and spread them evenly.

It's in the subdermal plane just underneath the dermis using a cannula. Typically it's a 22 or 25 gauge 2 inch cannula. It causes a biostimulatory effect by diluting it. As you can see on the graph, you lose the G prime, which is the lifting capacity. But what you do is you gain the ability to produce and upregulate collagen production, which happens specifically with CaHA dilution at month one dilution, and then it trails off if you dilute the product even more. But again, and this was driven by patients requesting correction of the sun damage in really the décollete area, these injections have the capacity again to induce collagen and elastin, and we have already documented and published on this in several articles. Also, the skin thickness is improved, and the quality of the skin is improved by using these diluted or hyperdiluted products. This is from an article that I published a couple of years ago, and this is really a diagram of possible areas of injection.

Obviously in off-label use of hyperdilute or dilute biostimulatory products. Again, cannulas are used. This is just markings from the literature showing the areas that we use on the décollete. Typically, again, a cannula injection. It's a subdermal injection, and I'd like to show you a video, and this is a video showing a 70 millimeter cannula. It's a 25 gauge cannula. Notice that the placement of the

injection is just subdermal. And you can see when I lift the cannula, you can see the outline of the cannula again. So distribution of the product is subdermal, purely subdermal, it's an even distribution. The injection ports are typically two or three depending on which area I'm trying to reach. It's only the sun damage area. I am not injecting the breast and for a number of reasons, one is the curvature of the breast and typically patients don't come in complaining of sun damage to the breast. It's mostly the décollete. So again, in my opinion, and this is just an anatomical schematic. the décollete lives outside of the breast glandular and triadic compartments. The breast goes from the second to the six ribs from the lateral edge of the sternum to the mid axillary line. We are medial to that and superior to that in patients that I have treated. There's no evidence of the microspheres when I'm doing surgery. And again, I've been doing surgery for 30 years and using injectables in this area for about 20 years.

So, the anatomical structures on the right, you can see that there are layers of fascia. There's an anterior fascia, there's the anterior laminal fat, and then the capsule of the breast that separate the area of injection. Again, the injection is a subdermal injection. It's hyperdilute, it's a small volume. The volume might be 1.5 ccs of calcium hydroxyapatite or 365.5 milligrams of PLLA distributed in that large area. So it's minor particles, small volume. The diffusion does not happen

because it's constricted by either fascia or ligaments. And this is just some pre and post injection photographs that you can see the benefit derived by the patient. This is, you can see the number of injections, typically three injections results. A little bit about the mode of action. The CaHA microspheres have to be in direct contact with fibroblasts. There's no evidence and no cytokine expression that shows inflammatory markers are induced with calcium hydroxyapatite, and the collagen that's produced.

It's just a typical ECM, so it's a structure, it's the triple helix, it's really natural collagen. And lastly, just in summary, in terms of time, so the placement is outside of the breast area. In my opinion, the microparticles reside in the superficial plane and they cannot pass into the breast tissue because of anatomical restrictions, such as the fascia and also the ligaments in clinical practice. Microspheres are never encountered in breast surgery and I've gotten done countless breast surgeries on patients who have been injected. And lastly, calcium hydroxyapatite is inert, does not elicit a systemic or local inflammatory reaction, and PLLA induces a very mild subclinical localized reaction to stimulate collagen production. With that, I'd like to end and thank you for your time.

Thank you. Our next speakers are Dr. Molly Wanner and Dr. Amir Moradi. Both have prerecorded presentations. If we can now move to those presentations. Thank you.

Thank you for giving Akeynathe opportunity to present. My name is Molly Wanner. I'm a dermatologist at Massachusetts General Hospital, and a co-founder of Akeyna. I would also like to introduce Dr. Anderson who will be present for the Q & A. Dr. Anderson is director and founder of the Wellman Center for Photo Medicine at the Massachusetts General Hospital. He's endowed chair and professor of dermatology at Harvard Medical School. Today I would like to talk to you about dermal filler application risks. Intravascular events are increasing. A recent study compiled published vascular filler complications from 2018 to 2023. 365 cases were reported compared with 48 cases in the period between 2015 and 2018 and 98 cases from 1906 to 2015, there was a 509% increase in blindness in the forehead area and neurologic complications doubled. Knowledge of anatomy is crucial to decrease the risk of complications. However, device mediated technologies can mitigate these risks.

Akeyna’stechnology is one such option. We can all agree that with adequate training in anatomy, severe complications are rare, but they remain a concern. Akeyna did a small survey of cosmetic dermatologists and key opinion leaders.

100% were concerned about filler complications and 100% were unsatisfied with existing methods. Akeyna has a smart needle or smart cannula that can provide information on blood vessel location. Our devices in the early design phase. Currently the needle, which you can see in black on the diagram, has a lure lock connection that twists on and off any syringe. It has an embedded optical sensor at the tip. It houses electronics and it has an indicator that flashes in the presence of blood. There's a proprietary algorithm that interprets sensor data which indicates blood vessels. It is designed to be easier to learn and use than the alternative. This is an example of data generated from preclinical testing to train the algorithm. You can see that the signal in the background and signal from muscle is higher than the signal from blood. When the signal drops, it indicates blood or a blood vessel. This is an example of Akeyna's technology being used to target a blood vessel. We see the needle being used and the signal on the bottom. This signal will suddenly drop once it hits the blood vessel, and this is confirmed by the presence of blood in the syringe. In summary, device mediated technologies have the potential to decrease risks of vascular complications. Akeyna’s sensing needle is one such option. Thank you for your attention today.

Hello, my name is Amir Moradi. I'm a facial plastic and reconstructive surgeon and have been practicing in San Diego for almost 26 years. I attended University of California San Diego for my undergraduate and medical school. From there, I went to Duke for my surgical training and I received my MBA degrees from Wharton School of Business. My experience across 50 plus FDA regulated trials gives me a more clear lens, allowing me to balance innovation with patient safety. And it is based on that criteria that I would like to address my experience as it relates to injection of calcium hydroxyapatite to the décolletage area.

I would like to take a moment and allow you to look at my disclosures. As you can see, based on clinical trial experience, I have been working with multiple companies, in particular relating to this project, I've worked with Merz on multiple projects including the décolletage and also injection of calcium hydroxyapatite to the hands. Now, it is important for me to state that no company has reviewed or approved today's remarks. My testimony basically reflects the published evidence that I have come across and also my personal experience in this matter. My goal is that through this recorded video, I can provide the panel with some information based on my experience with the clinical trial and also hands-on in office treatment of the chest for rejuvenation.

As you're well aware, the demand for aesthetic procedures has grown significantly in a fairly short period of time. And patients are looking for ways to have procedures done including the treatment of the décolletage. In relationship to the skin of the upper chest, the decollete or décolletage area. This is a very delicate skin, therefore, we cannot perform the deep lasers that we can perform on the face, on the chest, or even on the neck for that matter. Therefore, our options are very limited. This is where a treatment of this area has become a challenge for many individuals and it is very important to be able to provide a service and teach that correctly so that this can be done safely and effectively for this region, which in a way is a transition from face, neck and the chest. Many individuals that I see, for example, that don't feel comfortable with the lower aspect of the neck and upper chest have to wear clothing that are more restrictive for them when they would like to benefit or enjoy different fashion designs that they may like or that would make them feel better.

I believe that the protocol in which we followed for treatment of the calcium hydroxyapatite to the décolletage area was very well planned to get the best results and least amount of adverse effects. And that was, for example, one reason in my opinion that a hyperdilute Radiesse was used. And because that skin is very delicate and very thin and placing the hyperdilute Radiesse would significantly

reduce any kind of a bumps and so forth that one can see and allows for more of a ease of injection in that area. Again, for safety reasons, a cannula was used for the actual injections. So there was a 21 gauge needle to introduce into the skin and use a cannula in multiple directions, which I'm going to show in the next slide.

This picture describes the area of injection you can see in this zone here. Now it was chosen in that way to be outside the breast tissue and really point to where one is able to wear certain clothing and feel comfortable, confident about their skin and so forth. And so the point of entry was chosen by the investigator to be able to place the product in a uniform fashion and in multiple different direction. And using the hyperdilute Radiesse, I found the procedure to be very easy to administer and I ran into no technical issues while placing the Radiesse in that region.

Obviously you have access to the clinical evidence and the efficacy of the product, and also the adverse effects. Therefore, I want take time on that in our site and I do all the injections myself throughout my 50 plus clinical trials. I make sure I'm the one who administers a product. I found this to be fairly easy to administer. I'm certain you have access to the prior trials and publications on the subject. Just to add to that, from a standpoint of Radiesse and how it looks radiographically, I personally injected Radiesse for the FDA trials for Merz and I also was the one or one of the sites that injected Radiesse . And then we would take the subjects to the

radiology and an interim after the procedure and looked at the radiograph. And the study showed that that the evaluation did not, was not interfered at all by placement of the Radiesse.

As a matter of fact, the high calcium hydroxyapatite looked like a very thin cloud in the dermal region. In addition, throughout my 26 years in the private practice, we started using Radiesse early on because there were no other reasonable fillers. Collagen was the only thing that we had at the time. And so the safety profile is very robust, and also from clinical experience, all fillers have their limitations that that has to be respected. But there are multiple studies that have been done as you're well aware, and I've been involved in many of those studies including jawline hands and the décolletage. As I mentioned in my experience and my readings and my involvement with this product that I found the product is very safe in the clinical trials. I experienced this product to be easy to administrate, administer in the hyperdiluted form with adverse events that basically included the mild swelling and bruising that we see with the injection of all fillers. , With, the, in my opinion, with what could be a serious adverse event with any filler.

Let's talk about décolletage. Number one would be vascular occlusion. And again, in my opinion, it's important that one pays attention to the area of injections. The advantage of the décolletage is the thin skin that is not hypervascular with larger

arteries, and that's very important as this is not the case, for example, in the face. And the other thing is that, well, we are close to breast tissue where you inject ,and the main aspect is that you are actually injecting away from the breast tissue and glandular tissue. What could be consequence of that, as you are well aware, is that it can show up per se and interfere with reading of the mammogram. So those are the things that one has to look at, and I think that the protocol clearly stated to stay away from the glandular and breast tissue, so that issue with mammograms and evaluation of routine female breast would not occur or be interfered with. I did go back and look at some of the references as well, although I was familiar with those just so that I could be more educated in my discussion with you. And I would like to thank you for your attention and your time.

So I'd like to now pronounce the open public hearing to be officially closed and give us the panel now an opportunity to ask questions of the public hearing speakers as well as the preceding speakers from both FDA and the external portionof the meeting. So let's begin with questions for the open public hearing speakers. So Dr. Sandler,

Thank you, Howard Sandler. The, we've heard quite a bit about the benefits of dermal fillers and the decolletage area, but I just want to learn a little bit more about the adverse effect. FDA is asking us as panelists to discuss issues related to

filler removal. And so I'm just wondering whether the public speakers or maybe some of the previous speakers could comment on using Hyaluronidase to treat HA filler issues or whether the apparent absence of removal strategies for the other fillers is an issue for providers who are performing dermal filler procedures.

(Dr. Lorenc) Well, I'd like to take that question if I may. I have extensive experience using, I get a lot of referrals for HA melting, so to speak. Hyaluronidase can be used very safely. It does not affect native hyaluronic acid as far as calcium hydroxyapatite, there is a reversal or an eraser, sodium thiosulfate that can be used to disperse it. And on top of that, CMC reacts to hyaluronidase. I typically use Vitrase in my practice, I'm sorry, Hylenex in my practice. So I can reduce and prevent AEs using these particular erasers. So it has not been an issue specifically in the deck of bay area because I use a hyperdilute or typically a dilute one to two or one to three CaHA or PLLA at the dilution of one to 24 or 24 ccs per vial. So it's very dilute and it's very dispersed, very evenly in likelihood of vascular occlusion in my mind is minimal. As mentioned before, there are no terminal vessels and this is a very well dispersed very minorly particles to a relatively a large area.

Thank you.

(Diane Zuckerman) I'd like to just respond to that for a second if I can. And that is that the concern that I have is that anything that's used to reverse these adverse events is off-label and none have been proven and approved by the FDA. So I do think that's an important issue that it would be helpful to have approved products for reversing adverse events. And at the moment, we don't have that.

Next question from Dr. MataRrasso.

