

UNITED STATES OF AMERICA  
DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION

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CENTER FOR DEVICES AND RADIOLOGICAL HEALTH  
MEDICAL DEVICES ADVISORY COMMITTEE

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OBSTETRICS AND GYNECOLOGY DEVICES PANEL

+ + +

July 10, 2014  
8:00 a.m.

Food and Drug Administration  
White Oak Campus, Building 31  
The Great Room, Room 1503  
Silver Spring, Maryland

PANEL MEMBERS:

MICHAEL P. DIAMOND, M.D.	Temporary Non-Voting Chair
CHERYL IGLESIA, M.D., FACOG	Non-Voting Member
LISA E. MOORE, M.D., M.S.	Non-Voting Member
PAULA J. HILLARD, M.D.	Non-Voting Member
CRAIG D. SHRIVER, M.D., FACS, COL, MC	Temporary Non-Voting Member
KEITH ISAACSON, M.D.	Temporary Non-Voting Member
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CAROL BROWN, M.D.	Temporary Non-Voting Member
DANIEL SIMON, M.D.	Temporary Non-Voting Member
ROBERT F. MATTREY, M.D.	Temporary Non-Voting Member
MICHAEL R. NEUMAN, Ph.D., M.D.	Temporary Non-Voting Member
COLLEEN M. GALLAGHER, Ph.D., M.A.	Temporary Non-Voting Member
MARK A. TALAMINI, M.D.	Temporary Non-Voting Member
RUSSELL R. SNYDER, M.D.	Temporary Non-Voting Member
NICOLAS WENTZENSEN, M.D., Ph.D., M.S.	Temporary Non-Voting Member
KRIS MATTIVI, M.S., PT	Consumer Representative
JAMES GARDNER, M.D., M.B.A.	Industry Representative
DIANE ARONSON	Patient Representative
LCDR S.J. ANDERSON, M.P.H., OCN	Designated Federal Officer

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President/Chairman of the Board  
Sarcoma Foundation of America (SFA)

JUSTINE ATKINSON  
Executive Director  
Fibroid Relief

FRANK BONADIO  
CEO  
Advanced Surgical Concepts

K. ANTHONY SHIBLEY, M.D.  
OBGYN Specialists

DR. JOANN TRAINER  
Private Citizen

JOANNE JACOBSON, M.D.  
Private Citizen

MARGARET JACOBSON, M.D.  
Private Citizen

HOWARD SCHWARTZ  
Private Citizen

ELIZABETH PRITTS, M.D.  
Wisconsin Fertility Institute

SCOTT ELDREDGE, J.D.  
Burg, Simpson, Eldredge, Hersh & Jardine, P.C.

AMANDA LINDSEY  
Private Citizen

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M E E T I N G

(8:00 a.m.)

DR. DIAMOND: We're going to go ahead and call the meeting to order. This is a meeting of the Obstetrics and Gynecology Devices Panel of the Medical Devices Advisory Committee, and we'd like to call this to order.

I am Michael Diamond, and I'm the Acting Chair of the Panel. I am a reproductive endocrinologist by training, and I am currently Chair of Obstetrics and Gynecology at Georgia Regents University in Augusta, Georgia, where I'm also the Associate Dean for Research and the Vice President for Clinical and Translational Sciences.

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

For today's agenda, the Panel will discuss issues relevant to the safety of laparoscopic power morcellator devices, as it pertains to their potential to disseminate and upstage a confined but undetected or occult uterine malignancy during laparoscopic hysterectomy or myomectomy.

Before we begin, I would like to ask each of our distinguished Panel members and FDA staff seated at the table to introduce themselves. Please state your name, your area of expertise, your position, and your affiliation. And we'll start on my right-hand side, please.

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DR. GARDNER: My name is Jim Gardner. I am the Industry Representative on the Panel. I work with a medical device company called Cook, Incorporated, where I serve as their director of reimbursement and medical science officer.

MS. MATTIVI: Good morning. I'm Kris Mattivi, the Consumer Representative to the Panel. I am a physical therapist and a business analyst for WellPoint in Denver.

MS. ARONSON: Good morning. I'm Diane Aronson. I am a Patient Representative from the CDER program -- Patient Representative program.

DR. SIMON: Good morning. I'm Dr. Daniel Simon. I am an interventional radiologist by background. I am the Medical Director for the Vascular Access Center of West Orange in West Orange, New Jersey.

DR. GALLAGHER: Colleen Gallagher from the University of Texas MD Anderson Cancer Center. I am a clinical ethicist working as the Chief and Executive Director of the Section of Integrated Ethics and an Associate Professor in the Department of Critical Care.

DR. MATTREY: Good morning. Robert Mattrey from UC San Diego, and I am a radiologist.

DR. BROWN: Good morning. Carol Brown. I am a gynecologic oncologist, and I am the Associate Cancer Center Director for Diversity and Outreach at Memorial Sloan Kettering Cancer Center.



DR. HILLARD: Paula Hillard. I am Professor of Obstetrics and Gynecology at Stanford University School of Medicine.

DR. MOORE: Good morning. I'm Lisa Moore. I am a perinatologist at the University of New Mexico in Albuquerque, New Mexico. I am the Chief of the Division of Maternal and Fetal Medicine.

DR. IGLESIA: Good morning. I'm Cheryl Iglesia. I am a pelvic reconstructive surgeon and the Section Director of Female Pelvic Medicine and Reconstructive Surgery at MedStar Washington Hospital Center here in D.C. I am a Professor of Obstetrics and Gynecology and Urology at Georgetown University School of Medicine.

LCDR ANDERSON: Hi, I'm Lieutenant Commander Anderson. I am the Acting DFO for this panel meeting. I represent the Food and Drug Administration and the U.S. Public Health Service.

Thank you.

DR. SNYDER: Good morning. I'm Russell Snyder. I am a general OB/GYN. I'm also a GYN pathologist. I am at the University of Texas Medical Branch in Galveston, where I serve as the Vice Chair and the Director of the Division of Gynecology.

DR. WENTZENSEN: Good morning. I'm Nicolas Wentzensen. I am an M.D./Ph.D. working at the National Cancer Institute, in the Division of Cancer Epidemiology, focusing on female cancers.

DR. SHRIVER: Good morning. My name is Craig Shriver. I am a

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surgical oncologist. I am the Director of the Cancer Center at Walter Reed National Military Medical Center and Professor of Surgery at Uniformed Services University.

DR. ISAACSON: Good morning. Keith Isaacson. I am a reproductive endocrinologist and associate professor at Harvard Medical School.

DR. AFIFI: My name is Abdelmonem Afifi. I'm Professor of Biostatistics at the UCLA Fielding School of Public Health and former dean of that school.

DR. NEUMAN: Good morning. My name is Michael Neuman. I am a Professor of Biomedical Engineering at Michigan Technological University in Houghton, Michigan, in the Upper Peninsula of Michigan. My field of work is sensors and biomedical instrumentation in clinical trials of such.

DR. TALAMINI: Good morning. My name is Mark Talamini. I'm the Chairman of the Department of Surgery at SUNY Stony Brook in New York.

DR. FISHER: Good morning. My name is Ben Fisher. I am a developmental toxicologist. I am the Director of the Division of Reproductive, Gastro-Renal, and Urological Devices in the Center for Devices and Radiological Health.

DR. YUSTEIN: Good morning. My name is Ron Yustein. I am the Deputy Director for the Office of Surveillance and Biometrics in CDRH.

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DR. DIAMOND: Members of the audience, if you have not already done so, please sign the attendance sheets that are located on the registration desk directly outside of the meeting room. And if you've not already done so, also please place your cell phones on a silent mode.

Lieutenant Commander Anderson, the Designated Federal Officer for the Obstetrics and Gynecology Devices Panel, will now make some introductory remarks.

LCDR ANDERSON: Good morning. I will now read the FDA Conflict of Interest disclosure statement.

The Food and Drug Administration is convening today's meeting of the OB/GYN 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 this 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 U.S.C. Section 208 are being provided to participants in today's meeting and to the public.

FDA has determined that members and consultants of the Panel are in compliance with Federal ethics and conflict of interest laws.

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Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special Government employees and regular Federal employees who have potential financial conflicts when it is determined that the Agency's need for a particular individual's expertise 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 U.S.C. Section 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts/grants/CRADAs; teaching/speaking/writing; patents and royalties; and primary employment.

Today's agenda involves the discussion of issues relevant to the safety of laparoscopic power morcellator devices, as it pertains to their potential to disseminate and upstage a confined but undetected occult uterine malignancy during laparoscopic hysterectomy or myomectomy. FDA is convening this Panel to seek expert scientific and clinical opinion on the risks and benefits of these types of devices when used for these procedures, based on available scientific data. The Panel will make recommendations regarding appropriate use, premarket testing, labeling, and other risk mitigations, including the use of containment bags for these devices.

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

James Gardner, M.D., is serving as the Industry Representative, acting on behalf of all related industry, and is employed by Cook, Incorporated.

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

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

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

For the duration of the OB/GYN Devices Panel on July 10th to 11th, 2014, Dr. Robert Mattrey has been appointed to serve as Temporary Non-Voting Member, and Ms. Diane Aronson has been appointed to serve as Temporary Non-Voting Patient Representative. For the record, Dr. Mattrey is a member of the Medical Imaging Drugs Advisory Committee in the Center for Drug Evaluation and Research. Ms. Aronson serves as a consultant in the

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Center for Drug Evaluation. These individuals are special Government employees who have undergone the customary conflict of interest review and have reviewed the materials to be considered at this meeting.

The appointment was authorized by Jill Hartzler Warner, J.D., Associate Commissioner for Special Medical Programs, on July 3rd, 2014.

We would like to remind 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 other participants to advise the Panel of any other financial relationships that they may have with any firm at issue.

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

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

Transcripts of today's meeting will be available from Free State Court Reporting, Incorporated, telephone number (410) 974-0947.

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

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The press contact for today's meeting is Morgan Liscinsky.

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

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

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

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

Dr. Diamond.

DR. DIAMOND: Thank you.

We will now hear opening remarks from the FDA.

Dr. Ron Yustein.

I would like to remind public observers at the meeting that while this meeting is open for public observation, public attendees may not participate except at the specific request of the Panel Chair.

Dr. Yustein, you may now begin your opening remarks.

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DR. YUSTEIN: Thank you. Dr. Diamond, distinguished members of the Obstetrics and Gynecology Devices Advisory Committee, and members of the public here today, good morning. My name is Ron Yustein, and I am the Clinical Deputy Director in the Office of Surveillance and Biometrics in FDA's Center for Devices and Radiological Health.

Over the next two days, we will have an open public discussion on the use of laparoscopic power morcellators in uterine surgeries, with a particular focus on the risk of upstaging and unsuspected uterine sarcoma during the treatment of presumed fibroid disease.

I would like to start by extending a welcome and our gratitude to everyone in attendance at this meeting. I would like to thank the members of the Committee in advance for their participation and the recommendations you will provide, as well as FDA's invited speakers who will be presenting background information to the Panel later this afternoon.

Having an open and transparent discussion of the issue and related data among all major stakeholders is crucial to FDA as we move forward. And as such, I would like to also welcome the members of the public who are in attendance today, including industry, professional societies and organizations, patient advocacy groups, and patients and family members, many of whom will be speaking and presenting to the Panel today or tomorrow.

This slide lists the FDA staff, coming from multiple

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organizations and offices within the Agency, who have been involved in our evaluation of the current issue and who have assisted in the preparation of both the April Safety Communication as well as this week's materials, including the Panel Executive Summary and the questions. Many of these people are here in attendance today and will be available to clarify or answer questions you may have, and several will be making presentations later this afternoon.

Just so that we are all on the same page in terms of the devices we are talking about over the next two days, laparoscopic power morcellators are medical devices that are used during minimally invasive surgery procedures to assist in the removal of specimens larger than the incision or extraction site. They can use electromechanical or radiofrequency energy to fragment tissues into smaller pieces.

I wanted to remind the Panel that our meeting is considered a general issues meeting. We will be talking about the devices as a class and not singling out individual products or manufacturers, other than when citing specific public literature which is pertaining to the general discussion.

In addition, we are focusing on devices which are used during laparoscopic surgeries and will not be speaking to hysteroscopic morcellators, as we do not believe that when used in accordance with their intended use they pose the same risk as we are focusing on today and tomorrow.