Thank you, sir. I just want to clarify because the presenters who are all outstanding and many of my panelist colleagues are people that do these injections. Many people that are listening on this do not. Just want to clarify something that I think extremely important. We mentioned hyaluronic acid products, which are dissolvable as the prior speaker just said, but not FDA approved by things like Vitrase and hyaluronidase. And then we're talking about Radiesse, which is not dissolvable. So we're talking about two different products and at two different levels, one speaker talked about them putting in the fine lines. Another speaker talked about putting them in a deeper level. So I just want to make sure that everyone understands we're talking about two different products and at two different levels in the chest area. Thank you.

Thank you, Dr. Zuley, you have a question?

Thank you. That was exactly the question that I wanted to get clarification on because I thought I had understood exactly what the prior speaker just mentioned is that the microspheres are injected at a slightly deeper skin layer. And the speaker mentioned a fan like pattern. So I wanted a little bit of clarification around that should to understand if we need to be considering different levels of risk based on location of injection. Thank you.

(Dr. Lorenc) If I

may respond and product, if I may respond to that. So there are two different things. Injecting intradermally hyaluronic acid is for treating superficial deep lines. What I described is a biostimulatory effect of products like Calcium hydroxyapatite or PLLA. It's a superficial injection, purely subdermal. The cannula, and I purely use a cannula. Most of the practitioners purely use a cannula. It skirts the dermis and that's where the fibroblast live. And this is to make contact with the fibroblast and stimulate collagen. What it does, it improves the quality of the skin, improves the laxity and the fine lines. So it's a different treatment. They are different products. And I would have to disagree with my esteemed colleague, Dr. Matarasso, who we've known each other for many years. There is a treatment for calcium hydroxyapatite and I have applied it clinically and as I mentioned sodium thiosulfate, it is not approved. It's an off-label use. And the other mention

that I made was to correct the CMC, which is a component of calcium hydroxyapatite or Radiesse. I use Hylenex to reduce the bulk of it. So in my opinion, it is treatable and reversible.

(Dr. Matarasso) Well, thank you for clarifying that. I just meant not FDA approved for it, but he's a hundred percent right. And thank you.

Next, Dr. Hunt, you have a question?

Yes. Thank you. Kelly Hunt from MD Anderson Cancer Center. I just had a few comments. One is a lot of the discussion about the area that we're reviewing for these injectables is highly variable in terms of anatomy with different patients and different breast sizes, skin integrity, skin thickness, the amount of subcutaneous tissue. So while I think the anatomy is a critical piece here, that's something I think going forward we'll have to be described in more detail rather than a diagram of a triangular area on the chest wall because while the breast tissue may typically be lower, it might not be in many individuals depending on the breast size and so forth. So that's just a comment. But I do have a question about the CaHA and other injectables with respect to some of the imaging that was shown, suggested that the calcium goes away over time but creates a haze. And of course that can interfere, a haziness can interfere with imaging. And we've been talking about mammography, but there's also MRI imaging and you can get inflammatory changes related to

different injectables. So one question I have is, are there calcium deposits that occur in the tissue over time related to inflammatory changes from the injectables? And what is the experience with that? Thank you.

Yeah, I'm happy to respond to the first part of that, which I guess was a comment. This is Scott Hollenbeck plastic surgery and I'm representing in InSoma Bio. Yeah, Dr. Hunt I think brings up an important point and hopefully that was in my presentation. I had to step away, but I am a little concerned about the injection of materials into the breast and the location here and how there could be sort of a creep into that area. As I showed in some of the pictures, it's not very obvious where the décolletage, so to speak, ends and where the breast begins. And if it were very easy to distinguish that, I think our discussions here would be quite a bit different, for example, injection into the hand or something like that. But the whole essence here I think boils down to this. How do you ensure that materials that have never been considered for injection into the breast are not used to inject into the breast and under the context of the upper breast, lower chest décolletage area. So I totally agree with Dr. Hunt's comment. I'll pass on the second one to one of our injectors.

Anyone else have a response for Dr. Hunt's question? Okay, if not, we'll move on.

(Dr. Lorenc) I mean, if I may, I can give you clinical experience. So on the face, and I can refer to the face because it's just longer experience. I've injected the same materials into the face for many, many years, and I have done many facelifts on those patients. I'm lucky in that I have, my practice is split evenly between surgical practice and injectable practice so I can address it from both ends. I don't have an issue operating on a patient who had previous injection either of PLLA or calcium hydroxyapatite when I'm doing a flap on the facelift. So to me, I don't see it. It obviously depends on the timeframe. But if I may refer back to the injection clinically, and maybe this is a general statement, clinically we don't inject the breast. It's obvious that patients don't come in for injection of fillers, and I'm not talking about that as it's not mentioned and showed beautiful results.

But when it comes to fillers, patients don't come into my practice asking for filling injection of the breast. They ask for the correction of the lines of the anterior chest, and that's outside of the area of the breast. I also want to stress all of the data I have published on this extensively. There is no travel. Once you place the microparticle in the place, they don't travel, they don't get diluted. They don't cross the barrier between fascias or ligaments. That is not true. I have verified that using ultrasound. So I really want to stress that we don't see that. And clinically patient asks for correction of sun exposed areas, and that's that triangle that it's medially located.

And anybody, and I can only speak to my practice, I will personally not inject a filler into the breast knowingly because I don't think that's a good idea for all the reasons that you have asked.

But I always inject into the décolleté and I've outlined it properly. I showed you the video injection, which to me is a standard sort of triangle that is well confined. And I think that there are two different things. I just clinically don't see patients asking for filler injections into the breast. I have treated patients from mostly South America, and Scott showed a couple of images. I have seen patients with PMMA injected into the breast with acrylamide with everything in this world. Obviously we don't recommend it. It's not approved. It's illogical to do that. And I've only seen it on the other side as a treatment of a complication, but we certainly don't advocate that. We advocate injecting that central part to treat the superficial lines and the quality of the skin with the biostimulatory agent.

Thank you. Dr. Galandiuk, you have a question?

Yeah, no, it was interesting hearing different approaches from Dr. Curcio who mentioned that in the dermatological world there are many non-physicians doing these treatments. And I'd be interested from hearing from her what in the dermatological world the training is for non-physicians doing this procedure. I assume there are nurse practitioners that are doing this and from Dr. Hollenbeck

the other spectrum supporting that ultrasound should be used, which I assume would be physicians training to do this, to get a more accurate placement and assuring that's not intravascular in the correct plane and not in breast tissue. So I would love to hear more on that.

Thank you. Natalie Curcio. So in my practice that I've owned for over 12 years, I am the only injector of fillers and neurotoxins and person who performs cosmetic procedures like lasers in my office. So I've never had and worked with extenders personally, so I really don't know what their training is. I would assume many of them train alongside dermatologists or plastic surgeons, and it's state regulated as to who can perform what procedures. So in Tennessee, estheticians can do the same injections that I can. Other states have much more strict regulations. It has to be like MDs or has to be physician assistants or nurse practitioners. But I can't speak directly to that because I do all my own injecting.

(Dr. Hollenbeck) And to answer the question about ultrasound, it's more and more available and affordable. Many of us think of ultrasound as these gigantic machines that require extraordinary levels of training. What has happened over time is these have become smaller, more available in most clinics now, and many people are using them not necessarily in the way in which they might diagnose a breast cancer or diagnose some other advanced thing, but to help in their physical

exam and guide their understanding of the underlying anatomy. And I think in that context, why wouldn't you use an ultrasound? Because I do believe if a lot of people were doing this, especially if you expanded the skillset of injectors, there are blood vessels there as I showed, that could be impacted and that would be significant. And I do believe ultrasound could keep you for the most part from getting into the breast. And it would also, I showed pneumothorax as another one while hard to imagine happening. It could in theory in that upper chest, that very thin area with an unskilled injector could happen. So I wouldn't see why you wouldn't want to use ultrasound to guide it. We've adopted this in fat injection for buttock, for example, and that has improved safety when done properly. There's lots of reasons to think that ultrasound guidance is a good thing in this scenario.

Thank you. I'll make a comment to. This is Sachin Shridharani plastic surgeon in New York and speaking on behalf of ASAPS, the American Society for Aesthetic Plastic Surgery. So from the educational perspective, having been involved with training and educating hundreds if not probably close to over a thousand globally injectors with various launch activities and different partnerships with new products, similarly to including if you look at different areas of the world. So Australia and New Zealand for example, over 80% of those performing injections, there are non-physician injectors. And in the US the number continues to rise for

non-physician injectors. Injectables are not part of the medical school curriculum. And depending on what you train in may or may not be part of even your training paradigm outside of what they call the core aesthetic specialties of facial plastic surgery, oculoplastic surgery, oral maxillofacial surgery, plastic surgery and dermatology.

And so you do have physician injectors that have had no background or training in their training education and residency programs. And you also have that not part of nurse injectors, nurse practitioner PA school. Well, so back to what you're saying, most of the education that's done is done through employment in practices where they're employed and trained apprenticeships which function basically like mini residencies, observational ships, and then of course through the pharmaceutical partnerships where they provide training on anatomy and education for new product launches. So those are the main avenues that are provided for physician and non-physician injectors. And the lion's share of injectors now in the US are also non-physician injectors. So those are probably the key elements when you're asking about from an educational perspective and training, how does that process work? But it's not part of medical school curriculums and it's not part of a residency program for emergency medicine who emergency medicine physicians

can inject these products if they wanted to as well. Right. So those are probably the key I think, considerations there.

Thank you. Move on to a question from Dr. Minkis.

Thank you, Kira Minkis here. So I wanted to see if any of the speakers have either any data or anecdotal evidence for vasculature anatomy differences that might be affected by either prior surgery to the breast or chest area or history of radiation, which could certainly impact vasculature of that area as well. And it's a common location for radiation for breast cancer, for example, and maybe if there's anything from the European market after approval there.

(Dr. Hollenbeck) Yeah, I'll start with that one. I think the most common things you're going to see are exactly what you said, breast cancer associated radiation either in the setting of prior mastectomy or more commonly lumpectomy, so breast conservation. And that does extend up into this area potentially I would consider prior radiation in general to be somewhat of a contraindication to injection of material. We use fat a lot for that kind of purpose in the reconstructive setting as a biologic agent, but even in radiation has some problems. So it needs to be weighed out. I think that would be a relative contraindication. The other common one would be sternotomy from cardiac surgery, aside from unusual surgeries, it might've happened skin cancer resections, which those are very common in that area. I don't

see that as an issue, nor do I even see the sternotomy prior sternotomy as an issue. And that's going to be in your older patients that are actually going to fit into this upper chest skin wrinkling and coming in for that. So I don't think that would complicate anything. That's all the important structures are well below the sternum and there's no major changes that would occur. So the only one that jumps out at me is radiation. So I'll stop there. Thanks.

(Dr. Shridharani) I would echo what Dr. Hollenbeck mentioned also as a plastic surgeon who does inject this area with frequency radiation changes that they have on the vasculature, texture, quality of skin, decreased wound healing capabilities. All of those definitely I think lend way to wanting to probably proceed with caution. As a relative contraindication, we know what those radiation changes are. And I think injecting, if it's a biostimulatory material, you may not have the actual cellular material there in general with the fibroblasts and the activation of the tissues that you want at the histologic level to actually create the neogenesis pathway. So I think those, you may not even be able to get the true value that you would want out of a product that's banking on a healthy tissue bed to actually create the changes that go through again, that wound healing pathway. And as far as HA goes, you would want to be able to have tissue that can actually absorb that product. Well incorporate it well, has the texture quality of the skin to actually be

able to spread it, to improve that area also. So I would certainly echo what Dr. Hollenbeck said from a clinical perspective that there are definitely going to be those post radiation changes that have a deleterious effect on the tissue quality that may not make it as favorable for the best outcome.

Thank you. And before we move to a question from Dr. Zuley, I had a question for Dr. Hollenbeck during your presentation, I guess representing work at InSoma bio, have the Fractomer products that you discussed and displayed in one of your early slides been cleared or approved by the agency at this point in time for any indication?

(Dr. Hollenbeck) Yeah, thanks for that question. That's an important clarification. At this point in time, the product I showed called Fractomer has received an IDE for a very limited clinical trial phase one clinical trial. We have not actually used it yet or started that clinical trial. So I hope that wasn't implied that it's widely used or something like that. It is not. We have an IDE for an early phase one clinical trial. And the other important thing is I showed a lot of pictures and slides and everything. None of these materials to my knowledge are approved for injection into the breast FDA approved in this area. But obviously it does happen off label and perhaps even in ways that most of us would consider to be not ideal. And so that remains my main concern is by opening up a door that has less defined

anatomic terms, I would worry that those kind of events perhaps could increase. It's not that I would be opposed to injections into the defined area we talked about. Clearly, it's helpful. Clearly patients want that and are requesting it. My concern more is the extension of that area into breast and leading to some of those things that I was showing. And that's what I wanted to get across to the panel. Thank you.

Thank you. And then quickly, just to Dr. Wanner, kind of a similar question. The product that's being developed by Akeyna, where is that in terms of any total of regulatory approval from the FDA?

(Dr. Wanner) Thank you very much for that question. We're in the early design phase and have not started engaging in the regulatory process at this time.

Thank you. So Dr. Zuley, you have a question?

Yeah, thank you. So my questions directed at my clinical colleagues who are performing this, in breast imaging we are moving rapidly towards perfusion based imaging, MRI contrast enhance mammography. It's one thing to know, you may see a small amount of calcifications near an injection site or see a small mass, which would probably be a fat necrosis or a little glob of the material that was injected. But with these perfusion techniques, we probably will see edema on T2, I would imagine, and maybe some perfusion enhancements surrounding the

injection sites. So the question that I have is, should there be some sort of delay in perfusion based imaging for patients who receive these injections?

You might feel qualified to provide a response to that question.

(Dr. Shridharani) I think if I'm happy to weigh in, I think if we look at the principles of some of these different products, especially, let's talk about hyaluronic acid for a moment. There's certain products that are slightly more hydrophilic than others. So if we're talking about edema and the principles of them, we already are quite careful or should be quite careful on the indications of where we place these fillers. And so some of the HA's are not good candidates on areas, for example, in the tear trough region across the periorbital because they just draw in so much interstitial fluid that they increase actually kind of the periorbital edema and that's not aesthetic. So I do think that there are going to be modifications and uses of these products with principles or properties that maybe they're less hydrophilic in nature they are crosslinking so that the way that they are designed to stay in the tissue and longevity is also something that we keep in mind in the actual material itself, in how, like I said, on how the longevity or the way that the formula is for them would be more favorable in this region. Because again, the goal is typically not volumizing in bulk, its improvement of texture, quality and skin. So I think that would hopefully alleviate some of the elements when we're

talking about product utilization, product design itself. And as far as a slight delay, I think then that would just be a function of during the testing process to understand how long, what is the duration of that edema, so that way after X number of days or weeks, one could then proceed with routine screening mammography or advanced perfusion types of radiographic imaging that you're mentioning.

Dr. Matarasso you have a question.

Thank you. I just to comment, I appreciate I, the speakers have been excellent, but I know many people listening in are not people that do these procedures. So I just want to make two points. As I did earlier about two distinct products that we were talking about. From the jawline down to the decolletage a area is different skin. So the earliest speaker mentioned about how chemical peels and lasers are used, they really can't be used as effectively here as these other filler treatments where you could say, okay, I won't use the filler, let's say on the face, but you could use a laser or peel. So that's one of the reasons why this area is important because it is different skin and it can't be treated by alternative methods as well, which is why the speakers are discussing the fillers. The second point I want to make Diana alluded to a little bit is who is doing these procedures?

As she mentioned, in countries like Australia, 80% of the injectors are non-physicians. There are certainly extremely well-qualified physicians, nurses, PAs, but you can walk down any major city street and there are non-medical personnel using these products. Their store closes at five in the afternoon when the patient goes to the emergency room at night, there's no medical records. They don't know what was used. And when they talk about a supervising physician, it's one thing to have the supervising physician be a plastic surgeon, a dermatologist, et cetera, on premise at the time while it's being injected. It's quite another thing when you're in a storefront and the supervising physician, and I have nothing against psychiatrist, is a psychiatrist that's 20 minutes away that doesn't normally use this. So that's consideration about who's buying this and who's using it. It's one thing to have it done by Dr. Lawrence and his office who's had 25 years experience or a nurse that's in Dr. Shin's office doing it versus being in a storefront that closed at five o'clock with no medical records.

Thank you. So I wanted just to encourage the panel, do you have any remaining questions from this morning's session for our FDA speakers before we go to lunch? Dr. Galandiuk.

I just had a question more for some of the public speakers that talk. Is there any data on, it seems there's such a variety of practice versus subdermal versus

intradermal injection. Is there, and obviously everybody's doing this already off label, is there any data on how many individuals are doing the dilute subdermal injection versus how many are doing the intradermal injection?

(Dr. Lorenc) Well, if I can take that from the literature point of view, the hottest sort of topic is dilute and hyper dilute injections of biostimulatory agents, but it's a different injection. It's really a sort of global injection in that area to stimulate the fibroblast to produce collagen and elastin. It's not a specific injection. Sachin was referring to that for lines where you inject hyaluronic acid, it's a purely a volumizing agent versus PLLA. And CAHA and PMMA are BIOSTIMULATORY agents and they're hyper dilute to get an even distribution. In the literature, It's really trending towards biostimulatoryand certainly in practices, certainly in my practice, that's what I see. And social media also is trending that way.

(Dr. Shridharani) I'd echo a lot of what Dr. Lawrence just said in that realm. And a lot of that happens to be because a lot of the biostimulatory elements, when you look at various gene regulation and various studies, you're seeing that there's an upregulation of elastogenesis and neocollagenesis as well. So you're actually getting increased resiliency at the dermal level stimulation of the dermis and seeing increased overall improvement, which is exactly what your goals are without

necessarily having to do a serial technique. Both are incredibly valuable based on the indication, and both seem to be effective and safe and not being injected. Of course, once again in the breast, both have tremendous value in terms of what they're doing for the tissue quality with one more of an immediate effect. And we know there's benefit to needling. We know just even microneedling improves the texture quality of skin without even adding any type of volume or material. But the gene up regulation expression is definitely seen with the biostimulators, which is beneficial.

Dr. Hunt?

Yes, thank you. I just had a couple of questions about the imaging studies that were presented. And I apologize, I don't remember which presenters discussed this, but they talked about the lymph nodes and how the injections mimicked lymphoma. And so from that, I mean, I know that we see in large lymph nodes from many different procedures in the chest and neck area. And with the experience with the COVID vaccine, we started seeing a number of women come in with enlarged lymph nodes in the axilla from the COVID vaccine. But that was mostly just reactive lymphadenopathy that resolves over time. And so the comment about mimicking lymphoma, I was wondering if that was actually just data showing enlargement of lymph nodes from the injection procedures or was there actual

histologic or radiologic studies like PET CT that showed FDG avid areas in the lymph nodes from the injections?

Can you hear me? I'm M. Laurin Council, president of ASDS, and I had that in my presentation. I believe that there was histopathological confirmation. I will pull the paper now and put the final answer in the chat.

Thank you. Thank you. Dr. Alam.

Thank you, Murad Alam,, I had a couple of questions. I think Dr. Harris, you indicated we could ask FDA some remaining questions as well. I had a couple of questions. One, would it be possible, hypothetically, if these products were approved in the future for injection of the decolletage, if FDA could mandate how much volume could be injected or the location or at least recommend the location of injection or the technique of injection. So that's question one. To what extent would some further definition of how, where and how much should be injected could FDA mandate or would that be left entirely to, do you have practice and medicine issue? And the second question was, I think there was some mention of device cards that could be included to alert radiologists about the potential radiological implications of some of these substances. And I was wondering if it would be possible if such device cards were included within approval, if there could be some radiographic images included along with them, or would that be

purely just, Hey, be aware you might see this, or would there be some further instruction potentially available to radiologists who were presented with these device cards?

And then finally, I just wanted to make one comment. I don't know if FDA mentioned this. I looked through the literature, they didn't have this reference, but there was a lot of discussion about whether calcium hydroxyapatite could be reversed. And I think the FDA packet, it was presented as a possibility that had been mentioned, but there is at least one manuscript in journal investigative dermatology from 2022 in vitro and ex vivo investigation of intralesional sodium thiosulfate as a reversal agent for calcium hydroxyl appetite soft tissue filler that did show that the micro fears are reduced in size. So I just wanted FDA to be aware of that if they weren't already. But sorry about the long-winded questions. But one, can we specify further how the technique should be done and how much and where, and then can the device cards be fairly extensive in terms of providing information regarding radiographic findings?

This is Cynthia Chang. Thank you, Dr. Alam for the questions. So I'll try to address them for the first one regarding whether FDA can mandate information about where and how much to inject. This information is typically provided in the approved labeling for dermal fillers. And it's usually informed by the specific

information provided in the results for the clinical trials specific to the product, as well as any other available information such as what's known in the literature, et cetera. So hopefully that addresses the question. Typically in the labeling there is information about the maximum volumes as well as various other statistics, the median volume, et cetera, that was used in the clinical study, the volumes where there were more or less reports of various adverse events. That's usually specified in the labeling and the description of the pivotal study results for each specific indication that is approved for each product.

And there is often in the indications or in the labeling itself details regarding the plain of injection that is either included in the indications or which is recommended, as well as typically a breakdown of the different types of techniques that were used in the various locations of injection that were used in the clinical studies themselves. And so hopefully that addresses the first question. Regarding the second question on the device cards that could be provided to patients. I think we did not provide too much information in our proposal, I think in terms of what would be included in the device cards. And I think we would certainly be looking to the esteemed panelists here to provide their recommendations on what might be useful information and whether this proposal would be appropriate. And then I think regarding the third topic on reversal of calcium hydroxyl appetite, we're

aware that there are some reports, but as we've noted in the executive summary and in the presentations, there are no approved methods for removal for the various types of dermal fillers.

Thank you.

Great. So before we take our lunch break, I have a final question from Dr. Galandiuk.

Just a comment regarding the device cards. I'd love to hear from FDA and also from Dr. Abson, just echoing from the comment of Dr. Hunt regarding MRI imaging or other, perhaps other breast imaging. Because I'm a colorectal surgeon, I use MRIs a lot to evaluate patient if patients have any kind of interventional procedure like a biopsy in the pelvis or something like that, it causes a false positive in the MRI in terms of upstaging lymph nodes or causing you to think they're involved. Would there be a possibility of stating something about delaying time to getting an MRI or other breast from the time of a procedure, from an application of an intradermal filler because I think that might create some false positive imaging. I'd love to hear Dr. Zuley perspective or something from the FDA. Thank you. I

Thank you. So that's the same question that I have Susan. I think that that's something that we're going to have to consider. It depends on the inflammatory response and that may be based on the level of injection within the skin, the amount that's injected and the natural reaction that it causes from the product that's placed. But I think that that would probably be something that we would want to consider in the PMA that are put forward.

I do appreciate the comments and the questions. It is something that we're looking to our esteem panels to provide suggestions and considerations for the agency of what mitigations we should consider as part of the pre-market application, whether that is pre-market or post-market. Really looking forward to hearing your suggestions and comments related to that.

Great. Dr. Shuffett.

With respect to the device cards, it sounds like a great idea, but in practically speaking we never see device cards or a lot of information. For most our patients, we patients register and get their screening mammograms and if they have implants, sometimes they don't even know if they were silicone or if they are not silicone implants. So I don't think realistically any radiologist is going to get to see these device cards. A lot of times we have to try to infer what has happened to the

patient as history is not readily available either in our medical record or a lot of times from other facilities.

Dr. Hunt?

Yes, just in follow up to those comments about the imaging, I agree because I see patients who don't know what type of implants they have and so forth, but I do think that you could have information for the people who are doing the injections that depending on the patient's age and other personal history of breast cancer or family history and so forth, that they have baseline breast imaging performed before they do any procedures similar to we might do for patients who are considering breast reduction surgery and other procedures of that nature because unfortunately what happens is a lot of times patients have the procedure and then something is found on pathology or what have you. Then they come for imaging after that and it really complicates it. So I think giving information to the people performing the procedures about what should be done with certain age groups would be very helpful. Thank you.

Great. Well, I'd like to thank all of the speakers and of course the active participation of our panel. We're going to take time now for a lunch break. I'd like to see everyone back and ready to resume our panel meeting and discussion at 1:40 PM Eastern Standard time. So approximately 50 minutes from now.

Thank you.

It is now 1:40 PM I'd like to resume the panel meeting before we begin deliberating over the questions. I'd like to give Ms. Vuniqi an opportunity to make some clarifying comments.

Thank you Dr. Harris. Many of the questions today seem to imply that we may have large data or large volume of data available pertaining to the use of derma fillers in the decolletage area. However, that's currently not the case. The post-market data currently available is very limited, hence the reason we are requesting and asking our panel members to share your comments and feedback as it pertains to the benefit risk of such use. Many of the comments today were also made as it pertains to some products currently available potentially OUS. I do want to remind the panel that currently there is no products or medical devices that have been approved by the agency for use in the decolletage area. There was also comment suggesting whether migration is a concern and as part of the FDA presentations, we did highlight that post-market data, both MDRs, which are limited due to the fact that these devices have not yet been approved, but also literature do specify or provide some information of migration pertaining to certain uses and certain indications. And lastly, I also wanted to touch on removal, which is also a question that we intend to ask the panel for your input and guidance. Currently, the agency

has not approved any products or devices for removal of dermal fillers and there's limited data that we currently have available for that. I'd like to also invite Cynthia Chang for a couple of clarifying comments before turning it back to Dr. Harris.