As medical devices, laparoscopic power morcellators are

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regulated by FDA's Center for Devices and Radiological Health. They have been regulated as Class II or intermediate-level risk devices and are cleared for marketing via the 510(k) regulatory pathway. Clearance is based on the ability of the manufacturer to demonstrate substantial equivalence to a legally marketed device, commonly referred to as the predicate device. Your Executive Summary includes additional information regarding the type of premarket testing that has generally been performed by manufacturers and reviewed by FDA for laparoscopic power morcellators prior to FDA clearance.

As shown in the table on this slide, the earliest clearance for an electromechanical or power laparoscopic tissue morcellator was in 1991. The first 510(k) clearance for a power laparoscopic morcellator with an indication referencing gynecological procedures was in 1995, and the first with an indication specifically noting hysterectomy was in 2000.

Ms. Veronica Price from our Office of Device Evaluation will provide additional information and details on laparoscopic power morcellators and their review and regulation later this afternoon.

As noted in your Executive Summary, the formal wording of the indications for use for laparoscopic power morcellators differ slightly from manufacturer to manufacturer. However, several general uses have been cleared, including use in laparoscopic general surgery, urology, and gynecological procedures. A given laparoscopic power morcellator may be indicated for more than one of these three. Specific gynecological

procedures which appear in a laparoscopic power morcellator's indications for use statement include myomectomy and hysterectomy.

The table on this slide lists the laparoscopic power morcellator devices which currently have FDA clearance for indications which include gynecological procedures and are legally marketed within the United States. However, I would like to point out that following FDA's Safety Communication in mid-April of this year, Ethicon made the voluntary decision to temporarily suspend global distribution of their products listed.

Although this Panel has been assembled in response to a specific safety concern for power morcellators, it is crucial to evaluate the risks in conjunction with the benefits of the device. Neither can be assessed in isolation.

Laparoscopic power morcellators are essentially surgical tools which are intended to allow a surgeon to successfully complete a procedure laparoscopically, including hysterectomies and myomectomies. As such, when assessing the benefits of laparoscopic power morcellators, we need to consider the benefits of laparoscopic surgery when compared to traditional surgery.

As was presented in your Executive Summary and as you will hear from various speakers over the next two days, including one of our invited speakers, Dr. Sobolewski, as well as Dr. Corrado from our own Office of Device Evaluation, some of the benefits which may be conveyed over an

open abdominal surgery, beyond cosmetic benefits, include decreased postoperative pain, shorter hospital stays, faster recovery times, and fewer wound complications.

Your Executive Summary reviews several different potential risks associated with laparoscopic power morcellators when used in the intraperitoneal space, including damage to local organs and vasculature, dissemination of benign tissue, including fibroids and endometriosis, and disruption of tissue architecture which may make the identification, grading, and/or staging of an unsuspected malignancy difficult.

The major safety risk, however, which is the focus of this Advisory Committee meeting is the uncontained intraperitoneal morcellation of an occult and undiagnosed uterine sarcoma in symptomatic women presenting with presumed fibroids. This may result in a dissemination of malignant tissue within the peritoneal cavity, with a possibility for implantation and growth. This, in turn, may upstage in a malignancy that had previously been confined to the uterus. As presented in your Executive Summary and as will be presented by Dr. Chris Jones later this afternoon, the result may be the need for additional significant interventions as well as poorer long-term outcomes for the patient.

This slide presents a brief FDA timeline for events surrounding this issue, starting with receipt of a voluntary MedWatch report and patient communication in late December of 2013. Prior to that, FDA had not received

any MDRs related to the dissemination of malignancy by laparoscopic power morcellators.

As noted, FDA issued a Safety Communication in April of this year, in which we presented results of our literature analysis, suggesting that approximately 1 in 500 women undergoing surgery for presumed symptomatic fibroids may harbor an occult leiomyosarcoma and which discourage the use of laparoscopic power morcellators in surgeries for presumed fibroids.

Switching gears, I wanted to summarize at a high level the objectives for this two-day meeting. First, as I noted earlier, FDA believes that there is significant merit in bringing all the appropriate stakeholders, including physicians, patients, researchers, and industry, together to have an open and transparent dialogue to address the significant patient risk. This will allow different perspectives to be presented along with the respective scientific data which supports various aspects of this issue. This, in turn, will assist the Panel in providing fact-based recommendations for FDA.

With the help of several invited speakers, we will review current data regarding the epidemiology, detection, diagnosis and evaluation, treatment and outcomes associated with uterine fibroids and uterine sarcomas. This will serve to frame the discussions of the risks and benefits of laparoscopic power morcellators for uterine lesions.

During the course of the meeting, we plan to discuss potential

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strategies which may mitigate the risk at hand, including the level and quality of evidence which supports each potential mitigation strategy and to what degree the risk can be mitigated by its use and implementation either alone or in concert with other measures.

We will be asking the Panel to define specific patient populations or clinical scenarios, if any, where the benefits of use of laparoscopic power morcellators with specific mitigation strategies employed outweigh the risks which have been identified in gynecological surgeries and, vice versa, situations where, regardless of the use or effectiveness of a particular mitigation strategy, the risks outweigh the benefits. We will be asking the Panel to consider this question for several situations, including patients with presumed fibroids, patients with presumed gynecological disease other than fibroids, and patients with suspected or known malignant disease.

We will also be seeking input from the Committee regarding appropriate labeling for the devices, as well as suggestions on potential additional data and testing requirements.

Again, the discussions will assist the FDA in determining appropriate next steps from the Agency's perspective. However, we also hope that the discussion over the next two days will serve as a springboard for further discussions within the medical community, patient community, and device industry, as we all move forward in addressing the issue together.

I wanted to conclude my brief introduction by outlining the agenda for the next two days. You will see that it is quite an ambitious one.

After my presentation, we will hear from a variety of stakeholders who have asked to present their views or data to the Committee. This includes manufacturers of laparoscopic power morcellators, professional medical societies, patient advocacy and research organizations, as well as patients and family members who have been personally impacted by this issue. Subsequently, we will have four presentations from guest speakers who FDA has invited to the meeting.

First, you will hear from Dr. Shannon Laughlin-Tommaso, Assistant Professor in the Department of Obstetrics and Gynecology at Mayo Clinic in Rochester, Minnesota. She will present information related to the epidemiology, evaluation, and non-surgical management of uterine fibroids.

Next, Dr. Craig Sobolewski, Assistant Professor and Chief of the Division of Minimally Invasive Gynecological Surgery at Duke University, will discuss surgical options for the treatment of fibroid disease.

After lunch, Dr. Susan Ascher, Professor of Radiology at Georgetown University, will speak about imaging modalities and their use in the diagnosis and evaluation of uterine lesions.

And, finally, you will hear from Dr. Carmel Cohen, Professor of Obstetrics, Gynecology, and Reproductive Surgery at Mount Sinai Hospital in New York, who will give an overview of uterine sarcomas.

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We are extremely grateful for having these four individuals here to present on behalf of FDA and thank them for their time and expertise. The Panel will have a chance to ask clarification questions of the speakers after their respective presentations. In addition, all of them have graciously agreed to stay at our meeting through most of the two days, and the Panel, at the discretion of the Panel Chair, can ask questions of them at other times.

Following these four presentations, staff from FDA will deliver several short presentations summarizing the information in the Executive Summary, including our analysis upon which our April Safety Communication was based.

Following the FDA presentations, the Panel will be given time to deliberate and discuss the information which had been presented by FDA, our invited speakers, and speakers who had requested time earlier in the day during the open public session. We also hope to get to at least one FDA question for the Panel before we adjourn this evening.

Tomorrow we'll start with an Open Public Hearing, in which you will hear from several more members of the public who have requested the opportunity to provide you with their comments. The remainder of the day will focus largely on FDA's questions to the Panel.

With that, I would like to conclude my talk and once again thank everyone present today for their participation. FDA sincerely appreciates the time, effort, and expertise that those in attendance will be

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providing. We think this is a critical issue to address and look forward to the discussions and recommendations from all participants and attendees, information that FDA will take into account as we continue our evaluation and efforts related to this issue.

With that, I hand the meeting back over to Dr. Diamond and Lieutenant Commander Anderson.

Thank you.

DR. DIAMOND: Thank you, Dr. Yustein.

We will now hear from Ethicon, Incorporated. For the record, Ethicon is one of two manufacturers of laparoscopic power morcellators who responded to *Federal Register* notices call to industry requesting the opportunity to present during the meeting today. The information discussed during this section of the meeting should not be considered a representation of all laparoscopic power morcellator industry manufacturers.

Dr. Piet Hinoul, you may proceed.

DR. HINOUL: Good morning. I am Piet Hinoul. I'm the Vice President of Medical Affairs at Ethicon. I am a European board certified gynecologist and have performed many power morcellation procedures while in clinical practice.

On behalf of Ethicon, I'm grateful for the opportunity to speak at this Panel meeting. Ethicon's first priority is to our patients, and we appreciate the FDA bringing all the stakeholders together today to discuss the

role of power morcellation in minimally invasive hysterectomy and myomectomy.

Ethicon analyzed the data presented in the FDA's Safety Communication as well as the peer-reviewed literature and decided in April of this year to suspend global distribution of its power morcellation devices. The greatest driver in this decision was the higher than previously understood risk of encountering an undiagnosed malignancy, sarcoma in particular, when treating patients with symptomatic fibroids. Even though Ethicon's devices perform as intended and are labeled for this risk, we felt that we were unable to effect an immediate reduction of this risk, other than to suspend global distribution of our devices. We at Ethicon stand by this decision until there is a consensus from the medical community on how to mitigate this risk, and at that time we will reassess.

A large meta-analysis showed that laparoscopic procedures are associated with benefits, such as shorter recovery time, less blood loss, fewer infections, fewer wound complications, when we compare it to abdominal hysterectomies. Minimally invasive procedures thus can offer clear benefits to a majority of patients.

Approximately 50,000 of these procedures per year have been made possible due to the availability of power morcellation, which reduces a large mass to a size where it can be extracted through a minimally invasive access port.

When the use of power morcellation is discouraged in favor of more invasive abdominal procedures, patients may avoid or delay treatment, leading to a delay in diagnosis and also potential upstaging of a malignancy.

The medical community has long known that power morcellation poses a risk of spreading unsuspected malignant tissue beyond the uterus. As such, Ethicon's morcellation device labeling includes cautionary language concerning the potential for dissemination of malignant tissue.

In order to increase our own understanding of the frequency of diagnosis of unsuspected malignancy, our own epidemiologists performed a retrospective analysis on the Truven database.

From these insurance claims of about 70 million people, we identified approximately 340,000 women who underwent a hysterectomy or a myomectomy during the last three years. Of these women, 4% had preoperatively identified diagnosis of malignancy of the uterus. Additionally, almost 1% were coded to have malignancy after surgery. In this database, 2% of the women were coded to have undergone morcellation. And among these patients, the frequency of postoperatively coded uterine malignancy was significantly lower at 0.3%. Conversely, abdominal hysterectomies were associated with a higher frequency of postoperative coding for malignancy at 2%.

Both numbers are suggestive of selective views of specific

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procedures, and this is likely dependent on the preoperative risk factors as they were identified by the treating physicians.

A device-specific registry is unlikely to successfully answer the questions regarding the true incidence rates, let alone the question on how to reduce this risk for a specific population. Assuming an incidence rate of 0.3%, a study focused solely on power morcellation may require enrolling no fewer than 33 patients to identify 100 patients with an unsuspected malignancy. Such a study would only assess patients who were already preselected to undergo power morcellation, which today is 50,000 patients per year in the United States.

The FDA should consider a multi-pronged approach where manufacturers, regulators, and the medical community work collaboratively to mitigate this risk of encountering or upstaging an undiagnosed malignancy during gynecologic procedures. The risk cannot be reduced by merely enforcing greater regulation on morcellation devices. This relatively simple device does what it is intended to do. The issue today is the inability to identify certain malignancies or at-risk populations prior to the morcellation.

First, morcellation device labeling should comprehensively address all the risks of power morcellation, in line with recommendations as set forth by the medical societies.

Second, industry and academia should explore the possibility of new technological solutions, both from a surgical device but also from a

diagnostic perspective.

And, third, healthcare providers should be adequately trained on minimally invasive surgery and should ensure that all patients undergoing this surgery have effective preoperative screening, are appropriately risk stratified, and are truly fully informed of the relative benefit/risk profiles of all available treatment options.