Thank you. This is Cynthia Chang. So I wanted to touch on a couple of topics. The first is just a note that we wanted to just add a clarification regarding data and reports of interference of dermal fillers with breast imaging. We did want to add a clarification that we are aware of another dermal filler, not one that's approved in the US, but a hyaluronic acid based dermal filler that was previously used and marketed for breast augmentation outside of the United States. However, that dermal filler was withdrawn from use in this indication because the presence of the device made diagnosis of breast cancer more difficult and the device was reported to obscure the breast tissue and mammography and it was also detectable in ultrasound and MRI examination of the breasts and I believe that was mentioned in our executive summary document. One additional point I would like to make is that there were many comments made in some of the prior presentations regarding biostimulatory products. We just want to note that FDA has not approved any specific claims using the term biostimulatory in the labeling for dermal fillers. Thank you.

Okay, so at this time let us focus our discussion on the FDA questions panel members. Copies of the questions should have been included in your panel packs. I would ask that each panel member identify him or herself each time he or she speaks to facilitate transcription. Dr. Jodie Giordano will read all the FDA questions after which we will address each one separately.

My name is Jodie Giordano and I'm the acting Assistant Director in the division of Plastic and Reconstructive Surgery devices team four. The questions for panel discussion are as follows, decolletage refers to the area of the chest or cleavage between the breasts up to the collarbone beyond the anticipated adverse events of filler injections. Dermal filler injection into the decolletage area includes the following unique risks which are specific for this anatomic area, potential for dermal fillers to cause interference or other findings on breast cancer screening studies, potential for positive findings during clinical examination, proximity to breast tissue which may impact breastfeeding in the lymphatic drainage system of the breast panel. Question one. The benefit risk profile of dermal filler devices for the decolletage indication may vary based on patient specific factors such as their risk for breast cancer, risk for scarring or their age and potential to receive larger cumulative volumes over their lifetime.

Does the panel recommend additional risks to be considered for injection into the decolletage area? Does the panel have recommendations about specific subpopulations to be studied or to be excluded because the benefits may never outweigh the risks panel. Question two. Given the risks unique to this anatomic location, FDA proposes the following additional criteria to be incorporated in the pre-market and or post-market mitigation strategies for the patient subpopulation that may be candidate for injection into the decolletage area. To mitigate the risk of interference or other findings on breast cancer screening studies, we propose collection of baseline imaging such as mammogram, ultrasound or MRI, preferably within two years prior to injection and post-injection imaging. Evaluation of imaging by committee with experience and expertise post-approval study if imaging evaluation was not included in pre-market study inclusion of radiographic images of the implanted device and labeling. To mitigate the risk of potential positive findings during clinical examination,

we propose recommending device cards be provided to patients and included in patient records post-approval study to assess late onset adverse events and their effects on clinical diagnosis. To mitigate the risk that proximity to breast tissue may impact breastfeeding and the lymphatic drainage system of the breast. We propose pre-market follow-up until quiescence of inflammatory response in post-

approval study to evaluate effects on lactation in the lymphatic system. Does the panel agree with the proposed strategies for risk mitigation? Based on the risks discussed, does the panel recommend additional assessments or mitigations that should be considered and included? Does the panel recommend this data be provided in the pre-market study before approval to inform the patient in the labeling? Does the panel have recommendations on assessment of long-term adverse events or the duration of follow-up of the patients panel? Panel question three. Currently there are several approaches reported for treatment of adverse events after dermal filler injections such as aspiration, drainage, extrusion, excision or enzymatic degradation.

FDA has not approved any product indicated for enzymatic degradation or removal of dermal fillers. Does the panel have recommendations for how the benefit risk profile for dermal fillers injected into the decolletage should be evaluated considering the current removal options? How should the available removal options for a specific device be communicated to patients in the labeling and other patient materials panel? Panel question four. A patient preference study may help inform FDA's benefit risk assessment as part of the pre-market review of devices for this new indication. Considering the risks identified in the prior questions, which key risks would the panel recommend for incorporating into a patient

preference study to estimate the maximum risks that patients would be willing to accept? In other words, are there specific risks that the panel is most concerned about given the potential benefit for this new indication?

Okay, thank you Dr. Giordano. So we will now begin our panel deliberations. Panelists, once again, please identify yourself each time you speak and use the raise hand features that I can recognize you. So the first question, I think we're going to once again put it back up just so it's in front of us for a few minutes to review and think about and then please volunteer your questions. Dr. Alam.

Thank you Dr. Harris , Murad Alam regarding the first question where the FDA is asking, does the panel have recommendations about specific subpopulations to be studied? I think one subpopulation to be studied would be women who are potentially breastfeeding and or pregnant since there's been some theoretical risks posed, even though we don't have data and understand the limitations of the current dataset. But I think that would be a group that we would want to study. And another group could be patients with skin of color and especially patients who've had difficulties and these overlapping groups with wound healing because patients with skin of color may be predisposed and some other groups as well to not only adverse aesthetic outcomes like post-inflammatory hyperpigmentation, but especially in the presternal area, risk of keloids and other abnormal scars.

And I think one other additional risk to question part A and panel question one, does the panel recommend additional risk to be considered for injection? And I don't know exactly if that's what the panel is getting at, but I'm sorry the FDA is getting at. But I think one would be to specify the difference between injecting into the skin versus into the parenchyma of the breast. We've heard a lot that these are not intended for use in the breast, but the FDA might want to characterize any approvals as specifically excluding injection into the breast. Thank you.

Thank you. Dr. Zuley.

Thank you. This is Rita Zuley. So as far as part B question, does the panel have recommendations about specific subpopulations to be studied or excluded? I would suggest that we exclude patients who have had radiotherapy to the region. We may consider temporary exclusion of patients currently receiving treatment for breast cancer and or undergoing advanced imaging such as PET CT for any kind of cancer whereby the reaction or the material itself could obscure or cause a false positive on a PET CT, for example, or an MRI. Thank you.

Thank you. Dr. Hunt.

Thank you. I would agree with the recommendations that were made by the two speakers previously. I would also say that patients who have had chest wall radiation for other reasons should be our special population that need to be considered or excluded because they might not have received radiation for breast cancer. It might've been for other tumor types, soft tissue sarcoma, other types that could cause problems. And obviously I think most clinicians know that the skin integrity is just altered often after radiation treatment. So I think that that's definitely consideration for the FDA to include. Thank you.

So I just want to ask a quick clarification point for both your comments Dr. Hunt and for Dr. Zuley comments. So are you thinking that these patients should be studied to determine whether it's safe, the people who've had a history of radiotherapy or to study? Does this have an influence on MRI imaging in patients who are being actively treated for cancer or they should just be summarily excluded a request for study?

(Dr. Hunt) Well, my opinion would not be to just totally exclude them because you can have breast cancer treatment has changed so much now that often we're not using whole breast radiation, so that upper part of the breast might not have even been included in the radiation field, but those that are having post-mastectomy radiation that generally does include the entire chest wall and regional lymphatics.

And so those should be studied for consideration, you know, the way that radiation is delivered now, it often doesn't cause as severe effects like telangiectasias and other things that we've seen in the past with radiation, but someone who received radiation 10, 15 years ago probably has significant skin considerations that I think those patients should be studied separately. As far as imaging, probably there's a lot of patients who might get an MRI for some reason or another, but certainly if they're undergoing cancer treatment, especially if it's in the upper chest wall where it might interfere with MRI or PET CT interpretation, then those should probably be excluded. Thank you.

(Dr. Zuley) My comments would be that they should probably be studied, carefully studied, prior to inclusion, but not definitely excluded for the same reasons that the prior speaker just mentioned. The range of skin effects from radiotherapy is pretty wide. Some patients you can hardly tell they've had radiation. Other patients have significant long-term effects. And so I think understanding and designing a careful study, it would probably take time to accrue to really look at maybe the effects on different levels of radiation change in the skin and time from exposure of radiation to injection would be important. Imaging most certainly I would not exclude. I think it should be studied. Thank you.

(Dr. Harris) And just one other little clarification and I'll let others speak. So, I understand the issues around how there may be an inflammatory response to the injection that could be then misinterpreted by MRI, perhaps even CT or other imaging modalities. But in the issue of radiation injury to the skin, recognizing the FDA hasn't approved, doesn't have any labeling, any issues around bioactivity of these materials, it would seem to me that that would potentially prevent the injection from producing the response you wanted, but would there be harm associated with the injection in radiation injured skin?

(Dr. Hunt) I'll just make a quick comment about that in that the previous speaker had mentioned the timing of radiation. So the timing and the dose of radiation, all these can have such an important impact on the skin integrity, but I think that they need to be studied because perhaps it would help with some of the radiation change that we see in the skin. I don't know that it would be particularly harmful unless there are serious concerns about the vascularity of the skin. In some patients we see very severe changes from the radiation, but those are typically patients who are treated quite a long time ago. So, I think that it should something that should be studied and not necessarily excluded.

(Dr. Harris) Dr. Minkis.

So, I agree with all the points everybody made and I do think that post-radiation skin can be a little bit less predictable and even with very safe devices and lasers could sometimes act differently than we would expect and we've seen instances of ulceration from mild settings and things like that. Though I definitely think that it should be studied carefully and proceeded with caution and the vascularity also changes as well as the wound healing respond to the skin. The other point I wanted to make is regarding the age of treatment. There was some discussion about having baseline imaging and maybe a baseline MRI or mammography prior to proceeding, but the age at which a woman becomes eligible for breast imaging is 40 typically, unless there is an indication for earlier imaging. So are there going to be situations in which if we're recommending baseline imaging and the patient is otherwise ineligible for it, are we going to be putting somebody in a difficult situation from either their insurance standpoint or otherwise being able to proceed with such imaging?

(Dr. Harris) I may have misunderstood that part of that question, but was the, not your comments Dr. Minkis. But the question about I was under the impression that the issue was whether we would want to see a study in which the participants had a baseline imaging study prior to being treated with one of these products.

(Dr. Minkis) I think one of the prior panelists suggested prior to treatment that they would recommend that patients undergo baseline mammography or MRI imaging of the area so that after treatment if there are any suspicions and it's their first image, then they have no baseline to compare it to assess whether those changes are related to the filler or not. But I might have misunderstood that.

(Dr. Harris) Right.

(Dr. Hunt) So that was based on my comment. Sorry, this is Kelly Hunt. So, I meant that similar to what Dr. Lars Grimm just put in the comment, when patients are being considered for certain procedures like reduction mammoplasty, then we typically say you should have your imaging if you're eligible for screening based on your age and other factors that you should do the imaging before you proceed with the reduction mammoplasty or the injection, the other procedures. Not that everyone should have baseline imaging. So if that is how my comment was interpreted, that that's not what I intended, but similar to what was just put in the chat, that if someone is eligible for imaging, they should consider doing it before the procedure so that you have that baseline imaging in case there are any changes afterward, you can attribute them more to the procedure than go down a rabbit hole chasing something that is not really relevant. Thank you.

(Dr. Minkis) Thanks for the clarification.

(Dr. harris) Dr. Matarasso.

(Dr. Matarasso) Just to follow up on the comments about the mammogram, I certainly think in terms of exclusion, obviously we'll exclude pregnant or lactating women or minors. The problem with the mammogram issue is that you might have these injections every six months or every year. So while we do get a baseline, I get a baseline before a breast reduction on a patient. They're having that operation once and they won't need it until they become eligible age wise. The problem with the fillers is that you could do it in a 36-year-old, get a baseline mammogram, and then you'd have to do it again at age 37 and 38 and every time they come in for further injections. So that's something to think about. I am concerned about the breast, don't get me wrong, I just want to emphasize the frequency. In terms of who shouldn't have it, who I think needs to be excluded in addition to the pregnant and lactating people, I would probably consider those with bloodborne cancers and lymphomas because of the potential for travel or inflammation of the nose. Thank you.

(Dr. Harris) Thank you. Dr. Sandler.

Dr. Sandler) Thank you, Howard Sandler. I just wanted to say I appreciate the very on point radiation oncology radiation related questions from the panel. Thank you.

I would say though, regarding radiation, we're talking today specifically about the décolletage area, but these devices, these products are approved for multiple body parts already. Many of them could have been previously radiated. And to my knowledge, FDA has not labeled them as not as ineligible for patients with prior radiation. For example, had a neck cancer patient who might've had a resection and postoperative radiation might have some need or a desire for a dermal filler. And the issues I think would be the same in radiated irradiated tissue in any part of the body. So I just wanted to share that perspective. The other thing I was just going to mention related to question one B about specific, I'm sorry, about one A, about additional risks.It was mentioned a couple of times about lymphatic alteration and we even heard a little bit about the potential for transient lymph adenopathy or lymph node enlargement as a hypothetical concern. But one thing as a radiation oncologist I was thinking about was would there be alteration in lymphatic flow so that a radiation oncologist who is providing regional lymph node radiation might need to alter the radiation fields, the radiation treatment volume, given prior dermal filler injection? I just want to say that I don't think that's a significant risk, so I would not be concerned about that given the superficial nature of this placement and kind of medial and away from the breast tissue itself. Dr. Hunt as a breast surgical oncologist might have a different perspective, but that my perspective as of now is that it would not alter radiation planning.

(Dr. Harris) Any a quick comment Dr. Hunt before we go to Dr. Spector?

(Dr. Hunt) No, I agree. I don't know that it would, my point about the imaging and the patients is largely around the fact that we want some baseline if they should be having screening rather than them doing these procedures and then going in and having imaging afterward. It just complicates everything clinically for all the team members. So, thank you.

(Dr. Harris) Dr. Spector.

Dr. Spector) My comments support some of the other comments already made, particularly with respect to fibrotic processes and also particulate transport to lymphatics. And I would say this relative to question one A, what I'm not suggesting is these, risk is a pretty strong word. I would say certainly results to be followed, to be on the lookout for when it comes to the fibrotic condition I mentioned it falls under the heading I think of nodules. These might be fibroadenomas that have been found to form, in fact this was the highest of the MDRs, the nodules. The reason that's of some interest importance is that we've heard something about the inciting fibroblast to produce collagen to get the desired effective tissue filling, but those we haven't heard the source of the fibroblast. These fibroblasts based on many studies in many other organ systems, these

fibroblasts are derived from endothelial cells in a process called epithelial mesenchymal transition.

So it really speaks then as well to understanding what the vascular, vascularity is of this particular area that we're dealing with the décolletage area. How does that vascularity differ from the breast itself with respect to the potential to incite endothelial cells to become myofibroblasts inform these fibrous nodules? So it is a matter of keeping eyes open toward that. The other point speaking about the particulate transport was nicely mentioned by Dr. Hunter. There's no question, particles that are slowly resorbing like hot calcium phosphate particles and the PLLA particles, they're going to get into the regional lymph nodes. There's already a paper that she kindly shared which has found that and injections made in this region we're talking about. But this is a common occurrence of particulate debris generated by other prosthesis, prosthetic devices of the body. Now here again, the lymph adenoma, the lymphoma that have identified by the lymph node enlargement because the lymph nodes become packed with these particles have not in and itself caused a problem for the patient. But it's important to keep track of that because the particles in the lymph node, some of them will get out of the lymph node and into the general circulation and that's where they can cause a lot of problems. So these two points I'm just suggesting for in this question, one A,

keeping an eye out for, let's call it nodule formation. And the second also keeping an eye out to findings of regional lymph node enlargement, which would signal the fact that particles are accumulating in that lymphoma. Thank you. And I'm Myron Spector, I forgot to introduce. Thank you.

(Dr. Harris) Any other comments from the panel regarding questions one A, one B? Okay. Well, Ms. Vuniqi, it appears that… we're not going to question two yet. And please members of the panel, please correct me if I'm not going to accurately summarize the collective opinion because there seems to be some overlap between things that we think are potential risk factors that should be highlighted and patients be informed of, and then other issues that we think should actually be studied as part of a process prior to either pre-market study or post-market study. So with that caveat in terms of, I'm not exactly sure where all of these comments fell, we certainly wanted to highlight the need to consider patients who are breastfeeding or pregnant, perhaps even be excluded from receiving these injections. But also patients with darker complexions or known wound healing issues including a history of radiotherapy were identified as a potentially higher risk population. Patients undergoing active therapy for breast cancer or other treatments that involve active imaging would be a group that would likely be excluded rather than studied. And then a history of lymphoma or other blood

cancers would be another high risk group. So once again, with the caveat of not knowing whether these are subpopulations to be notified or thought to be at higher risk versus groups to be included in pre or post-market studies, do you feel Ms. Vuniqi that you have a adequate understanding of the panel's perspective on question one?

(Dr. Vuniqi)Thank you Dr. Harris. I do. I did want to ask a clarifying question related to patients that may be of higher risk of breast cancer. I don't think I heard the panel deliberate on that or provide any suggestions. I'm curious if there's additional comments pertaining to that subpopulation.

(Dr. Harris) Well, Dr. Hunt raised her hand. Maybe she'll have the

(Dr. Hunt) Thank you for that question. I don't really see why someone who's at higher risk of breast cancer should be excluded. But just as Dr. Zuley put in the chat, they should have their imaging performed and usually someone who is at higher risk is getting more frequent screening than every two years, but an average risk woman may be getting screening every year or every other year. So I think that you could include information about patients who are having high risk screening or that are eligible for breast cancer screening based on age and other factors that they should have the imaging performed at some period before the injection that like Dr. Zuley has put in the comments. But I don't think that just

because someone's at higher risk for breast cancer that they should be excluded. I do think that patients with bloodborne cancers, I agree with the comment about that and the question about lymph nodes and so forth, but I am not sure that you should exclude everyone because we have a lot of patients who are actually cured of lymphoma and leukemia and other things. So I wouldn't necessarily want to label them as being excluded from these injections if that's something that they and their physician chose as the right thing for them. But just to understand that it can complicate potentially if they do get lymph node enlargement that they need to be aware of that. And as I said, just with other things that we do like the COVID vaccine, we didn't tell people they shouldn't get it because it would cause lymph node enlargement, but that we just needed them to be aware of that as a factor that could come up in the treatment and follow up. Thank you.

(Dr. Harris) Dr. Shuffett

(Dr. Sheffett) My concern is not so much on mammography if the injections are done as intended, dermal or subdermal. For example, when we do tomosynthesis imaging, we can pretty much identify skin from breast. So if there is an artifact or something we can't see, it might not be that difficult to see through on tomosynthesis, but if in some states, such as my state where people who are doing the injections are not medically trained, and if there is an alarming number of

people who are getting injections into their breast, then we're going to have problems. And so in that situation, I would be more afraid of for people who are high risk undergoing these injections until we're really clear as to what the mammograms are going to look like after and the MRIs are going to look like after.

(Dr. Harris) Dr. Zuley.

Thank you. It's Rita Zuley. So one suggestion that I have for FDA to consider is that for patients who are going to receive advanced imaging, specifically contrast based imaging, that there would be a delay, the patient would be notified that they should wait six months, something, in the beginning during these pre-market studies to try and avoid unnecessary identification of inflammation from the injection until we understand that timeframe better. The other comment that I wanted to make was I feel, and I agree with the prior comment that the patients who have implants and nursing, but specifically implants, especially silicone implants should be excluded because we look at lymph nodes very carefully with those implants looking for implant-based anaplastic large cell lymphoma, and we would not want to be confounded by a reactive node. Thank you.

(Dr. Harris) Dr. Grimm.

(Dr. Grimm) Good afternoon everyone. Lars Grimm. I think the other way that I internalize the risk benefit profile for high risk patients is that these patients are frequently getting more frequent and more extensive imaging, but also more frequent physical exams, oftentimes in a high risk clinic. And what that means is they're at a higher risk of false positives. Someone's going to feel a lump under the skin surface, patient's going to feel a lump that's going to prompt additional imaging, potentially biopsies and things like that. So we could find a baseline for, hey, how frequent are there false positives in the general population? But in the high risk population, you would expect that rate of unnecessary workup, for lack of a better term, to be much higher. And that's something to both in no way exclude high risk women, but to make them mindful of if they're going to undergo this type of procedure. Because these women are absolutely going to have an impact on their quality of life as a result because they're already very concerned about the risk of cancer, they know they're high risk and then they're definitely going to have a higher risk of false positives as a result. So they kind of feedback on each other.

(Dr. Harris) Thank you. Dr. Spector.

(Dr. Spector) Yes, I'm Myron Spector. Yes. In direct response, I think to Dr. Vuniqi's question regarding breast cancer, there's a wide array of materials now being used for dermal fillers. One specific question could simply be, is there

anything that would indicate that this particular material could incite the breast cancer formation? And I bring it up this way because if you once again, just go to literature and look for breast cancer and EMT epithelial mesenchymal transition, you will see that EMT process generates cancer stem cells. So I think it would be judicious to have some checklist item dealing directly with that point.

(Dr. Harris) Okay. Any other comments? Alright, well then we will move on to question number two. If we could briefly display question number two to refresh everyone's memory, just take a moment to reread. Okay. So why don't we have Dr. Alam start off our discussion or comments?

(Dr. Alam) Thank you Dr. Harris. Dr. Murad Alam. Regarding panel question number two from FDA, I certainly don't have any comments pertaining to A or B, and I would like to comment on C, which is methods to mitigate and inform patients and providers about the potential risk in interference with radiographic studies. We're fortunate to have many experts on radiographic studies. I'm not one of them, but just listening to them, it seems like even the very experienced practitioners and researchers on this teleconference have seldom seen this and have limited understanding of how they would assess fillers in the context of trying to rule out breast cancer. So to that end, I would suggest in addition to doing a study in which we had baseline imaging and then subsequent imaging that the images

obtained from that study be potentially kept in some repository such that when radiologists were confronted with the challenge of determining whether a finding was truly concerning for malignancy or just artifactual relevant to the prior filler, they would have some resource they could consult and some images they could look at that they could considered appropriate to make that determination. So I think that's one thing that could be done with data coming out of the study that would mitigate risk potentially about interference with radiographic studies. Another element to maybe mitigate risk or at least suggest when it should be viewed as more concerning would be to track lifetime volumes of injection. That would be obviously something that the practitioners were injecting this have to do, but maybe there could be a request from FDA that I think generally practitioners do this anyway, but to reiterate the importance of recording how much they injected and where such that if there were a question, it'd be easier to determine whether that would be related to the filler or something else. And also that might allow for some post-market surveillance over the long term regarding whether the injection volume was associated with any associated problems in the future, including risk of malignancy. Thank you.

(Dr. Harris) Thank you. Dr. Ballman.

Thank you. Karla Ballman. Yeah, and I just want to echo, I mean there was a lot of conversation around the first question as to whether or not in practice if this is approved, there should be baseline images regardless of that, I just don't think there's any data. So I do endorse what the FDA is planning either in a pre-market or post-market in terms of getting the data on potential issues that might come up with imaging. I know that they said pre baseline, so within two years and then some post, but some consideration might be given for time period after sort of the injection. You know, like maybe the effects go away over time or as was mentioned before, if there's more volume and continually the patient is continually getting the injections, what impact might that have as well? But data is necessary.

(Dr. Harris) Thank you. Dr. Grimm.

Thank you. Lars Grimm. To address a little bit of Dr. Alam's point, one of the challenges for a breast radiologist is that the types of materials that we're talking about are very different. So it's not like, hey, we want to see, does someone have a silicone breast implant rupture? We know what silicone looks like classically in ultrasound, we have special sequences on MR. We're talking about a number of different compounds which could have different appearances. The volume of injection and the location of the injection was the dermal or subdermal could affect our imaging. And oftentimes what we're seeing is not the actual material itself

that's causing problems, but it's the potential reaction of the body, the fat necrosis, the inflammation, the secondary findings that can show up on imaging. And it's also worth mentioning, this is an area, the definition of decolletage is a little bit murky as we've discussed, but the upper inner portion of the breast is oftentimes an area where we don't necessarily get great images of.

And so we're talking about an area that might've been in completely visualized before now because it's fuller, maybe we're getting more or less imaging of that area. It's an area that's not as accessible for mammography given the technique that we use in compression in our standard kind of CC, cranial caudal and medial oblique views. So it is a little bit tricky to feel confident that we're really going to get good imaging of it and that we're going to consistently understand what we are seeing, even if we had a wonderful registry that showed a bunch of cases because there's so much variability in what might be out there.

(Dr. Harris) Thank you. Dr. Zuley.