Evaluation of the treatment algorithm must include potential intraoperative mitigation techniques, such as the use of a closed system, that would eliminate or limit tissue dissemination. While closed systems such as tissue containment bags make intuitive sense, these closed systems should be reliable, they should be easy to use, and accommodate tissues of variable sizes and shapes.

In addition, full visualization of the mass to be morcellated, as well as the surrounding vital structures, is essential. Otherwise critical organs could be injured, which would offset any mitigated risk of spreading unsuspected malignancy and this life here safe.

The preoperative diagnostic screening protocol warrants reevaluation by the medical community through focused technological and clinical research. This should allow better characterization of the individual patient's risk. This research must be independent of morcellation because linking the research to a device would inherently introduce an unwanted selection bias.

Hagemann and others suggested one such protocol regarding preoperative workup of patients scheduled for uterine morcellation that included cervical cancer screening and endometrial biopsy and imaging. Systematic implementation of these types of screening guidelines could significantly reduce the individual risk of encountering an unsuspected malignancy.

Current morcellation devices and future closed system devices should continue to be evaluated as Class II devices with special controls. In line with the FDA's mandate to consider the least burdensome approach, Class II offers appropriate tools to provide reasonable assurance of the safety and effectiveness of power morcellation devices even in clinical use.

However, the issue as stated is larger than the power morcellation per se. A data-driven benefit/risk characterization of all fibroid treatment options is warranted. Data may very well already reside in multiple databases, as demonstrated, for example, by our own claims analysis.

In conclusion, industry, regulators, and the medical community should collaborate to use this data, apply technological and diagnostic advances, and assess preoperative screening protocols to answer three questions.

First, how do we identify the low-risk patient populations?

Second, how can we ensure that these low-risk patients can

continue to benefit from minimally invasive surgery with power morcellation?

And, three, how do we respond to the probable increase in number of invasive procedures and their inherent risks?

We at Ethicon stand by our decision to stop distribution of our power morcellation devices until reasonable answers to these questions have been formulated and guidelines are agreed upon by the medical community, at which time we will reassess.

Once again, we appreciate FDA looking into this important topic, pulling together the stakeholders here, and for the opportunity to participate in this discussion.

I thank you very much.

DR. DIAMOND: I would like to thank Ethicon for their presentation.

Do any members of the Panel have any brief clarifying questions?

Dr. Hinoul, if you'll come back, I see one.

DR. TALAMINI: This is Talamini. Thank you for a clear presentation. I have two questions about the data -- clarifying questions.

Did Ethicon use any other methodology to try and confirm or look at any other data to confirm or look at that number? And, number two, how reliable do you consider the claims data analysis that you did, relative to other number stats?

DR. HINOUL: Thank you for the question. Yes. So we looked at the peer-reviewed literature and we looked at the data that was presented by the FDA, and we did the same statistics as we all did and came to the same conclusion.

The Truven database -- and, of course, 10 minutes didn't allow us to go into depth, and we will certainly be happy to share it with you -- has a lot of limitations. It's based on claims. It is only coding. It doesn't mean that the 1% of patients that were coded as having malignancy postoperatively were not possibly suspicious before they had their surgery. Maybe the surgeon was taking an approach of an abdominal hysterectomy because he thought there was a possibility of malignancy.

But I do believe -- and it was only a first analysis in the short period of time we had preparing for this meeting. But I do believe what it points to is that there is a significant number of patients where you finalize your diagnosis postoperatively, and it seems to be in that 0.1% to 1% frame. The limitations are, of course, that there are a lot of issues with coding. It's not very specific. For morcellation, there's no specific coding, so it was only limited to 2% of patients. So there are lots of limitations that we can discuss at length at some point. But I do believe it points to the fact that malignancy postoperatively diagnosed between 0.1% and 1% seems the rate that it points up.

DR. DIAMOND: I saw one other question. Please remember,

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Panel members, also that we'll have the opportunity to ask questions during our deliberations later this afternoon.

DR. WENTZENSEN: Nicolas Wentzensen from NCI.

In your claim data, do you have -- do you see evidence of clear use of morcellation when it should not be used, like if there's a preoperative diagnosis of malignancy and then there is -- I mean, could you derive that, or is that not possible? I'm trying to interpret the 4% preop malignancy.

DR. HINOUL: I do not have that answer right now, but I do believe that we would be able to identify patients where we had a preoperative diagnosis of malignancy that were subsequently morcellated. Yes, we would be able to distill that from the database.

I think there's a lot more data in those databases than I've presented here, which was very brief. And all we wanted to do is to show that there's a lot of information out there, epidemiologic data which is under question that could be utilized to get a stratification of risk.

DR. DIAMOND: Okay, seeing -- oh, I'm sorry. We have one last question at this point.

DR. NEUMAN: Michael Neuman.

You presented data showing that, in fact, you've taken the device off the market. But I'm wondering about the other devices that have already been sold to various institutions. FDA has done some things to inform these institutions of problems. I'm wondering if you, as a

manufacturer, have done anything in that regard as well.

DR. HINOUL: Of course, sir. Thank you for the remark. Yes, we have sent to all our customers a Dear Doctor letter fully informing them of the risks, fully informing them of the FDA documentation, clearly explaining the issue and why we stopped distribution for now.

Thank you.

DR. DIAMOND: Thank you.

We will now proceed with the Open Public Hearing portion of the meeting. Public attendees are given an opportunity to address the Panel, to present data, information, or views relevant to the meeting agenda.

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

LCDR ANDERSON: Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the Open Public Hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the 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, the financial information may include a company's or a group's payment of your

travel, lodging, or other expenses in connection with your attendance at 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 the issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

DR. DIAMOND: For the record, all Panel members have been provided written comments received prior to this meeting.

For today's Open Public hearing, we have received 13 requests to speak. Each scheduled speaker representing a medical professional society and/or a patient advocacy and research organization will be given eight minutes to address the Panel. Each scheduled speaker who is not representing a medical professional society and/or a patient advocacy or research organization will be given five minutes to address the Panel. We ask that you speak clearly to allow the transcriptionist to provide an accurate transcription of the proceedings of this meeting. The Panel appreciates that each speaker remains cognizant of their speaking time.

The first speaker is Hal Lawrence from the American College of Obstetricians and Gynecologists.

DR. LAWRENCE: Good morning. My name is Dr. Hal Lawrence, and I'd like to thank the FDA for giving me the opportunity to speak today on behalf of the American College of Obstetricians and Gynecologists, also known as ACOG.

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As the nation's leading group of physicians providing healthcare for women, ACOG advocates for quality healthcare, maintains the highest standards of clinical practice and continued education of its members, promotes patient education, and increases awareness of changing issues facing women's healthcare.

But I don't speak today just on behalf of obstetricians/gynecologists. I am an OB/GYN. And I have no financial disclosures to report.

In my comments today, I won't repeat the details of ACOG's special report on Power Morcellation and Occult Malignancy in Gynecologic Surgery, which we released in May of this year. We have already provided that report to FDA representatives. And, of course, as you've already seen, the Committee members today will hear an abundance of data from other presentations. Instead, my remarks are intended to add some perspective for the Committee members to consider.

Let me start off by saying that without a doubt, it is tragic for any woman to undergo the experience of having a uterine sarcoma worsen because of the use of a power morcellator. It is essential that we, the gynecologists, the regulators, and the industry, work to minimize the threat of this. I assure you that no gynecologist wants this outcome for his or her patient, and we do not take this lightly.

That is why ACOG released our special report which addresses

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the risk and benefits associated with power morcellation. The report discusses the incidence of undiagnosed uterine sarcoma being spread by a power morcellator and lays out steps that a gynecologist should take to evaluate and mitigate the risk for each individual patient. That report was not the result of new research, but rather of a thorough review of the current literature.

Our work reflects science, and I believe we do ourselves and our patients a disservice if we respond to emerging safety concerns in a way that does not reflect science. That is why I urge the Advisory Committee to focus its deliberations today and tomorrow on the available data, as ACOG did.

Admittedly, the data are limited regarding power morcellation and occult uterine sarcoma. Additionally, there are factors that complicate our attempts to calculate risk, for example, the rarity of uterine sarcomas and the sample size.

Despite these challenges, our assessment of the incidence of occult sarcoma diagnosed following power morcellation is approximately 1 in 500 women. This is not statistically different from the FDA's estimate of 1 in 350. The evidence that is available demonstrates that power morcellation can be a treatment option for certain women, based on each woman's unique needs when considered among the full range of treatment options.

When used during a minimally invasive hysterectomy or

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myomectomy, it can help certain women avoid the inherent risk and potential significant morbidity and mortality associated with a total abdominal hysterectomy.

As physicians, we realize that all procedures have risk. Our job is to recognize that risk and to take steps to mitigate that risk. After all, we clearly state in our report that in certain cases power morcellation should not be used. But as long as gynecologists have patients who might benefit from power morcellation, patients who might be spared the mortality associated with total abdominal hysterectomy, who are at low risk of a uterine sarcoma, who want a less invasive surgery and faster recovery, then power morcellation should remain a treatment option for them to consider with their gynecologist.

Let me reiterate. When a patient is diagnosed post-morcellation with an occult malignancy, when a patient has any postoperative major complication, it's devastating, devastating to everybody: the patient, the family, and the physician. But it is unacceptable that in an effort to avoid one risk, we subject women to another.

Every physician in this room knows that there is not a one-size-fits-all treatment option for patients. Each patient is different from the thousands of patients who came before her, and we must consider each patient's needs in making our treatment decisions. And we must have a variety of treatment options to consider in order to choose the best one for

each patient, the one that best reflects her unique medical and personal situation.

In fact, ACOG has previously recommended vaginal hysterectomy because it is associated with better outcomes and fewer complications than the alternatives of laparoscopic or abdominal hysterectomy. But, still, one surgical procedure is not right for all patients and that's why we need options and why patients need options.

It is appropriate for us to discuss the potential complications with power morcellation because that will help to increase the awareness among patients and physicians about the associated risk and benefits of that procedure. It will help to emphasize to industry the need to improve diagnostic tools and for the creation of more data for us to consider. We stand here welcoming that discussion.

It is also appropriate for the FDA to take steps such as calling for the establishment of a registry. This will help us gather the data that we need to better understand the risk associated with power morcellation, and it will further promote patient safety and help us to tailor patient care in the future.

I also urge caution against the adoption of solutions that may on the surface appear to be the answer, but are not tested and may give a false sense of security. Currently available surgical bags could be torn by a morcellator or are of an insufficient size to capture the tissue being removed.

We still lack a reliable tool to diagnose a uterine sarcoma prior to surgical intervention. Widespread use of fibroid biopsies has been urged but would potentially lead to dangerous false negative results because patients often have multiple, even dozens, of fibroids, and the biopsy could miss small spots of malignant tissue.

In some ways, it may seem easier to recommend a ban on morcellation. That would, of course, remove the risk associated with that specific procedure, but it would also leave physicians and patients with fewer options, patients at the lower risk of an occult malignancy who might otherwise have to undergo a total abdominal hysterectomy.

Complications and risk are unfortunately part of healthcare. We should not hold one procedure -- in this case, power morcellation -- to a higher standard than other procedures. What we can do is work together to improve the use of those procedures in the future as we make complex, important treatment choices with and for our patients.

I urge the Committee today to recognize the importance of treatment options for all physicians, including obstetricians and gynecologists.

And, again, I thank you for your time. Thank you.

DR. DIAMOND: Thank you.

Are there any brief clarifying questions for Dr. Lawrence?

DR. LAWRENCE: Thank you.



DR. GALLAGHER: Just one, sir.

DR. DIAMOND: Hal. Dr. Lawrence.

DR. GALLAGHER: Thank you. This is Colleen Gallagher.

I'm wondering. You mentioned a registry. What exactly would you -- which patients would you want registered and for what? Could you explain that a little bit, please?

DR. LAWRENCE: First off, that's a great question, and I don't think it has a simple --

DR. GALLAGHER: You used the word, and I just want it to be clear. What do you mean?

DR. LAWRENCE: I don't think it has a simple short answer because I think we really need to look at a registry that takes on all patients undergoing hysterectomies for uterine fibroids or leiomyoma. And that's 40% of all hysterectomies. And we need to look at the different procedures that are used in accomplishing that hysterectomy and whether that's abdominal, whether that's vaginal, whether it's manual morcellation, whether it's transvaginal uterine coring, whether it's power morcellation. And we need to look then to see what the demographic data are of the patients; ethnic issues, age issues. We need to look at how the surgical procedure went, and then we need to track outcomes and have that hard data to reflect and guide us as we move forward. So those are the big-picture issues that I would put in there.

Thank you.

DR. DIAMOND: Thank you. One more question.

DR. MOORE: I'm Lisa Moore from the University of New Mexico.

Until we get the data, are you suggesting that we postpone the use of the morcellators or to continue the use of the morcellators?

DR. LAWRENCE: I am not suggesting that we stop the use of the morcellator until we get the data. What I am suggesting is that we look at what we already know as different risk factors for patients. And as we said in our document back in May, patients who are -- where you have a considerable risk that there might be an occult malignancy, those are patients that should not undergo morcellation. But patients that we don't think that there's that much of a risk, those are patients that that option should be discussed with.

DR. MOORE: But isn't there currently no way to identify patients who might have an occult sarcoma?

DR. LAWRENCE: I'm sorry, I didn't hear that.

DR. MOORE: Sorry. There currently is no reliable way of identifying those patients who might have an occult sarcoma?

DR. LAWRENCE: There currently is no preoperative testing techniques that are of high efficiency or effectiveness, that is correct. However, there are patients lower in age who have a much lower incidence.

And if you look down in the mid-thirties, there's a much lower incidence. And there are patients older in age. Although sarcoma goes up, depending on their genetic backgrounds, the incidence is less. So I think what we have to do is look at the criteria that we have to help guide us as far as the overriding risk for any one particular patient and not just look across the board to ban something for everybody.

DR. DIAMOND: Dr. Lawrence, we have one more question from Dr. Yustein.

DR. YUSTEIN: Actually it's not a question for Dr. Lawrence; it's just a clarification for the Panel. I think Dr. Lawrence used the words "FDA" and "registry" in the same sentence, and I just want to be clear that FDA has not called for a registry. I think what Dr. Lawrence was suggesting was that he was suggesting that FDA call for a registry.

DR. LAWRENCE: I think that's what I said, yes.

DR. YUSTEIN: Okay, I just want to make it clear that we have not called for a registry.

DR. DIAMOND: Thank you.

DR. LAWRENCE: Thank you.

DR. DIAMOND: We will go on then. The next speaker is Anna Mazzucco representing the Cancer Prevention and Treatment Fund.

DR. MAZZUCCO: Hi. I was actually told tomorrow I was going to speak to you.

DR. DIAMOND: Okay. Then I think we will go on to the next speaker. All right, the next speaker is Mark Thornton from the Sarcoma Foundation of America.

DR. THORNTON: Good morning. My name is Mark Thornton, as mentioned, President and Chairman of the Board of the Sarcoma Foundation of America.

The SFA was founded in 2000 with the mission of finding the cure for this disease. Since then SFA has gained over 8,000 members and has raised over \$5 million in research funding, basic translational research, in order to foster development of new and better therapies for sarcoma.

The SFA has no conflict of interest today. We do not get any funding from any device industry company. No board member is connected with the device industry, and there are no medical advisory board members that are GYN physicians.

I'll proceed now to our statement.

The Sarcoma Foundation of America, in addition to funding translational research in sarcoma, has a robust government affairs function to try to reform the policies of institutions to allow for better outcomes for patients with sarcoma. SFA has been instrumental in reform of regulatory cancer policy on a range of issues important to children and adults with not just sarcoma, but rare cancers in general. We appreciate today the efforts of FDA, as well as the assembled Panel, to address the safety hazards of

morcellator devices.

The SFA also has a patient registry of over 2,350 sarcoma patients. Regarding uterine leiomyosarcoma, we have data on 139 patients in the registry. Last year, the SFA began a program in ULMS to develop targeted individualized therapies for women suffering from this disease. But far more vital than salvage treatment after metastasis is the prevention of the disease and curative initial surgical intervention. This is a paramount philosophy and not just ULMS management, but sarcoma management in general.

All too often in our community we hear stories from patients regarding general surgeons who have approached soft tissue tumors with the default mindset of it being benign, only to be startled when the pathology report returns revealing a sarcoma. It has been a frustrating lament for surgeons specializing in sarcoma surgical management, and therefore we very much commend the FDA for addressing the dangers of a morcellator in upstaging an existing ULMS.

However, we have also heard from female members with sarcoma in our community who, being well informed of today's issue, spoke not just to the risks of the device, but to its benefit. Since there is evidence that fibroids can decrease fertility, for example, and removal of these fibroids may increase fertility, many women are uncomfortable with potential government-imposed restriction on methods that affect reproductive choice and reproductive health.

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As sarcoma patient advocates, it is unusual, to say the least, to have the intrusion of such a volatile issue as choice impact what is a natural reaction to simply ban the device. Today, instead, we are at a unique intersection of oncology policy with women's health and choice policy. But fortunately we know that it is the OB/GYN community that has had to struggle at this intersection long before we ever heard of the word "morcellator." Therefore, we trust in your collective judgment and wisdom to advise FDA as to the best manner to find common ground at this intersection.

Consistent with other FDA-regulated products where data emerges showing a similar strong shift in the risk/benefit ratio, the SFA advocates for the following:

1. Action within the OB/GYN surgical community for an immediate voluntary moratorium on using morcellators until the bag containment morcellator technology meets expectations to decrease risk of tumor seeding from the morcellation procedure and have a more proper risk/benefit ratio for the device.

2. Regarding the FDA, we advocate that as manufacturers return to FDA with their next-generation products (i.e., the bag morcellator containment unit), that the device be treated as a Class III device so as to optimize knowledge of the risk/benefit profile of the products. And in accordance with the FDA Amendments Act of 2007, a risk evaluation mitigation strategy, or REMS, policy should be applied to the device as well.

Given implementation of this strategy, it would seem to strike the right balance between working towards the future promise of this technology for the enormous number of women dealing with the pain, bleeding, and other significant fertility issues of uterine fibroids, while dealing with the current unacceptable safety risks of an unperfected product and procedure being used today on these same women.

In closing, we again thank FDA for grappling with these important issues. We know that although the issues are complex, common ground can be found to strike the right risk/benefit balance while preserving a woman's right to choose.

Thank you very much.

DR. DIAMOND: All right. Thank you very much.

The next speaker is Justine Atkinson from Fibroid Relief.

MS. ATKINSON: Good morning. My name is Justine Atkinson, and I am the Executive Director of Fibroid Relief. We are a patient education and support organization created by the Focused Ultrasound Foundation, and we seek to educate women with fibroids about noninvasive treatment options. We are funded primarily by individual philanthropic donations to the foundation, and we also receive support from focused ultrasound manufacturers. We have paid our own travel today, and we are very pleased to be here.

Fibroid Relief has watched with great interest as the media

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coverage of morcellation safety in hysterectomy and myomectomy has created concern and confusion among women. Fibroid Relief is dedicated to educating women with fibroids about noninvasive treatment options and empowering patients to seek treatment and symptom relief as soon as possible to maximize their options. We want to take this opportunity to share with the Panel and the public a few important facts about fibroids, treatments, and choices.

Number 1: It's important to keep in mind that the vast majority of uterine fibroids are non-cancerous. While 8 in 10 women will develop fibroids by the age of 50, in more than 99% of cases the fibroids are benign. There has been much concern about morcellator devices spreading cancer, and we urge the decision makers in this room and the media reporting on this topic to put the real risk in context and to keep in mind the unintended consequences of scaring women away from treatment. Our sympathies go out to the women who have found their fibroids to be cancerous, and we recommend improved screening that may help identify any malignant lesions prior to treatment.

Number 2: We know that most women with fibroids prefer noninvasive treatment options which do not use morcellator devices because they do not involve surgery. Fibroid Relief's national survey of nearly 1,000 U.S. women, published last year in two peer-reviewed medical journals -- and conducted with leading fibroid experts from the Mayo Clinic, the Cleveland

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Clinic, and the University of North Carolina -- found that an overwhelming 76% of women with fibroids do not want to have surgery of any kind, and more than half are afraid that they will need a hysterectomy. For those who are concerned about morcellators in particular, it's important to remember that there are a couple of treatment options available that offer no chance of disseminating fibroid cells at all, cancerous or not, such as uterine artery embolization, or UAE, which blocks the uterine artery with small particles to decrease blood supply to the fibroid; and focused ultrasound, a noninvasive, no-incision technology that uses waves of ultrasound energy to heat and destroy fibroid tissue. In addition, focused ultrasound is conducted using magnetic resonance imaging, and MRIs can identify suspicious lesions prior to treatment and prompt further examination.

Third: Also important in this discussion is the fate of the millions of women in America who have asymptomatic fibroids and those not in immediate need of intervention. Some articles have quoted the incidence of sarcoma as high as 1 in 350 women with fibroids, which means there would be thousands of asymptomatic women with a potentially undetected sarcoma. In addition, what is a woman with a new diagnosis of fibroids supposed to do? Should all women undergo hysterectomy on the remote chance that they are harboring a sarcoma even if they are asymptomatic? Of course not. Yet this is what proponents of banning morcellation are ultimately advocating, namely, eliminating any possible chance of a woman

dying of uterine sarcoma by performing a hysterectomy. This negates the concept of watchful waiting, and it irresponsibly eliminates noninvasive options such as focused ultrasound or embolization.

Fourth and lastly: We do not want this debate about morcellator devices to needlessly scare women into avoiding treatment altogether. We already know that women are waiting too long to talk to their doctors, as our survey found that, on average, women delay seeking treatment for three and a half years, with 32% of women waiting more than five years. What's more, a delay in diagnosis can cause unnecessary growth of fibroids and limit the effectiveness of treatment options. So while there are pros and cons for every treatment method and fibroid treatment is not a one-size-fits-all approach, it's important that women today know to educate themselves on the risks and benefits of every procedure and to work with their doctor to choose the treatment course that is best for them.

Thank you.

DR. DIAMOND: Thank you.

That was the last of our consumer group presentations for this morning. I'd like to ask the Panel if they have any brief questions for either Dr. Thornton or Ms. Atkinson.

(No response.)

DR. DIAMOND: Seeing none, we will proceed. The next speaker will be Frank Bonadio.

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MR. BONADIO: My name is Frank Bonadio. I'm the CEO of Advanced Surgical Concepts. I'm here to present a solution to the problem we face today in power morcellation, to allow the safe extraction of a large organ or tissue through a small 15 mm incision.

In this slide, we see Dr. Ralph Clayman performing one of the first morcellation procedures on a kidney, taken from an article in the *British Medical Journal*. As you can see from the schematic drawing on the right, the specimen is placed into a bag and the bag is drawn to the surface of a gas-filled abdominal wall. There is no internal vision within the bag and no space within the bag. This practice was largely abandoned for open abdominal morcellation, which has led to the dilemma we face today.

In 2011 Dr. Tony Shibley had the idea to take a containment bag in the same way Dr. Clayman did, but make one simple methodological change. Instead of morcellating within a bag pulled to the surface of the abdomen, he figured, why not inflate the containment bag with the specimen inside to create a large space for morcellation with vision.

Here is a video of what Dr. Shibley -- if it plays -- first saw when he did his first case. And it's playing. The uterus now lies in a bag that is completely contained. The bag is inflated with CO<sub>2</sub> gas, pressurizing it to lift the abdominal wall and retract the underlying organs, while all the while protecting the abdomen from the risk of dissemination of cancer cells. As you can also see, the use of this method further helps the surgeon by establishing

a clear border between the internal organs on the one side of the barrier and the uterus on the inside.

This brings us to a new definition of containment, one that allows vision in a large working space to perform safe morcellation. It defines a barrier between the abdominal organs and the target tissue and completely contains tissue fragments, cells, and fluids throughout the entire morcellation and extraction procedure. The last thing we need to ensure is that this approach can be standardized and made simple for any surgeon.

That's the definition of containment.

Okay. ASC has been working with Dr. Shibley to develop a product that is easy to deploy, easily encapsulates the uterus, and establishes insufflation pressure allowing vision and a larger working space and, most significantly, complete containment.

This slide shows what we are calling the PneumoPort. It has a flexible access port, which you can see on the left, and a PneumoLiner containment bag which is introduced into the abdomen using a narrow cylindrical tube, which you see on the right.

Okay, here is a picture of a deployed PneumoLiner that contains the uterus ready for extraction. It's gone too far. We're missing a slide. Anyway, here it is. In this slide, we see the contents of the PneumoLiner after an extraction was completed. Critically, these tissue fragments and fluids were never exposed to the abdomen. There was no

need to look for fragments or perform abdominal washings, as they were at all times maintained within the bag.