Thank you. Rita Zuley. So one of the things I was thinking about, and this goes back to Dr. Hollenbeck's comments about the lack of clarity on what this region represents. Could be, just a suggestion to FDA, that there's a map that has to be filled out during the PMA process trial where the amount and where the injection occurred is mapped so that it can be correlated with follow-up and perhaps

additionally, during the PMA process, there are images of the area, physical images of the area to demonstrate what the area looked like previous and then if there are complications, what those complications look like so that when follow-up imaging occurs, it can be correlated back to those physical images that the person who did the injection took. Thank you.

(Dr. Harris) Thank you. Dr. Matarasso.

(Dr. Matarasso) I have a question for people on this call and the FDA.Probably 75% of these injections are done by non-medical people. And so recording the volume, the location, giving informed consent is fine for everybody on this call. What do you do when a non-medical person or a salon is injecting it? How do you follow volumes? Complications? Informed consent? That's my question. Maybe the FDA can address that.

(Dr. Karol Gutowski) Alan, this is Karol. We actually tried to address this at one of our ASPS patient safety meetings, and I think your concerns is exactly what came back from the group. While we can try to regulate ourselves, and we're used to doing this when these things are being done in strip malls and other places, we're not going to get the data that we need because people are not going to cooperate with this. It'd be sure easy to have an app that you can scan what you did and

download all the information to a central area. That actually working with the way that these products are being used and delivered, I don't see it happening.

(Dr. Matarasso) The only possible way, and I didn't want to say it and I don't want to get ahead, I'd like to hear what the FDA has to say. Thank you, Karol. The only possible way, and I don't see it being feasible, is through the manufacturers. The manufacturers for breast implants, you have to fill out a checklist. They know who they sell it to and so on and so forth. But even though there are non-plastic surgeons putting breast implants in, there really aren't any non-doctors. Hopefully. The problem with this is you heard the statistics in Australia, 80% of them are not done by physicians and you can regulate all medical personnel, nurses and so on, and Pas. You cannot regulate somebody who works in a salon. I would love to hear what the FDA's thoughts are on that.

Hi, this is Cynthia Chang. I can start to address that comment and it's definitely an excellent question, Dr. Matarasso. So FDA does not regulate healthcare providers or their training, and you're right that FDA regulates the medical device manufacturers. That said, in the labeling, we do provide information recommending that the injections should be reserved for qualified providers with expertise in dermal filler injection often. We've also provided information in our public communications we where we educate the public regarding the importance

of qualified providers in addressing and mitigating the risks of these dermal filler procedures due to some of the catastrophic adverse events that can happen and have been reported. And I do want to note that for certain dermal filler devices that have approved since 2021 for certain new indications that might pose specific risks, FDA has included conditions of approval requiring that manufacturers must provide a device specific use training program and that manufacturers may only distribute the device to providers that implement and complete the training. And so these conditions include that the manufacturer should develop a method by which the public could verify that a provider has completed the training and that information about the provider training should also be provided in the labeling. So that's some of the information that we are able to provide in terms of our authority in regulating the manufacturers and their role in distributing the products.

(Dr. Harris) Thank you. Dr. Galandiuk. I think you're still on mute.

(Dr. Galandiuk) Do you think this might be something where you could actually get patient buy-in and whether it be from dermatological, surgical or aesthetic societies, where they could make an app that patients could use where they could document their procedures? I mean, it might not be as accurate as a medical person would fill it out, but at least they could document the times that they got injected the locations, again, with less accuracy than a medical professional, but you could

get perhaps more accurate adverse events reporting than you would from medical professionals.

Hi, may I make a comment? Sachin Shridharani from New York. So I think one of the things that, as I'm hearing this segment of the conversation and what Dr. Matarasso's points were spot on, and I was the one who mentioned earlier about some of the elements in the ANZ region globally, and again, what's starting to mirror in the United States as well, that you do have non-physician or non-core providers performing. This is obviously well beyond the scope of FDM. You're talking about scope of practice, which is regulated as state by state level and in that lens. So I think when you start really thinking about how do you treat sensitive anatomic areas, first of all, you don't even have to have it on the label to treat it, right? I mean, you can use any one of the various HA or use this because it can be used off label. But as you start thinking about mass adoption education training, what you're mentioning Dr. Galandiuk is it's not necessarily the issue of regulating the physicians will create an app. It's like we were saying, we're using these colloquial like saying, okay, strip malls or wherever it is, you think about the mass utilization, mass adoption, that person is not regulating themselves, right? We help manage very complex adverse events. I'm an advisor and an adverse event specialist, for example, for deoxycholic acid, for Kybella, for global and domestic

complications. A number of times someone has an adverse event that doesn't know how to manage the adverse event. That as a medical director that is not in the core specialty that does not know how to manage. In fact, many of these different providers who are non-physician providers actually pay a medical director a fee per month to oversee their practice signing chart. So their medical director is not even someone who feels capable or is boarded in the specialties that could help manage this complication. So part of it is that even we created this app, so who would be compliant with it? Dr. Gutowski, Dr. Hollenbeck, Dr. Matarasso, Dr. Lorenc , myself, or dermatologic colleagues. We're all going to, because we're also already part of the fat transfer registry or fat grafting registry, part of the breast implant registry. The PA, nurse injector, aesthetician, depending on where they are and who they're injecting, is not going to probably comply with that. It is just going to be beyond scope. They don't have to because there's no professional board that they answer to. They're not interested in being part of the American Society of Plastic Surgeons. They're not capable or they're not going to be part of that professional board or that professional society. So they are just seeing themselves as mercenaries treating and injecting because they do it few hours a day and create value and financial elements and then go back to their normal day-to-day routine. And if they have a complication or adverse event, they call a hotline or try to get support when that adverse event occurs, and then hopefully someone will help bail

them out to do the right thing or take care of the patient or just send them to the local ER. So I think that becomes really the issue when it comes to the registry to the apps; is that compliance is key and going to be provided by those who are actually responsible. It's the ones who aren't on this call that are the ones that are just going to treat with whatever they have, wherever they want. And because there's no real board or any type of true ramification, should there be an issue.

(Dr. Galandiuk) Well, I was actually suggesting patients keep the data. That it's a patient.

(Dr. Shridharani) Oh, I see. Sure. Right. Fair, understood. So that could be a possibility, but again, as we had even talked with some of our colleagues from breast augmentation, we prefer to perform a breast augmentation on Monday. By Friday, the patient's asking me were we above or below the muscle? They don't recall even in that lens a week later, what was the actual plane of insertion or anything. They're just excited about the fact that they have their procedure. So I think the likelihood of even a patient complying with that's probably

(Dr. Matarasso) That's been tried,, as Sachin knows with breast implants, they got a credit card size piece to go on their wallet that said that they had whichever the manufacturer was and the size. And I can tell you the smartest and the most successful people in the world most of the time have no clue about that. At least

now we have a registry for breast implants. If you think that Mrs. Jones is going to keep track of how many times she's had an injection of an HA someplace in her body, a few miles from me as a bridge, and I can share it with you because can't rely on the patient to do this. I'm sorry, I have to cut to the chase and the FDA's going to tell me they can't do it. It's the manufacturer who they sell to and so on. As Sachin said, the societies were already regulating all the doctors on this call. We can't regulate the patients. We can't regulate social media. I don't know if you can do anything with the manufacturers. I apologize for interrupting.

(Dr. Harris) Dr. Alam.

Thank you, Dr. Harris. Murad Alam, I'd like to comment on the last two questions. I'd like to comment on previously and under panel question number two. One FDA asked, does the panel recommend this data be provided in the pre-market study before approval to inform the patient? And secondly, does the panel have recommendations on assessment of long-term adverse events or the duration of follow-up of the patient? So to answer the second question first, at least in my opinion, if one of the risks we are trying to track is whether or not these materials could increase the incidences of malignancy over the long term, then at least some sub cohort of the patients receiving this would need to be tracked for a long period of time, 10 years or longer. That obviously could not be done. Well, not obviously,

but I suspect that would be impractical in a pre-market study since that would delay approval for a very, very long time. But I think that would be feasible in a post-market study for at least a reasonable subset. And it would have to be a relatively large number of patients. It couldn't be a very small number because as we know, the denominator is important and if we had a very small number being followed for a very long time, we could miss a small effect in terms of elevated malignancy risk. Regarding the first question, does the panel recommend this data be provided in the pre-market study? I think all of this data, except for what I just previously mentioned, probably could be provided in a pre-market study and therefore could inform patient behavior. But the long-term risks of malignancy, if any, could really only be tracked in a post-market study. Thank you.

(Dr. Harris) Thank you. Dr. Zuley.

Thank you. Rita Zuley. So I think that the comments that at least I was making and I think we had been discussing is the requirements of a pre-market study. Certainly once the product is approved and available for general use, the sorts of people or skill sets that are going to be using them is going to be outside of scope of FDA. Because FDA is here today trying to understand how to create a pathway for vendors to get approval for their device. In that scope, the vendors are going to select people that are going to participate in their PMA data collection. And so as

part of that process, that was where my comments were founded, is a map of where the injections were done, what was the agent used, what was the volume used, what is the repetition of that use, what does the baseline imaging demonstrate. And then perhaps to be reasonable if clinical symptoms arise, there is maybe an ultrasound or some sort of imaging performed to document what that looks like so that we have some data around initial appearance. And then perhaps for those people who are of screening age, we collect at least one year follow-up imaging or the report thereof to document what was visible on imaging. Outside of that, once approval is gained, then I agree completely with Dr. Alam's thought that there should be long-term monitoring for increased cancer risk. Thank you.

(Dr. Harris) So I just want to make sure we give the as much feedback to the agency as possible. So this question is obviously asking about the proposed mitigation strategies that they've listed in question two and whether one, we as a panel agree with these strategies and or do we have suggestions for others? So we've suggested some other things, but I want to make sure we go through the ones that they've listed. So when you look at the subpart A, this issue of, we've been talking about collecting baseline data and it seems like everyone agrees that that's a good idea, post-approval imaging we've talked about and this idea of including radiographic imaging of the implanted device in labeling. We've had a little

discussion about that. I'd like to hear anybody has any other comments because the comments I heard earlier suggested that that would be difficult and impractical or at least not a feasible source of information for people to use. Any other thoughts about this radiographic imaging and implanting in the labeling? So, our panel is somewhat agnostic when it comes to this particular suggestion. Dr. Hunt, did you raise your hand there?

(Dr. Hunt) Well, I was just going to say, so you're wanting to put, or you're clarifying if something should be in the labeling about imaging before or after, or…?

(Dr. Harris) No, this is actually, I read the question as saying the actual inclusion of radiographic images themselves about what these implanted device look like if they're seen by x-ray, by MRI, by CT, by ultrasound, and putting that actually in the labeling. Now, maybe I'm misinterpreting the question, but that's my interpretation of the suggested mitigating strategy.

Yeah, I think that would be challenging to do because you would have to specify the timeframe and it might be quite a bit different depending on volume of injection and other factors. So I'm not sure that that's really feasible.

Dr. Chang, did you have a clarifying comment for us?

Yeah, so I just wanted to clarify that we do have precedent for providing some example images for some of our aesthetic products for one of the dermal fillers for the hand. I believe there are some example images that are provided in the labeling, and we also have some images. Again, they are examples as there could be many variables, but there is also one for a breast implant as well where example images are provided in the labeling.

(Dr. Harris) But are those images being provided to show you the way it should look or the way it shouldn't look? Or what are they actually showing? I mean, what's the purpose of them being there?

Well, I believe the purpose is to provide an example of how the device may look in the images themselves.

So then that hearkens back to the other comments that were just being made that there may be such variability in terms of what's being injected, how much is being injected, that it may be hard to have an image that will inform all of those possibilities. But Dr. Hunt?

Yeah, I guess we could get the information from our breast imaging specialist, but I think it's much easier to show like a mammogram or an MRI to see what a breast implant looks like. But in terms of the area, this triangle that we're talking about, I'm not sure that a standard, well, certainly as someone mentioned before, a

standard mammography doesn't usually include that area very well. And then also, so would you try to do an x-ray and then you would have to do, it wouldn't be sort of a standard PA and lateral chest x-ray and or a CT scan is going to give completely different. That part of the chest I just think is going to be difficult to provide sort of standard imaging, whereas with a hand, you could see how you might be able to do standard imaging of the hand to demonstrate that.

(Dr. Harris) Any of the comments on that point. So then on the sub part B of this question, ways to mitigate potential positive clinical findings, the issue of providing device cards to patients and including them in patient records. I think I'd heard some skepticism about the feasibility of that earlier, but any other comments about providing device cards to patients and their medical records?

(Dr. Matarasso) It doesn't hurt if that's all you have.

(Dr. Harris) And are we thinking these device cards would lift all the potential ways in which the injection could result in a false positive clinical finding? Not a false positive, but a potentially confusing clinical finding. So we'll include nodules, lymphadenopathy, erythema, lymphatic obstruction, edema. Is that what we're thinking?