And now I'll play that video. It's basically uncontained morcellation on the left and contained morcellation on the right.

And I'm going to introduce Dr. Tony Shibley to talk a little bit about his clinical experience.

DR. DIAMOND: You have about one minute left for your portion of the presentation.

DR. SHIBLEY: Thank you. I'll try and be as brief and quick as I may. Thank you. I certainly appreciate the Committee.

I am a general OB/GYN with 20 years experience in a private clinic, practicing at two community hospitals. The simple technique that I developed, that you saw briefly here, has been adopted by all of my partners over the last two years, and we've performed over 200 cases using this technique. I have also informally trained physicians within my community and nationally. And given the immense interest in this technique, I've received multiple and multiple inquiries from around the globe.

Given the technique that I've developed, tissue extraction without containment is no longer acceptable. Contained extraction without direct vision, as has been alluded to previously here, is not giving us a safe margin of distance between the target tissue that we're trying to remove and the abdominal contents. In the containment world, what we've been doing

essentially has been playing pin the tail on the donkey. We've lost kind of the basic tenets of surgery. Once we approached contained removal of specimens, we've lost our visualization, and we've lost our safe working space between target and other organs.

I presented my initial feasibility data in 2012. This study included one patient with an unsuspected ovarian malignancy. That patient was not upstaged. This year I participated in a multi-center collaborative project with seven other high-volume academic minimally invasive surgeons from Harvard and Johns Hopkins to study this technique further. These findings have been accepted to the *Green Journal* and the title of this project is "Contained Power Morcellation within an Insufflated Isolation Bag." I think it's important. And I'd like to close with a recent case from one of my partners. All of my partners have adopted my technique.

This is a 56-year-old woman with postmenopausal bleeding. She had a comprehensive preoperative assessment that was negative for malignancy and was noted to have a 10 cm uterine fibroid. On April 18th of this year, she underwent a primary procedure by my partner using my contained morcellation technique. The patient had a supracervical hysterectomy, meaning, the uterus was amputated from the cervix, placed within the containment bag, the bag was insufflated, and morcellation was carried out. The pathology report surprisingly and unsuspectingly was leiomyosarcoma. This patient was referred to the gynecologic oncologist, and

on June 2nd of this year she underwent a secondary surgery. This surgery included removing the cervix, taking biopsies from throughout the abdomen, obtaining pelvic fluid, and abdominal washings from throughout the abdomen. All of those findings were negative for any malignant cells.

That's dramatic, that this confirms that contained morcellation within an insufflated bag does not increase the patient's risk and in fact gives many benefits for our patients, including allowing them to continue to receive the benefits of minimally invasive surgery, but adding the safety features.

I think this is the natural progression in medicine, if we're doing medicine right. We're taking what we've learned, we're stubbing our toe along the way, and we're keeping our patients front and center to protect them. We're trying to make our procedures better and safer at all times.

DR. DIAMOND: Thank you, Dr. Shibley.

The next speaker is Sara Trainer.

DR. TRAINER: It's JoAnn.

DR. DIAMOND: I apologize.

DR. TRAINER: Good morning. My name is Dr. JoAnn Trainer, and I'm here representing myself as a mother, grandmother, healthcare professional, and healthcare consumer. My only conflict of interest lies in the fact that I am the mother of Dr. Amy Reed, who was one of the latest casualties of uterine morcellation.

So I'd like to start off my presentation with asking the Panel members to put themselves in the place of a gynecologic surgeon who is facing their patient after having a morcellation procedure. The first question they would ask is, "Doctor, did you upstage my cancer?" Now, for me, that would have seemed ridiculous before this tragedy with Amy, because for me and my colleagues, we always believed that there was a surgical code out there which said all growths of unknown pathology should be considered malignant unless proven else wise. Well, that's not the case.

The second question would be, "Why did you cut up my tumor inside of my abdomen if you didn't know what it was?" Again, how do you answer that question? Your own review of the literature of 1 in 350 women who receive this morcellation procedure and then go on to find out that they have an unknown sarcoma states that these women are in total shock. There's no way to preemptively understand what the pathology is ahead of time.

In a similar public health tragedy, the *New Yorker* reporter, Paul Brodeur, in his book called *Outrageous Misconduct: The Asbestos Industry on Trial*, writes that statistics are human beings with the tears wiped off. No truer statement can be spoken when looking at the 1 in 350 number. In fact, I believe this is just the tip of the iceberg, since many women have died not piecing together the procedure used to remove their uterus with the subsequent upstaging of their disease and death. And that's what we're



talking about here, upstaging disease and death. We're talking about cutting up unknown pathology. We're talking not about women's rights, not about fertility; we're talking about taking a mass that we don't know what it is and upstaging a woman's disease.

So how do you answer that question? Do you say, "Oh, it's common practice, because numbers quoted before this time seemed so incredibly small, and at this point in time we still don't know what those numbers are"?

I heard a registry mentioned. How many women do we need to see die before we can come to a conclusion that it doesn't make sense to cut up a mass in someone's abdomen?

The argument that treatable but undesired morbidity is associated with removing these large fibroids, utilizing a larger incision or intact procedure, does not justify the lives of so many. And also, how would you explain to your patient that no one will really know the consequences of utilizing morcellation, because there's no feedback mechanism in our current 510(k) approval process for devices?

In fact, in 2011, the IOM made a surprisingly strong statement, in which they stated that the current process should be scrapped because it could not directly evaluate the safety and effectiveness of these Class II medical devices. In the opinion of the institute, the FDA needed to scrap the whole thing because there was even no way to improve or adjust it to

guarantee the benefits of safety and efficacy for these devices.

So today my request of the Panel, as guardians of public health, is that you act to ban the use of morcellation in cutting up of tissue anywhere, anywhere in the human body. I also request that this 510(k) process be replaced with a system that requires the same rigor that pharmaceuticals undergo in demonstrating safety and efficacy before coming to market, because perhaps by taking these steps and taking them now, the final question, "Doctor, why hasn't the FDA stepped in and done anything to protect women from this horror," will never need to be asked.

Thank you.

(Applause.)

DR. DIAMOND: Thank you.

The next presentation is Dr. Jacobson and Dr. Jacobson.

DR. J. JACOBSON: Good morning. My name is  
Dr. Joanne Jacobson. We have no financial relationships to disclose.

I am a full-time anesthesiologist in Marin County, California. I attend today with my sister, my aunt, and family, and to represent my parents, Dr. Lyle and Elizabeth Jacobson, who are physically unable to attend. We are here because of the tragic iatrogenic and preventable death of my sister and my best friend Elizabeth Jane Jacobson.

Elizabeth died January 8th, 2013, nine months after her uterus was morcellated during laparoscopic hysterectomy. This was performed by a

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surgeon who boasted that he never had to convert anyone to an open procedure and who spent more than one hour morcellating her uterus in order to remove it. During that hour, he managed to spread a uterine leiomyosarcoma throughout her pelvis and abdomen. From that hour forward, Elizabeth never had a chance.

She had a second surgery performed by a GYN oncologist. He removed her cervix and spent four hours picking pieces of her uterus out of her pelvis. Even so, he left her colon studded with tissue, foregoing the colectomy that would have been necessary to remove much of the debris. The pathology on the tissue he did remove showed no leiomyosarcoma, meaning she was Stage 1 before she was morcellated. Because morcellation upstaged her cancer, Elizabeth never had a chance.

Four weeks after her second surgery, she began to complain of fatigue and pain. On a Friday evening she had a CT scan. By Sunday her pain was so severe she begged me to take her to the emergency room. She called her oncologist, who told her, "Your tumors are back." Terrified, she turned to me and asked, "What did he mean, my tumors are back? I thought I only had one." Instead, she had eight large masses in her pelvis and abdomen, too many to treat surgically. She opted for aggressive chemotherapy, requiring hospitalization for each cycle. We watched our beautiful sister suffer horribly with severe pain, nausea, vomiting, weight loss, and relentless abdominal distention.

After four cycles of chemotherapy with no regression of her cancer, she died at home, surrounded by her family. We were left with our grief, our rage, and the conviction that because her uterus was morcellated, Elizabeth never had a chance.

DR. M. JACOBSON: Our sister, Elizabeth Jacobson, never had a chance because a power morcellator was used with the enthusiastic endorsement of an industry that conveniently ignored sacred tenets of modern surgical practice and the most fundamental principles of medical ethics.

I am Dr. Margaret Jacobson, a family physician, hospice and palliative medicine specialist, ethics committee chair, and Elizabeth's oldest sister.

My brilliant, loving, and beautiful sister never had a chance because the surgeon who performed her procedure, with the imprimatur of his colleagues, operated with the assumption that her fibroid was benign. Every other surgical discipline, by contrast, assumes the tissue is malignant until proven otherwise. To disrupt and disseminate tumor is considered a terrible accident at best, malpractice at worst.

Elizabeth never had a chance because her gynecologist, with the endorsement of his specialty, felt comfortable leaving debris in the form of bits of uterine tissue behind. Every other surgical discipline, by contrast, follows Halsted's tenets and pays meticulous attention to leaving the body

cavity in pristine condition. To leave detritus behind is anathema, a violation.

Most importantly, Elizabeth never had a chance because her gynecologist, with a callous indifference of a surgical specialty and an industry, was able to write off certain women as collateral damage for the purported greater good of faster recovery. Their attitude, that I've only seen once in my career, violates every ethical principle in medicine.

Laparoscopic uterine morcellation is an elective procedure for which there are alternatives. Uteri are never morcellated emergently. And to dismiss even one woman's life as acceptable in the service of the economy is inherently unethical.

Today you will likely here a manipulation of statistics to justify this procedure. It is, however, incorrect and unethical to compare universal risk of morbidity and mortality to certain morbidity and likely mortality for a subset of patients.

Unlike patients who undergo open or vaginal hysterectomy, Elizabeth Jane Jacobson never had a chance. That is the difference here and the reason that you must remove this device from the surgical armamentarium.

Thank you.

(Applause.)

DR. DIAMOND: Thank you.

The next presenter is Colleen Daley.

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(Off microphone response.)

DR. DIAMOND: Okay, I apologize.

The next presenter then is Howard Schwartz.

MR. SCHWARTZ: My name is Howard Schwartz, and I'm not a medical professional. I'm just here to give you our story.

My wife, Sandra Brown, passed away on December 15th, 2013, from respiratory failure/leiomyosarcoma. About 10 years ago Sandra had some discomfort because of fibroids. Her doctor suggested she have them removed, but Sandra was not ready for the surgery. Over the years, the fibroids had evidently shrunk and the physical exams confirmed this.

About a year before her passing, the fibroids had grown and gave her some discomfort. The surgeon said obviously the fibroids were not cancerous. And since both of us were avid bird watchers, we went cross country searching -- bird watching for the months of March and April 2013. Sandra scheduled her operation to remove the fibroids on April 13th, 2013. We arrived home on April 21st. On that date, April 23rd, little did we know that she was handed a death sentence. We were not informed there was even the remotest chance that a process of morcellation, for which we knew nothing about, could possibly have accelerated cancer growth. Had we been informed of this possibility, Sandra would never have taken that chance with her precious life.

When it came to her life, Sandra was not a risk taker. Any hint

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of this outcome, we certainly would have chosen a different procedure, and she would be with me today enjoying life. If the surgeon had presented even the slightest risk or even suggested the possibility of cancer in the fibroids, neither of us would have consented to the robotic surgery and morcellation.

Sandra spent her whole adult life being health conscious, from running every day, biking and kayaking and boating, to eating healthy and doing floor exercises every day after she ran. She was always aware and lived a healthy lifestyle. She won't be adding to her life list of birds we have seen. She won't be kayaking. She won't be solving the *New York Times* crossword puzzles in pen. Her family will never hear her voice again.

Sandra was exceptionally brilliant. She graduated from Northwestern University with distinction, had two master's degrees, and had a management position with a large corporation. Five days before passing, while in the hospital and somewhat drugged, she finished the *New York Times* Sunday crossword puzzle in pen. I saved that paper.

To spend one's entire life being so health conscious and then be struck down by a procedure for which we were never warned of the risks is unfair, unfair to me her husband, her mother, her sisters, her family, and her friends.

After her passing, I received a note from her primary care physician: "Dear Mr. Schwartz, we are all very sorry to hear of Sandra's death. She had been so healthy that we rarely ever saw her, but we will miss

her. We know this holiday season will be difficult for you. You have our sympathy. Sincerely, Dr. R.R. and staff."

Sandra had everything to live for, a devoted husband, a passion for bird watching, a wanderlust to travel the world and the means to support it, a loving and supportive family and friends.

We did not have the opportunity to have informed consent to this procedure, and as a result, I have lost my wife, my best friend, and my companion. I cannot go into statistics of what percentage of women have become victims of morcellation, but if it happens to your loved one, the answer is 100%.

The lives of a minority subset of women with occult or missed uterine cancers cannot be sacrificed for the benefit of the majority or to alter women's choices. That is inconsistent with our social values in the year 2014 and the United States. Please do the right thing and stop morcellation for the removal of fibroids. How many thousands of women will thank you, even if Sandra is not among them.

For Sandra Brown, I am her husband, Howard Schwartz. Thank you.

(Applause.)

DR. DIAMOND: The next speaker is Elizabeth Pritts.

DR. PRITTS: My name is Dr. Elizabeth Pritts.

Our group performed a meta-analysis of the world's literature

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addressing the prevalence of occult leiomyosarcoma, and a systematic review of morcellation outcomes of these tumors. We performed an unlimited online search, followed by hand searches of all references over a broad amount of time, including all languages. We included peer-reviewed surgical studies. The primary indication had to be fibroids. The tumor had to be reported as leiomyosarcoma. If histopathology was included, it had to be consistent with that diagnosis. However, if there was no histopathology included, the diagnosis was, as reported by the authors, leiomyosarcoma.

We excluded non-peer review data, tumors with inconsistent criteria. And when all specimens were sent to pathology without explicit results, these were excluded from the primary outcome evaluation, which was the prevalence of occult leiomyosarcoma in fibroid surgical studies where the pathology was explicitly reported.

For our secondary outcome, we included those fibroid surgery studies where pathology was not explicitly reported. We identified over 4,800 articles and included 130 with explicit pathology and another 235 without.

For the primary outcome for the 130 studies including over 28,000 women, pathology was reported for everyone. In the studies where the data were prospectively collected, the estimated prevalence was 1 in 7,450 women.

If you look at the secondary outcome and assume no explicit

reporting of pathology coincides with no malignancy, we can add over 38,000 more surgeries. As you can see, the prevalence drops for both groups.

Why do our numbers differ from the FDA? We completed computer and hand searches, included all languages, over a broad period of time extracted more data, included only peer reviewed and stratified for prospective versus retrospective. We evaluated more studies. We included more women.

We conclude that the best available prevalence estimate is from prospectively collected data, and that suggests one occult leiomyosarcoma for every 7,450 surgeries for fibroids.

Due to the issue before us today, there are two important questions that need to be addressed. In our systematic review, we attempted to do this.

First: Is morcellation worse than en bloc uterine removal? There were six relevant studies identified. Three showed worse outcomes, one no difference, and two were too small for meaningful conclusions. However, all of these studies suffered from significant design flaws. I could go into them, but today I do not have the time. We concluded that the data are too heterogeneous and biased to form any scientific conclusions.

And, incidentally, when we're talking about these data, I recently read that it has been established that motorized morcellation during surgery for these tumors adversely affects survival. However, in these six

studies, they included all types of morcellation. They involved very few documented power morcellation cases. So we found two, zero, one, zero. And in two studies where types of morcellation were mixed, they did not tell us how many were power morcellation. We conclude that there is no evidence that specifically motorized morcellation adversely affects survival.

It leads us to the next question: Is power morcellation worse than hand? We identified one comparator study. However, the numbers were too small and the staging too heterogeneous between the groups to compare. So we completed our systematic review of all published cases, in which type of morcellation was identified and survival outcome reported. Survival was no different for these 32 women.

Based upon the best available evidence, we conclude that the prevalence of occult leiomyosarcoma is 1 in 7,450. There is no good evidence that en bloc removal is safer than tumor morcellation, and there is no evidence that power morcellation is different from any other morcellation type.

Thank you.

DR. DIAMOND: The next presenter is Dr. Perate.

(No response.)

DR. DIAMOND: Not seeing her, we will go on to the next speaker, which is JoAnn Trainer. Actually, Dr. Trainer has already spoken. Next, we'll go on to Scott Eldredge.

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MR. ELDREDGE: Good morning. Mr. Chairman and members of the Committee, it is a true pleasure and honor to speak before you today. My name is Scott Eldredge. I am an attorney from Denver, Colorado. The law firm is Burg, Simpson, Eldredge, Hersh & Jardine. You might have heard of my law partner, Alan Simpson. He's a retired U.S. senator from Wyoming. Senator Simpson is known for speaking rather frankly. I think when I've concluded, you might assume the same thing about me.

I am a trial lawyer. And by the way, it's very nerve racking for me to be here in a room with so many physicians. I won't hold it against you if you won't hold it against me.

I represent a number of women who have been injured by the morcellation process. I teach law school at the University of Denver College of Law. I teach medical malpractice law there. And I wanted to give you a brief perspective from a trial lawyer's thoughts about the morcellation process and the upcoming litigation.

What I teach my law students is torts become actionable if you have duty, breach, causation, and damage. And for the purposes of my talk today, morcellation can be summed up in two issues. Number one, is the injury preventable? Number two, was the injury predictable? You've heard heartrending stories from victims today that answer both of those questions in the affirmative. It clearly is predictable and clearly has been preventable. There is no safe alternative.

Now, I'm not speaking as a scientist; I'm not qualified. I'm not speaking as a physician; I'm not qualified. And I'm certainly not qualified to speak as a statistician. And I was interested to learn the statistics that were presented by the last speaker.

Ladies and gentlemen, the statistics are irrelevant, because if you are a patient undergoing morcellation, there is either a 0% chance that you will have cancer that will spread or a 100% chance that you will have cancer that will spread. And that is predetermined by your physical condition, which cannot be known by the physician doing the procedure.

Now, this is not the first time that I have been disappointed by a position taken by the American College of Obstetricians and Gynecologists. I assure you, it will not be the last time that I am offended by positions taken by the American College of Obstetricians and Gynecologists. Why would that organization take a position that this procedure should not be banned when there is no possible way that they can tell their patients that it's safe to go forward? They can say, statistically, you're probably all right. There's a likelihood that you don't have cancer. You're in your twenties, so you'll probably be all right, but I can't guarantee that. Until the physician can offer a guarantee to a woman that she is not going to undergo a spread of her cancer and take what could be Stage I removable cancer to Stage IV fatal cancer is an irresponsible position that I'm frankly outraged that ACOG has taken.

Last comment. We heard a position statement today from the gentleman from Ethicon, and he made a comment that I found very interesting. He said that Ethicon decided to take the position that they did to remove their product from sales when they learned that the prevalence of occult tumors was greater than they had previously anticipated. I would respectfully ask this Committee, as you decide whether or not this procedure should be used and these products should be banned, is what numbers did they know before they took the steps? Did they think it was 1 in 500, 1 in 7,000, 1 in 350?

Again, no risk versus low risk. Clearly, this is not a no-risk procedure. And when a physician tells you, as we've had physicians tell you here today, all procedures have risks, absolutely that's true. Absolutely that's true. But this risk is unique; it's predictable, it's preventable, and I would respectfully suggest it should be banned.

Thank you.

(Applause.)

DR. DIAMOND: Thank you.

The next presenter is Amanda Linegg, if I'm pronouncing that right.

MS. LINDSEY: Lindsey.

DR. DIAMOND: Lindsey?

LCDR ANDERSON: Lindsey.

DR. DIAMOND: Lindsey. I'm sorry, yes.

MS. LINDSEY: I want to thank you guys for letting me be here. I'm just representing my family.

Statistics. I don't get it, because there are several families here who have been affected by this morcellation. My mom, 64 years old; there's no reason she should be dead. She died in March. She had a power morcellation, and within four weeks her one tumor went everywhere and there was nothing they could do. They tried. They went back in, they closed her back up. So then chemo. I don't know how many people have witnessed cancer and what it does to people, but it's awful. She tried. She did six rounds of chemo, and finally she said, "That's it, I'm done. I want to go home and die."

So me and my dad spent a month with her. She didn't eat, she couldn't drink, she couldn't talk, she was out of her mind. And that's what it did to her. It killed her in a most awful, horrendous way.

My mom was an accomplished quilter, a grandmother, a vegetarian. She never drank, she never smoked, she never had fibroids. She was a very healthy women, and she took very good care of herself. And this procedure was presented to her as hey, you know, you're not going to have a lot of pain, and it's going to be great, and you're going to be back in your regular routine. And that's not the case. I mean, as soon as it was done, I mean, that was it. That was her death sentence. It took eight months to kill

her.

And statistically, okay, so there are people here who, obviously, their families were affected and they lost their family members. But I know if this procedure is allowed to go on, that there will be more women. More women will die; more families will be affected. These women aren't going to be able to have children. They're not going to be able to see their grandparents -- their grandchildren grow up. And my parents were married for 45 years. Now my dad is alone, and he shouldn't be. And it sucks. And that's all I have to say.

Thank you.

(Applause.)

DR. DIAMOND: Thank you.

That was our last speaker for the morning. I would like to ask the panelists whether -- Panel -- whether there are any members of the Panel that have any brief clarifying questions for any of the speakers.

Dr. Hillard.

DR. HILLARD: I have a question for Dr. Pritts, which is the status of the data that you presented and the paper. Has it been submitted, peer reviewed?

DR. PRITTS: Yes, we're in conversations with several journals at this time to fast track the publication.

(Off microphone comment.)

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DR. PRITTS: Oh, I'm sorry. Dr. Elizabeth Pritts. Thanks.

DR. DIAMOND: Thank you.

Other questions at this time from the Panel? We will have a chance during the deliberations this afternoon to ask other questions as well.

I'm sorry, I didn't see your hand.

DR. MOORE: I'm Lisa Moore, and I have a question for -- I think his name is Dr. Shibley, the guy with the PneumoLiner.

I'd like to know how many cases you've done with your PneumoLiner and what were the complications, and did you experience loss of containment in any of those cases?

DR. SHIBLEY: Could you say that again?

DR. MOORE: I'd like to know how many cases you've done using the PneumoLiner.

DR. SHIBLEY: Over 100, myself. Combined with my partners, over 200.

DR. MOORE: Any complications during those cases?

DR. SHIBLEY: No complications during those cases.

DR. MOORE: No tears or loss of containment?

DR. SHIBLEY: No. There have been some tears identified in the -- remember, this is a technique; it's not a device at this time. And in using some existing technology that's available, the bag has to be manually introduced into the abdomen, and we've noticed some tearing placing the

bag within the abdomen, and that's been identified by loss of gas when instilling the gas into the bag, and that's been corrected by replacing the bag.

DR. MOORE: So that would have been -- so you've experienced no spillage into the abdomen?

DR. SHIBLEY: No, we have not had any spillage into the abdomen. No.

DR. MOORE: Thank you.

DR. DIAMOND: Thank you.

Other questions from the Panel?

Dr. Isaacson.

DR. ISAACSON: Keith Isaacson.

I'm sorry, Dr. Shibley, I was going to ask you a question as well. Just as you've done -- if I understood correctly, you've done 500 cases -- 200.

DR. SHIBLEY: Yeah, it's greater than 200 as a collaborative group. The publication that we submitted and has been accepted to the *Green Journal* was 73 patients in 4 institutions with 8 physicians.

DR. ISAACSON: And out of the ones that you've looked at, have you had cases of leiomyosarcoma?

DR. SHIBLEY: The last case that I presented was a case of leiomyosarcoma of one my partners.

DR. ISAACSON: That was one case.

DR. SHIBLEY: There's another case that I'm aware of that was

also contained, and my personal communication with the physician is that the staging procedure and follow-up was also negative on that case.

I think it's worth mentioning that I've had two ovarian cancers now and one fallopian tube cancer, and I've managed it with this technology -- with this technique, and none of those cases have been upstaged on their follow-up surgeries.

DR. ISAACSON: Thank you.

DR. DIAMOND: Thank you.

Dr. Afifi.

DR. AFIFI: Abdelmonem Afifi. I have a question for, I think, Dr. Pritts about the prevalence of occult --

DR. DIAMOND: Dr. Pritts.

DR. PRITTS: Yes. Dr. Elizabeth Pritts.

DR. AFIFI: It's fundamental, in studies of this type, to know both the numerator and the denominator. In the papers that you have identified, I could see that it's easy to know the denominator. What was your process of guaranteeing that the correct numerators were also counted?