(Dr. Matarasso) That's a checklist versus a card. The card that we used for the rest plants was a credit card that said the manufacturer and the size, the checklist that we do now is like a six or seven page thing that lists all the things you mentioned. So if you wanted to do something similar or both,

(Dr. Harris) So the device card would be simply to inform the patient what has been done and what's in them, not necessarily to listing particular.

(Dr. Matarasso) It would be you'd need 10 device cards,

Right? Dr. Galandiuk

(Dr. Galandiuk) I think you could easily do the product just so you'd know what type of artifact would show up on the x-ray,

But

Then you could also have a QR code on it that could then link you to further information like the different side effects and more information.

Okay. Dr. Ballman?

Yes. This is Karla Ballman, and I just want to weigh in. Even though I realized that many, many, many patients probably don't use it, I still think it would be a good idea to do for those that do use it, it would be helpful.

(Dr. Matarasso) Doesn't hurt

Dr. Grimm.

I'm just going to push back a little bit on that because I think it's adding on a regulatory, but it's adding something that's actually not really going to help at all. If I see something on imaging and someone gave a card to the technologist that said I had an injection, that's not really going to change how I interpret that imaging. It's not necessarily going to change the provider in a breast clinic who feels a lump that can't tell with their fingers, whether it's an injection granuloma versus a cancer versus a sebaceous cyst or something. I feel like we might be adding administrative, regulatory, something for the patient to hang onto that's actually not going to provide any real benefit. And I appreciate the argument. It can't hurt, but just adding more stuff for people to do and hold on, is in some ways a form of hurt. Although I recognize that that's a bit of an exaggeration in the word. I'd be curious what the other radiologists feel about this though.

Dr. Minkis, you have your hand up?

Yeah, I kind of agree with Dr. This is Kira Minkis. Just the other day, I had a patient who had a nodule on her lip and was a physician and reported a remote history eight years ago of having filler in her lip, and we went down the entire differential diagnosis. Ultimately, I still had to do the biopsy and it did end up being resolved filler from eight years ago. So I'm not sure, and this was a physician

who knew exactly what she had and when she had it, it really did not help me clinically in making my assessments and I still had to proceed with biopsying the area. I also think that this is a procedure that people might get from various physicians or providers, some that will hand them the card, some that won't hand them the card. If somebody is getting this annually, are they going to keep track of 15 different cards and how much information will be put on there? So I'm a little skeptical about the utility of this for the reasons that Dr. Grimm said and just practically speaking.

Dr. Shuffett.

I'm skeptical as I said before, but the only reason I think it could be useful that if somewhere down the line the person did develop a lump and knew that they got injected in that area but couldn't remember what was injected into that area, if they had a card, they would have a record of it and say this was what was injected into me. And then correlate that with the pathology. If the cancer showed up, for example, and it might be regular breast cancer may have nothing to do with it, but at least you have the history somewhere. But in terms of the utility for us in imaging, we would never see these cards. It wouldn't change our management.

Thank you. Dr. Zuley.

Thank you. I agree. Doubtful we'll see the card except for the exceptional organized patient and I don't think that it would change what we do. Having said that, we have to do radiology pathology correlation on everything that comes back and the pathologist needs to understand what material they may see under the microscope. And so if there's an opportunity to have that information for correlation, I don't think that's going to hurt. Thank you.

Okay. And Dr. Minkis,

I just wanted to comment on that last point about the pathologist. I don't know if there are any pathologists on the call right now, but from a dermatopathology standpoint, these fillers or calcium hydroxyapatite and PLLA, they all look different. And the nodules that they present with, whether it's a granulomatous reaction or due to biofilm or infection or something like that, or the filler itself, they all look very different histologically. So I'm not sure the card would be necessary or really play a role in distinguishing them from a dermatohistologic standpoint.

Thank you. And I think we have made comments about and seemingly thinking that the idea of a post-approval long-term study would be valuable and would provide would be really the only feasible way to provide some of the information about long-term effects of these injections. And then just to clarify, so I think we

are thinking as a committee that a study that would look at the timing, the effect of the injection and timing of imaging thereafter would be of value as part of the pre-market evaluation. So patients could be given a specific recommendation to wait six months, three months, 12 months before they get an MRIs, for example, the breast after they've had an injection. And any comments or clarifications about that? Should your hand is up or just not down from last time? Dr. Shuffett? your had your hand up.

I'm sorry. I noticed to put it down.

Oh, perfect. Okay, no problem.

Sorry.

And then lastly, any thoughts about a post-approval study to evaluate the effects on lactation and breast lymphatic function? There've been some thoughts about excluding those patients altogether rather than studying them. Dr. Grimm?

Well, there might be value in doing that study. I think it would be extremely hard to do both in terms of recruiting enough patients. The majority of the, well, most of the discussions have been about the very superficial nature of these injections. So, you'd need a large sample size for patients that actually got injected deeper. The majority of breast tissue is in the lateral and inferior portion of breast rather than

the upper inner. I think feasibly it would be very challenging to do that study and adequately power it to find a meaningful difference or conclusion.

Thank you. Dr. Zuley.

I thank you. I agree with Dr. Grimm. And the other point I wanted to make is that the majority of the people receiving these injections are going to be postmenopausal or very late premenopausal and highly unlikely to be lactating. Having said that, in the PMA process, if a patient becomes pregnant within X months of injection, I think that it may be useful for FDA to require the doctor to collect data and report back the outcomes of any patient who happens to be pregnant within six months or something like that. Thank you.

(Dr. Harris) And just to point for point of clarification, what is the theoretical concern that we would have about an injection that occurred in a woman who was lactating? Are we thinking that this material would end up in breast milk and be in the baby and affect their GI tract or something? I'm just curious. Concern.

(Dr. Zuley) That's actually a new concern that I hadn't even thought of and a very good one. I think people had been discussing more obstruction of ducts and mastitis, but I think that you raise a brand new topic. Thank you,

Dr. Grimm.

Yeah, I had assumed the latter that it was an inflammatory reaction, scarring, cicatrization, something that impedes the flow of milk rather than transmission to the baby.

Okay. Alright.

(Dr. Matarasso) So, my suggestion about not in lactating females was actually not for obstruction of the duct. We don't let women take a baby aspirin while they're pregnant. So why in the world would we have put a drug into them? That was really what I was thinking. But having said that, if we do say it shouldn't be done in lactating women and what's the timeframe? In other words, the one that had the injection two months before I got pregnant, then there's nine months of pregnancy and how long a period of time before it's safe to lactate, that's 11 months. Is that enough now? So, my thought was not obstruction of the duct, it's just that you don't give anything to lactating women. So just something to think about if that's the path you go down on.

Hey, Dr. Minkis

Just wanted to echo the points that were made earlier. I think this is going to be really a minority of patients. I think most of the people seeking rejuvenation of the chest wall are older and probably less likely to be pregnant and or lactating. But I think that collecting that data, if that's an option, would be helpful going forward. I

think it's going to be extremely difficult to appropriately have a large scale controlled study on this, but I also think it's going to be a minority of patients where this is going to be a concern.

Thank you. So, Ms. Vuniqi, do you feel like you have a sense of the panel's thoughts on question two?

I have a couple of follow-up questions if I may. There's been a lot of discussion around potentially the age of population that may be receiving derma filler injection in the Décolletage area. So I'd be curious to hear from the panel if you have any recommendations pertaining to potentially the age that these devices should be restricted. I've heard a lot about potentially older or 40 and up mention, but I'm curious of other potential age groups that should be considered or not and I'd like some clarification around that there. The second point, there's been a lot of discussions around who may be performing or injecting these derma fillers and I'm curious to hear from the panel if you have any recommendations around type of training that should be provided for those that may be performing these types of injections.

Dr. Alam?

Thank you, Dr. Harris. Murad Alam. Regarding the first question about age group, I think this is an area where one should be cautious because it's hard to have a specific boundary since based on people's ethnicity and skin type, they age differentially. So I think if you had a fairly, if you said, well, everyone above hypothetically above 40 can get this, you might be discriminating, might be too strong a word, but you might be adversely impacting patients with skin type one for instance, who might be very bothered about this in their twenties or thirties, but now wouldn't be eligible to get this treatment. So, I think it should probably be just in adults and then that way you would fail to exclude those people who really wanted the treatment but just couldn't because of an arbitrary time point. The second issue about training, I think training is always a great idea based on how this is injected and how superficially it's injected. I'm not sure there would need to be different types of training than there are for other injectable products. And I certainly agree with previous speakers that changing scope of practice is really not within the purview of FDA, of course. And I don't even think that's really necessary or feasible, but I think training is really good and maybe based on the discussions we are having here that could help guide the types of training that would be best. But I don't think special regulatory structures beyond that are necessary. Thank you.

Ballman?

Yes, Karla Ballman here. I don't see any reason to restrict age, so I agree with Dr. Alam. If there, I mean to me my more concern would be sort of the issue of missing or misdiagnosing either positive or negative for breast cancer and that happens in older women. So, I think unless there's data to drive why an age restriction should be there, I would not think there should be one and I'm not going to comment on the second issue.

Thank you. Dr. Matarasso.

So to follow up on this and to be overly practical, despite the Fitzpatrick type and for those non skin doctors on the phone that's named after a dermatologist, it's one through five. Five are albinos and five are the darkest skin people. So as we all know, the very dark skin, Mediterranean, olive, whatever, skin ages better or ages differently, not better. And a very light-skinned person is more in danger. Practically speaking, it's going to be uncommon for this area to be treated under the age of 40. I'm not making a recommendation, I'm just telling you it's going to be rare to see somebody under 40 in terms of the age, and I don't have a necessary opinion on this. I'm just going to tell you and compare it to breast implants. Again, you can't have silicone breast implants if you're under 22. If I'm not mistaken, it's 21 or 22.

So are we doing the same thing to the 17-year-old person with hypomastia and saying, well, you have to wait five years. So I just throw it out for consideration In terms of regulating training, this goes back to that, and this isn't scope of practice because the scope of practice we handle ourselves. It's non medical people, the people that are doing it within medical specialty, so to speak. The dermatologist that has a nurse doing it, they're getting trained. The problem is regulating training on the other 80% of people that are doing this that don't fall into that. So those are just some thoughts, not recommendations.

Dr. Grimm,

I just want to clarify that the age 40 that was thrown out was in reference to when breast cancer screening starts and not in reference to when people thought this should be or should not be allowed. So it was a tangent to when women are already getting screening mammograms, so would not use it.

(Dr. Matarasso) No, I appreciated that, but I'm going to tell you, it's going to be very rare to see someone at age 32 with enough sun damage to want to do this. So 40, it just happens to coincide. I knew what you were saying.

And just to clarify, so our thinking would be if you encountered the person who had collected enough sun damage at age 34 to want one of these injections, would

our recommendation be that they get a mammogram or an MRI before they get their injection so they have a baseline?

(Dr. Grimm) I think that's still the recommendation. Years ago we used to recommend that women get a baseline years before they start regular screening. So that's the thought process, recognizing that it's going to be uncommon

(Dr. Matarasso) For whatever it's worth. We do the same thing with a breast reduction. It's not necessarily recommended, but I do it in my patient population, the 28 year old's having a reduction, I tell them get a baseline and then you don't have to do anything until you're 40. I also do it breast implants, although it is not mandated. But yeah, I think that if we're going to have a baseline, then it should be what was just suggested.

Dr. Zuley.

Thank you. So if we're going to allow this in 22 and up, I have some concern about recommending a mammogram on a young person who has radio sensitive tissue and perhaps no elevated risk to make sure there's nothing in the area that may or may not even be included on a mammogram. The Society of Plastic Surgery, and please correct me if I'm wrong, my plastic surgeon colleagues, I believe no longer recommend typical baseline screening mammography prior to breast reduction or breast augmentation.

(Dr. Matarasso) Yes,

You're right.

(Dr. Zuley) And so they've stepped away from that. And so I have some hesitancy about adding that boundary here. Thank you. I was just suggesting in the event it was already present during the PMA process specifically with the intent for FDA to collect data on the incidents of complications,

Dr. Matarasso) I apologize. Again, they do recommend that if you have a silicone implant that every two years you use a mammogram or some high intensity focal ultrasound that is recommended

Dr. Zuley) Ultrasound or mr. Yes, every three to five years.

(Dr. Matarasso) I thought it was every two, but I will defer to you

Dr. Hunt.

But apologies, but not prior to.

No, no,

Not as a baseline. Okay. Thank you. Correct. Dr. Hunt?

Yes, thank you. I would agree that doing mammography, especially requiring a mammogram in a very young patient is going to be problematic from the fact that usually the breast tissue is very dense and they might not qualify for screening

mammogram in terms of insurance, things of that nature. So, I do think that something should be included about speaking with your physician with respect to screening breast cancer screening recommendations based on your age and because some of these very young individuals might qualify for high risk screening with MRI and other things. So, consult with your physician before you start this. I mean, we say that for so many things because the patient may not be aware of their risk, may never have had risk assessment, but just to tell 'em to get a mammogram I think would be problematic. Thank you.

Okay, thank you. So, Ms. Vuniqi, are we okay with question two?

Yes. Thank you Dr. Harris and the.

So let's move along to question three. If we can project that for everyone's memory. Take just a second to read through this again. Dr. Alam.

Thank you, Dr. Harris. Murad Alam. Regarding question three, I think the question here is whether or not Hyaluronidase other reversal strategies should be approved. We do have experience with hyaluronidase. We know it works, albeit it's an off-label use. Many dermatologists and plastic surgeons routinely keep this in their practice. And while I can't say I've ever used it at the decolletage, we frequently use it on the face when patients just don't like how something might look and it seems to work just fine. The question about whether or not this would

be important to approve to manage adverse events though is a different one. In general, when we use hyaluronidase, it's to modify the aesthetic appearance of the filler and then in rare instances, if there is concern about intravascular injection to try to mitigate the outcomes of that, whether it's local necrosis or potential vision impairment. So those are the reasons we use hyaluronidase at other anatomic sites.

So from that standpoint, I guess the question is if FDA wants hyaluronidase or wants to consider moving this towards approval, what are they expecting to get out of it? If the issue is you had an inflammatory reaction and that was causing some adverse events, then it's possible that the use of hyaluronidase could mitigate that. However, if the problem is that radiographic findings are being confusing because of the injection of the filler, I'm not sure the hyaluronidase would do anything for that because it's usually injected locally and locally. And if there was some diffuse effect that was confusing to a radiologist, we would probably just make it a different confusing effect after the hyaluronidase. So might be useful for inflammatory reactions, probably wouldn't be useful for radiographic findings. Thank you.

Ms. Vuniqi?

Yes. I just want to clarify the question here. We're not intending to really ask the panel whether hyaluronidase or other removal options should be approved. The

intent of this question is related to how the removal methods should be considered as part of a benefit risk profile for dermal fillers in use in the décolletage area.

(Dr. Alam) Can you clarify that? What do you mean by, I mean if it's not for adverse events? What do you mean by benefit risk profile?

(Dr. Ballman) So, the benefit risk, my understanding is the benefit risk profile of the filler, understanding that there is no approved method for removal.

(Dr. Vuniqi) That's correct,

Dr. Grimm.

Yeah, I'm still confused about this question. I guess the point I was going to make was to say even if you had a magical removal option that would completely remove the filler on imaging, we would still see a lot of the secondary effects from inflammation, fat necrosis.

(Dr. Harris) My interpretation is that if you're undergoing some treatment and there's no way to easily reverse it. So, if you started having a bad inflammatory reaction, you're not going to be able to curtail that without a way to remove this. And so, does that make us think as a panel that does that impact our assessment of the risk of this intervention or this treatment? Because we don't have an easy way to reverse it if there's a problem with it, not so much related to what it looks like on an x-ray or imaging study.

Gotcha. Then I see my time.

Dr. Ballman?

Yeah. Thank you. Karla Ballman. Yeah, I just wanted to say I think patients need to be informed, and I would say even on the label that at current time there is no approved method of removal.

Dr. Sandler?

Yeah, it looks as if the question is related to specific concerns about fillers in the Décolletage area. And I'm not an expert in this area, but it does seem as if the issues would be no different or not substantially different in the Décolletage area versus facial injections. And so I don't think this particular panel today raises new questions about how to handle the removal options.

Dr. Minkis?

Hi. Thank you, Dr. Harris. Kira Minkis. Yes, I completely agree with Dr. Sandler that I don't see how this is different than injecting in the facial region where risk of necrosis and even retinal artery occlusion and other risks might be more substantial. So, I'm curious whether that labeling specifically states that because I think it's the same issues and if anything, lower risk given higher dilution and more superficial injections in the Décolletage.

Thank you.Dr. Galandiuk.

I think this comes more to the patient card and that would be given to the, that this should be included there. And I think it's one of the things that I think it should also be recommended somehow in the labeling that individuals who are administering this should have these agents, even though they're not approved available at that facility in case there would be some reason to remove them.

(Dr. Harris) I think it's going to be difficult for the FDA to be recommending that people have something available for use that they have not approved. Okay. I think there's a problem with that, but understood.

Dr. Alam.

Thank you, Dr. Harris. Since I may be misunderstood, Murad Alam, this question before, I just wanted to indicate that I do agree with Dr. Minkis and Dr. Sandler because I think the only distinction between the face injection site for these fillers and the décolletage injection site would be the risks pertaining to injection into the breast and then potential risk of malignancy. And as we've already discussed, the hyaluronidase would not be helpful in mitigating those. And as such, there doesn't seem to be any differential reason to approve hyaluronic acid based products for injection versus non hyaluronic acid-based products because the concerns we have would not be mitigated by hyaluronidase either way. So the current reversal

strategies wouldn't impact which fillers could be safely used here as versus not. Thank you.

And can our panel think of ways perhaps other than putting it on the label, that the available removal options should be made, that information made available to patients, even though these aren't approved by the FDA?

I think as you said earlier. Murad Alam. Dr. Harris, I think that's very challenging to communicate to patients that they should be apprised of non FDA approved removal strategies.

Maybe Ms. Vuniqi could comment, is our assessment of that difficulty accurate or is that something that you think the FDA could do?

We definitely like to hear from a panel of what your recommendations may be. So we can consider internally of our abilities of what can be included and how that language might look like.

Dr. Minkis.

Thank you. Kira Minkis. I just wanted to mention that this goes back to what we had discussed earlier about as physicians, we always have a discussion with patients during the informed consent process about what the procedure we're going to do entails and risks and benefits. And in that discussion, there's usually also a discussion of potential ways to mitigate risk or to treat complications including off-

label use of hyaluronidase and or other ways to treat potential complications. Obviously this is very difficult for the FDA to regulate on a larger scale, but that's certainly something that we as physicians discuss with patients when doing these procedures.

Thank you. Dr. Galandiuk.

Can you state, state in either in the card or that's given to patients or whatever, that there are no FDA approved methods to reverse this, but that these other agents have been used for this and mentioned hyaluronidase and forgot the other ones, sodium, whatever it was that was used for the other product?

Well, that would be your recommendation. I'm assuming. Ms. McCall, you're on your mute.

I'm going to piggyback on what Dr. Galandiuk just said and saying that there are options, but they are not FDA approved. I would not use the term off-label. In my experience as a patient advocate, that tends to panic a patient and they go down the wrong pathway. And that is not something that a clinician needs. And I really believe that the discussion between patient and clinician is the most important part.

Thank you. So Ms. Vuniqi, how do you feel about your assessment of the panel's feelings on question three?

Thank you for your feedback. I have no further questions. Thanks Dr. Harris.

So we'll move to our final question. Question four, if we can project that for the panel please. Okay. So Dr. Galandiuk, do you still have your hand up from before or do you have a new raise here? Okay. Thank you. Dr. Alam.

Thank you Dr. Harris, Murad Alam, regarding the key risks that should be recommended for incorporating into a patient preference study. I think based on our panel discussions, the most important risk appears to be that of complication of screening for breast cancer due to indeterminate radiographic findings, either with traditional or the more modern techniques we were told about. So, I would suggest that's probably the risk that we should really focus on. We'd also spoke a little bit about pregnant and breastfeeding women, but that seems somewhat less important given that that's not a common patient population. And the risks there are quite theoretical and in general, we don't do many things in pregnancy or breastfeeding, so there's no differential issue here perhaps. And then the final risk of long-term risk of having a malignancy secondary to some changes, inflammatory or otherwise induced by the filler, I think is also a risk.

But again, that's a theoretical risk that would probably be evaluated in a post-marketing study. Hopefully that wouldn't exist, but it'd be premature to alarm patients about something that we have no reason to believe is actually likely to happen. So, I think it's the screening issue that we would have to assess. And I

think as someone who does do some qualitative research, I think in this patient preference, I know FD is very expert on this, I think one thing to really think about is how this study is presented to patients. And I'll give you an example. Since the findings about vascular occlusion at the glabella area possibly and other areas of the face causing risk of vision impairment, in the last five years, I've told all my patients, if you want to inject here, that could cause permanent blindness in one of your eyes. I think it must have told a thousand patients this, and not one patient has wanted to do that least in my practice. So, what I'm saying is if you make this sound scary enough, all the patients are going to say absolutely not. I would never ever do that. So, I think it has to be nuanced in a way so that not just the risk, but the likelihood of the risk, the likely problems associated with the risk are conveyed in a fair and balanced way. Thank you.

Thank you. Other comments, Dr. Shuffett

Another thing that should be disclosed to patients is the potential increase in cost to them. If they do develop complications or feel areas of concern or their physician feels a lump, they may have to undergo diagnostic studies, which will cost possible biopsies, which could be pain and suffering and anxiety, which had they not had this done may not happen in the probably worst scenario. If there is evidence that it does go into the breast tissue, just for example, like with silicone, we can do breast

MRIs to see around the silicone to make diagnosis. But breast MRIs are very expensive and not covered by a lot of insurance, just so they know that there's the potential of increased costs and anxiety.

Thank you. Other comments? I think we'd have to also mention the possibility of lymphadenopathy, which is just another mass that might then prompt an evaluation and workup. Dr. Zuley.

Thank you. Rita Zuley. I also think that we should include a comment about loss of bone density if the drug is injected close to the periosteum.

Thank you. Dr. Minkis.

I think that the most important point is what you just mentioned about injecting it on the periosteum because I believe all of the cases have been in facial injections on the jaw and temple and forehead that were on the periosteum, whereas here it's a much more superficial injection, so it really shouldn't hopefully lead to any bone resorption. So, I think that's important to distinguish.

Thank you. Other comments? We can take down the question please. Hay. So, Ms. Vuniqi, how do you feel? You have a sense of the committee's opinions regarding question four?

Appreciate the feedback that has been provided. If there's other suggestions or comments for consideration, we'd like to hear it, but I don't have any additional follow up questions.

Thank you. Okay. So at this time, I would like to ask our representatives, Ms. Rachel Brummert, our consumer representative, Ms. Lynn Pawelski, our industry representative and our two patient representatives, Ms. McCall and Ms. Chauhan, if they have any additional comments for the panel and for our meeting.

No, I do not.

Okay. Ms. McCall? No. Thank you, Ms. Pawelski.

I just want to thank this group where I might've had some comments. You all brought the conversation around, and so this is one of the best panels I've ever been on. I served on this panel once before and you all, whenever there was something I thought even to ask or interject, you brought the conversation around. So, I really appreciate this group of experts that have been assembled here. Thank you.

Thank you. I don't know if Ms. McCall you on, I'm sorry, you already talked to us. Ms. Chauhan, are you with us? I don't see her on the call.

She is not

Okay. And Ms. Brummert doesn't seem like she's on the call. Okay. Well, today, but at this time, the panel will hear summations and comments or clarifications

from the FDA prior to adjourning. Is that going to come from you, Ms. Vuniqi or from Dr. Chang?

Hi, this is Cynthia Chang. Today we've heard a variety of different perspectives and thoughtful questions about the question of, or the topic of dermal filler injection into the décolletage. We've also heard about a variety of different risks that should be considered by the FDA as well as by practitioners and patients. And we really appreciate all of the thoughtful comments and feedback, again, from a variety of perspectives, including the impact on breast cancer screening, the impact to the diagnosis and treatment from the patient perspective, the impact of different materials on the different risks that have been raised, as well as some of the decision making process that a patient might go through, and the information that may be helpful to communicate to the patients by the providers. We've also heard about the importance of training and the role of the practice of medicine and the informed decision-making process and patient preference as part of ultimately the patient's decision in consultation with the healthcare provider in choosing to go forward with an aesthetic treatment such as dermal filler injection into the décolletage. So, FDA really appreciates the thoughtful discussion questions and recommendations that have been provided today, and we will certainly take all of these comments into consideration as we move forward. Thank you.

Thank you. So, I would like to personally thank the panel, the FDA, the invited speakers, and all of the open public hearing speakers for their contributions to today's panel meeting. As such, this meeting of the general and plastic surgery devices panel is now adjourned.