DR. PRITTS: Yes. Every test we completed, we had to have pathology for every single patient. If a study was presented and they said we excluded any cancer patients or we excluded any patients, or 20 patients did not have any pathology, these were also excluded. We found 22 leiomyosarcomas in the total number of patients. And when we ran our

meta-analysis, we compared both retrospective and retrospective. So we included all of the studies. However, they're obviously weighted based upon science and based upon quality of the evidence.

DR. AFIFI: Do you believe that the identification procedures from 1960 through 2014 were uniform enough to guarantee that they're comparable?

DR. PRITTS: Absolutely not. The only leiomyosarcomas that were identified came from about 1989 and later. We probably included some leiomyosarcomas that were not, because, in 1994, Bell introduced the Stanford criteria that showed the histopathology, and he compared that with the outcomes. And so they changed the staging for leiomyosarcoma in 2003, the WHO and the ACP. And so we may have included more leiomyosarcomas that would not be termed leiomyosarcomas now, but if there was no histopathology, we included it.

DR. AFIFI: And do you have any way of knowing how many were excluded?

DR. PRITTS: No. And it's interesting because there are several registries in the European countries, and they register every single patient that's coming through to have a surgery for fibroids. However, what they publish is only the benign outcomes. They exclude all the cancer outcomes, all the malignant outcomes. So data are out there.

DR. AFIFI: Thank you.

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DR. PRITTS: Thanks.

DR. DIAMOND: Thank you.

DR. WENTZENSEN: Nicolas Wentzensen from NCI.

I'm also struggling with the two different estimates that we have on the table. And when you did your analysis and you looked into the same set of studies that the FDA looked at, did you come up with the same estimate, and then when you added the other studies, the numbers became -- I mean the prevalence became much lower? So can you explain that a little more?

DR. PRITTS: Right. So we believe that the FDA missed many, many, many studies. When we went through their data, we found there was one letter to the editor that was included that had some data represented. They include only English articles, and the letter to the editor was in English. However, the original paper was in French. We went back to find the original paper and translated it, and we did include that in our data. The only other that we did not include was an abstract, and it was never subsequently published.

They also excluded any studies where multiple diagnoses were included and outcomes were included. So if people had fibroid surgery and pelvic prolapse surgery, they included those patients, they included the outcomes. And if the data were extractable about just the fibroid patients, we extracted those. And I know that FDA did not do that as well.

DR. DIAMOND: So we may want to hold that question in part until this afternoon, after the FDA has a chance to give their presentation on where their numbers came from.

Dr. Brown.

DR. BROWN: Carol Brown.

For Dr. Pritts again. You mentioned, I believe, six studies that said that there was an adverse effect on survival for patients who had morcellation with leiomyosarcoma. I wanted to know if in any of those studies, did any of them report on other factors associated with prognosis of leiomyosarcoma other than stage, such as mitotic rate, rate of atypia, type of atypia, and control for those?

DR. PRITTS: Yes. So just for clarification, there were six studies identified. Only three showed worse outcomes. And there was one study that looked at mitotic rate and showed differences. However, in all of these studies, they included patients that had been referred 13, 6, 16 months out from their original surgery. So we are seeing biased data because we're seeing the patients after they have been referred for a recurrence, and we don't know the denominator of the patients who were never referred. And that's the main problem. Now, most of the authors talk about that in their discussion section.

DR. DIAMOND: Thank you, Dr. Pritts.

Other questions from the Committee?

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(No response.)

DR. DIAMOND: Seeing none, we're a little bit ahead of schedule, but I think we'll go ahead with our break.

We will now pronounce the Open Public Hearing to be officially closed, and we will not take any additional speakers today.

We will take a 10-minute break. Panel members, please do not discuss the meeting topic during the break amongst yourselves or with any members of the audience. And we will resume at 10 minutes after 10:00.

(Off the record.)

(On the record.)

DR. DIAMOND: We'll now go ahead and reconvene the meeting. FDA's Elaine Blyskun will now introduce our first invited speaker, Shannon Laughlin-Tommaso, on the agenda topic of general introduction to fibroids.

Ms. Blyskun, you may begin.

MS. BLYSKUN: My name is Elaine Blyskun, and I'm Chief of the OB/GYN Devices Branch at FDA. I will be introducing our four guest speakers.

First off is Dr. Laughlin-Tommaso. Shannon Laughlin-Tommaso, M.D., M.P.H., is an assistant professor and consultant in the Department of Obstetrics and Gynecology at Mayo Clinic, Rochester. Dr. Laughlin-Tommaso completed medical school and residency at Loyola University in Illinois. She subsequently completed a research fellowship at the National Institute of

Environmental Health Science in Durham, North Carolina, and completed a master's degree in epidemiology at the University of North Carolina. Her work has addressed the prevalence of uterine fibroids and how they are affected by pregnancy. She was awarded a scholarship from the National Institutes of Health for her current research on the long-term cardiovascular risks following hysterectomy.

Dr. Laughlin-Tommaso will be presenting background information on the biology, epidemiology, and clinical aspects of uterine fibroids and nonsurgical treatment options.

DR. LAUGHLIN-TOMMASO: Good morning. So as she mentioned, I'm at the Mayo Clinic, and my specialty there is fibroids and abnormal uterine bleeding. In addition, I'm one of the minimally invasive gynecologic surgeons there. And I'm so pleased to be here this morning to give you the introduction on uterine fibroids.

I have to mention that I have no financial disclosures, but I am currently helping with a clinical study that evaluates the safety of one of the focused ultrasound devices. I'm also one of the co-investigators on an NIH-sponsored randomized controlled trial which compares uterine artery embolization to focused ultrasound, and I've been a co-investigator on an epidemiology study of fibroids, called the Study of Environment, Lifestyle and Fibroids.

My role today is to discuss the biology, epidemiology, and the

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public health impact of fibroids. Then I'll discuss the clinical presentation and the effects on quality of life. And lastly I'm going to provide an overview of the medical and minimally invasive fibroid therapies.

So what are fibroids? Fibroids are benign smooth muscle cell tumors, and that's where they get the term "leiomyoma." And to note, leiomyoma, myoma, and fibroids are all interchangeable. They arise from a single cell, and they're monoclonal. But within a single uterus, you can have multiple independent tumors which can act differently and can be of different cell type. They are bulky fibrous -- I'm sorry. They're laid on bulky fibrous extracellular tissue, which is mainly made of collagen. And that's where they get the term "fibroids," because they do appear very fibrous. But they're actually physically active -- physiologically active extracellular matrix, which means that it is changed by growth factors, and it's stimulated by hormones, and so it's constantly remodeling itself. And that goes into how fibroids act, which we'll talk about in a couple slides.

As I mentioned, they are hormonally dependent. They only occur between menarche and menopause, and they increase with increasing age, up until the age of menopause. There are estrogen, progesterone, and aromatase receptors in the fibroid tissue, and these have been major targets for medical therapies for fibroids.

Parity is related to a lower incidence, so it's also time since the last pregnancy. So the more pregnancies and the more recent pregnancies

actually have a lower incidence of fibroids. And we think that is due to the remodeling that occurs with that extracellular matrix after delivery.

Forty percent of fibroids will have a chromosomal abnormality, and those usually occur in trisomy 12, a translocation of 12 of 14, or certain deletions. And the deletion of 1p is currently undergoing a lot of investigation for its role in the malignant potential.

So we're going to have a full talk on leiomyosarcomas, and I'm only going to briefly mention it here to differentiate leiomyosarcomas from fibroids.

Leiomyosarcomas are tumors with a high mortality rate that have four histologic patterns typically. It can be atypical nuclei; high mitotic activity -- so a lot of cell division; necrosis; or a higher cellularity to extracellular matrix than what we see in a typical fibroid.

There are such things as fibroid variants, and these can have one of the above abnormalities but, by definition, cannot have all. These fibroid variants usually follow a benign course. But what makes it difficult is that if a typical fibroid has necrosis or it has high cellularity, it makes it more difficult to differentiate from what we consider a typical fibroid or from a leiomyosarcoma. And I will have an imaging talk later to discuss that.

Fibroids grow at different rates, and this is a relatively new finding. The clinical thought for fibroids for many years was that they grow at a constant slow rate until the woman either needs treatment or she goes

through menopause, and after menopause it's thought that they recede. Some people thought, though, that around the time of menopause, fibroids would suddenly increase in size because of the hormonal changes.

In the only longitudinal non-pregnancy study of fibroid growth, what they found is that fibroids within the same uterus can grow and actually shrink at different rates. And when we put all the fibroids together across all of the women in this study, we had a range of growth from -90%, meaning shrinkage by 90%, to growth of 140% in six months time. The median growth is about 9%. And what we found around the time of menopause is that for women older than age 45, the growth rate among white women actually decreased to about 2%, but for black women the growth continued at the same rate up until menopause.

That has major implications as to the treatment of fibroids around the time of menopause. You may be able to give a treatment that could temporize the fibroid growth in a white woman at a younger age than for a black woman because that growth rate will continue afterwards. So there are some differences that we have to look at. And throughout the talk I'm going to be talking about this racial disparity between African-American and white women.

Fibroids are very common. If you look across studies and look at only self-reported or symptomatic fibroids, the estimate is about 25%. But if you look at pathology specimens of all uteruses, there's about an 80% rate

of fibroids. And this was confirmed in ultrasound screening studies where up to 80% of women who were screened by ultrasound had fibroids by age 50.

There are two major incidence studies of fibroids, of self-reported fibroids in the U.S.: the Nurses' Health Study and the Black Women's Health Study. And in both of those, the incidence rate among black women was about three times that of white women.

And what we see here in this graph, this is a graph combining all of the incidence studies around the world. Most of these did occur in the U.S., and what we see is actually relatively similar incidence rates across different studies. So the top line here is for black women, and the bottom line here is for white women. Only Sweden has an outlier as a low incidence. Very interestingly, what you see is that the curves are parallel for incidence, but they occur about 10 years apart.

So for black women, fibroids start to occur, and that incline goes up at about age 25 and rapidly rises. But for white women, that incline started at about age 35. And that's such an important age difference. So that's a 10-year difference at a time when black women may not have finished their families. They may just be ending their educational training and just starting their careers, whereas for white women between 35 and 45, they may have already completed their families. So this makes a major impact on treatments for fibroids.

As far as the public health impact, there's about 400,000 new

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cases per year, and there are over 30,000 myomectomies that occur in the U.S. And direct and indirect costs were reviewed per patient and that included time-off work loss due to either the symptoms or to the treatment. And those estimated costs were between \$30,000 and \$39,000 for myomectomy.

Fibroids are the leading cause of hysterectomy. They are about 40% of all the hysterectomies. And direct and indirect costs there were similarly high: \$31,000 to \$42,000 per patient.

And, again, what was seen was that among all of the surgeries, black women had a larger burden from the cost of fibroids and treating fibroids than white women.

So let's switch gears and talk about how do women present clinically. How they present really depends on where the fibroid is and what size the fibroid is at presentation.

So here I've demonstrated an atypical uterus that has multiple, multiple fibroids. But what you can see here is that there are all different kinds. So there can be pedunculated submucosal fibroids. And the submucosal fibroids, by definition, have to lay just underneath the mucosal or the endometrial layer, and they can either be pedunculated on a stalk or they can be just pushing into the uterine cavity. The intramural fibroids are generally thought to be completely contained within the myometrium. And the subserosal fibroids are those that distort the external side of the uterus.

Submucosal fibroids can present very early on when they're 1 cm or 2 cm in size. However, when we see subserosal fibroids, they're generally much larger at the time of presentation, and that goes into how they present.

So the submucosal fibroids, even if they're small, can already increase menstrual cramps and pain and heavy menstrual bleeding. And submucosal fibroids have been associated with anemia from having menstrual bleeding, even in comparison to other women with having menstrual bleeding. They also cause problems with fertility and with pregnancy. Implantation occurs right at that endometrial layer. And so any kind of abnormality there could cause a problem potentially. However, the bowel and bladder symptoms are generally not found until the uterus is of a very large size or the subserosal fibroids that are large enough to compress other organs have gotten to the size to do that. So that's more of a 6 cm or 7 cm in size when we start seeing those women present.

And what I show here is just three different images. This is comparing uterine size filled with fibroids to that of pregnancy. And so on the far left, you see that it's a normal size uterus. In the middle, that's compared to a 12-week size pregnancy. And you can already see compression of the bladder and of the bowel, and it's starting to fill the pelvis. So another symptom would be pain during intercourse. But some women, as we heard this morning, do delay treatment, and they can present

once they are about the equivalent of a five-month pregnancy or the fibroids can be up to the umbilicus. And these patients do present when they already appear pregnant or even feel pregnant because of the pressure that's constantly going on in their pelvis.

As I mentioned before, black women are disproportionately affected. So when I said the 25% on average, that was for everyone. But actually, among black women, about 40% of patients report menstrual pain and cramps due to fibroids. They also have a threefold increased risk of anemia and about a two-and-a-half-times risk for hysterectomy. They also have a sevenfold risk of myomectomy. And that's most likely because they're getting their fibroids earlier and they typically have more fibroids than white women. And myomectomy is a fertility sparing option, and so that number would be not unexpected. When the uterus is removed, they're of higher uterine weights, and what we see is more fibroids in a larger fibroid volume.

Now, this is from the survey that Justine Atkinson mentioned this morning. This was published in 2013, and it was a national survey of women with fibroids. And this is for both African-American and black women -- I'm sorry -- and white women. And they went over how fibroids affect their quality of life.

So for relationship impacts, what you see is 14% of women report that they have trouble caring for their children at certain times of the month. Fifteen percent have an impact on their friendships, and 22% say

fibroids impact their partner relationships. Twenty-nine percent report missing work days. And that does go into some of the indirect costs because that can be quantifiable. But the next few bullet points are really hard to quantify.

So women reported that 24% reported lost potential, 27% reported that they were unable to do part of their job, and 12% feared that they're going to lose their job secondary to their symptoms. Fifteen percent reported that they could not travel due to fibroid symptoms, which of course would limit their ability to work certain jobs.

Women also have a lot of fears about fibroids. So 77% fear that they're going to grow over time, 53% fear that they would have cancer, and 25% feared that they would be unable to become pregnant due to their fibroids. And this, again, was twice as high among African-American women than white.

But they're also very concerned about the treatment that they will have to undergo. So 81% are concerned that the treatment will be very invasive, and 64% fear that their sexuality will be changed by the treatment. Overall, 49% wanted a fertility sparing option, and this was twice as high among African-American women than white women.

So now on to fibroid evaluation. In general, when the patient presents, we want to evaluate her symptoms in comparison to the size of the uterus and the location of the fibroids. The best way to start is with a pelvic



exam. And, again, what we want to see is where are the fibroids, how large is the uterus, and whether or not they are in front or behind and whether that matches their symptoms.

We may follow that up with an ultrasound. And what I've shown here is just an ultrasound with a fibroid in it. It doesn't show up very well on the screen, but I'll try to outline the uterus here and the fibroid in the middle there.

And so you can see that you can clearly differentiate the fibroid from the rest of the uterus. That fibroid appears to be in the middle of the cavity. So it wouldn't be unexpected that the patient may be concerned with menstrual cramps or bleeding. We can also see if the fibroids are on the outside of the uterus. This is only showing one fibroid, but many women present with multiple fibroids. If she presents with heavy menstrual bleeding, you may want to check an endometrial biopsy or your blood counts to make sure that she's not anemic.

If we're going to go under -- do any minimally invasive therapies or even in some cases myomectomy, we may perform a pelvic MRI. And this is a coronal view of a pelvic MRI. And what you can see here again is the uterus on the outside there, and then the fibroids are very clearly delineated. So the pelvic MRI can give a bit more of a 3-D view of the fibroids and be able to tell a little bit more clearly whether or not they invade the wall. And they're better for when there are many fibroids in the uterus or the

uterus is a very large size.

So in this case we can tell that these fibroids are completely within the uterus, and we can decide at that point whether or not she should undergo one of the minimally invasive treatments or a surgical resection of the fibroids. And for that, it also helps sometimes to do a hysteroscopy, and we can do these in the office, as well. So if we had an ultrasound like the first one I showed that indicated a fibroid in the middle of the uterus, you may perform an office hysteroscopy to see if it would be resectable.

Hysteroscopic resection of the fibroid is a minimally invasive technique outpatient surgery, and it is recommended in many cases, which we'll go over in a few minutes.

So when do we want to treat fibroids? Fibroids that are symptomatic can really be treated at any age. And, again, imaging is going to help to determine if the fibroids are related to the symptoms. And then you have a couple options. You could treat the symptoms of fibroids or you can treat the fibroids themselves.

For fertility issues, which I think will be reviewed in another talk, you do want to treat the submucosal fibroids. And as I mentioned, those can be hysteroscopically resected. And that is recommended to reduce the chance of that interfering with fertility and also, in some cases, miscarriage.

Now, the second point of intramural fibroids > 5 cm, that's a little bit more controversial, and I won't go into that topic today. But there

are reasons to remove fibroids that are not submucosal for fertility issues as well.

Two of the treatments that can optimize future fertility are myomectomy, as I mentioned, which is the gold standard for treatment of fibroids for fertility, but also the focused ultrasound ablation. And I'm going to be talking on that topic, so I'll go over the pregnancy risks at that time.

When do we not need to treat fibroids? Fibroids that are asymptomatic or happen to be an incidental finding on imaging do not need to be treated. Patients can be reassured and you can do watchful waiting. If the patient begins to have symptoms, then a reevaluation with an exam and an ultrasound would be appropriate. This is especially important in postmenopausal women. So postmenopausal women who are incidentally found to have fibroids may have had them throughout their premenopausal years, and most likely these fibroids have calcified, and overall, you can reassure the patient. However, if it's a new finding or they seem to be growing, that would be considered abnormal, and further evaluation should be done.

The other thought was any rapid growth of fibroids would be considered a leiomyosarcoma. But that is not found to be true, especially with our fibroid growth study. What we found in a secondary study was we followed the fibroids over the course of the three intervals and the fibroids actually grow at all different rates and can grow and then shrink. So some of

them had very rapid growth, as you saw -- 140% increase in six months -- but then they would stabilize or they would even decrease in size. So rapid growth is not indicative of leiomyosarcoma necessarily. And those patients can be monitored if they don't have symptoms and just proceed with expected management for them.

However, if the patient does want treatment, and one of the major symptoms would be bleeding, then you have a lot of options that don't necessarily target the fibroids. So one option is for NSAID therapy. That's a therapy that can be done just for five days around the time of the menstrual cycle. Tranexamic acid similarly can be taken for five days around the menstrual cycle. And they both reduce bleeding. NSAID is about 20% to 40% and tranexamic acid about 40% to 50%. Contraceptive hormones, either combined estrogen-progestin or progestin alone, can also reduce bleeding symptoms and provide contraception. So it may also be a good first line for treating bleeding associated with fibroids.

And what I show here on this ultrasound is the uterus is here, the fibroid is out here. And so sometimes what you want to be careful with is that a patient could have fibroids that are unlikely to be related to her bleeding. So if the endometrial lining is here and the fibroid is a subserosal one, you may have a completely normal cavity. You can actually treat the bleeding symptoms without treating the fibroids. If the cavity is normal, you can place a levonorgestrel-releasing intrauterine device.

If you have fibroids, there's a slight increase in expulsion rate for the IUD. However, it's a very good device. It was FDA approved for heavy menstrual bleeding in 2009, and it reduces bleeding about 70% to 80%. We generally make sure, in some imaging technique, that the cavity is fairly normal if there's any concern that that fibroid could be resectable or it could be in the uterine lining.

Endometrial ablation also generally requires a fairly normal cavity. However, you could also resect a fibroid before performing endometrial ablation. This is a surgical procedure, and there are many different ways to do an endometrial ablation, which ablates the lining of the uterus to decrease bleeding. And it's highly effective also. It decreases bleeding about 80% to 90%. But, again, for some of the second-generation endometrial ablation devices, they were never tested with submucosal fibroids. So they are not technically approved to be used in the presence of submucosal fibroids.

There are a couple of medical options for which you can treat both the fibroids and the bleeding. And the first one I list is leuprolide acetate, or better known as the brand name Lupron. This is a GnRH agonist. There are also antagonists that can be used to decrease fibroids and bleeding. Lupron puts the patients into a temporary menopause essentially. So it withdraws the ovarian hormones and can control bleeding because it decreases their periods and then also shrinks the fibroids. It's highly effective

for this. It shrinks fibroids about 50%.

However, it only is active when it's in the patient's system. You can do a three-month depot shot of the Lupron, and you can continue the patient on the treatment. But most patients have a lot of side effects from this. So they'll have menopausal side effects, including hot flashes, memory loss, irritability, and a lot of patients want to come off of the treatment, even if they've been given some add-back therapy with other hormones to try to prevent that.

This has been approved for use really before preoperatively, where you want to reduce the bleeding, increase the patient's blood counts, and reduce the size of the fibroids before surgery. Sometimes it's also used around the time of menopause, where you think the patient is close enough to menopause that shrinkage of the fibroids and decrease of the bleeding will get her through to the menopausal transition.

Ulipristal acetate I mention here. It's not currently available in the U.S., but I bring it up because there has been a lot of targets for the progesterone receptors. This is a selective progesterone receptor modulator, and it does control bleeding in head-to-head trials with both Lupron and placebo. It has been shown to control bleeding in more than 90% of women, and it does shrink fibroids as well, and there were less side effects than Lupron. So I think, in some fashion, we'll be seeing a progesterone receptor medication in the future.

I'm going to switch to the minimally invasive treatments and start with uterine artery embolization, which has been around for about 20 years for the treatment of symptomatic uterine fibroids. And the way that this works is a catheter is placed through a sheath in the common femoral artery in the groin, so a small puncture is made there. The catheter is sent through the anterior iliac and selectively catheterizes the uterine arteries.

Once the position of the catheter is confirmed with contrast injection, the embolic agents are instilled to achieve a stasis of the blood flow. And that's demonstrated here in this close-up picture. What you're seeing is the embolic agents going in and closing off the blood supply to that fibroid. After the procedure, the sheath is removed, and you can achieve homeostasis either by compression or using a closure device.

Who are the candidates for UAE? So UAE provides a very global treatment to the uterus. So patients who have a few large fibroids are great candidates, but also those patients who have multiple small fibroids. There is a relative cutoff of about 10 cm, and contraindications include any genitourinary infection, malignancy, or severe vascular disease. One of the relative contraindications is an iodine contrast allergy. And you want the patients generally to have good renal function so that they can clear that iodine contrast out.

And it is recommended to resect any submucosal fibroids hysteroscopically before UAE -- and those are especially those fibroids that

are well within the cavity -- because they can try to pass after the UAE, which can be painful for the patient and also increase bleeding. They aren't able to reabsorb into the wall, as well, and so it can also cause chronic vaginal discharge or bleeding. There are cases where submucosal fibroids that are only just barely distorting the lining can undergo UAE. So it's not a contraindication completely.

The details. It's about an hour-and-a-half to a two-hour procedure under fluoroscopy. Patients stay overnight for pain control. And they have that puncture in the groin, so usually they have to have a compression of that area for a while, and they have lay flat for a while after the procedure.

The major risks other than hematoma formation, which I mentioned with the puncture site, is amenorrhea. And that amenorrhea rate increases with age at the time of the uterine artery embolization and can be as high as 40% in women over 50. And that likely is due to the second point there, which is that markers of ovarian reserve have shown lower ovarian function after uterine artery embolization when compared with myomectomy. However, similar decreases in ovarian function have been seen with hysterectomy. So the thought is that some global treatments of the uterus can actually affect the ovaries. It's thought to be collateral blood flow between the uterus and the ovaries decreasing the ovarian blood flow.

Unique to UAE is the post-embolization syndrome, which can



last one to seven days. It is a syndrome of pain, nausea, vomiting, elevation in the white blood cell count, and general malaise. If patients have symptoms like that after seven days, you generally want to examine them for infection, because infection and even sepsis has been seen in fibroids after uterine artery embolization.

Symptom relief from UAE is very good. I present here a couple results from two and five years after UAE. But at five years, heavy menstrual bleeding was improved in 83% of women. Seventy percent had decreased urinary frequency. Eighty-five percent reported satisfaction. And that was very similar to the patients who had undergone hysterectomy out at five years. At three months, fibroid volume was reduced by about 42%, and I've seen numbers anywhere from 40% to 60%. But, interestingly, patients report that their symptoms are very improved even if they have small fibroid reduction. So those two were not related.

What we look at for a lot of these minimally invasive treatments is reintervention rates, so requiring another fibroid therapy. And the rate in one study was 28% at five years. And that has generally hovered in most studies around 30% to 35% or lower.

Pregnancies after uterine artery embolization are a little more controversial. In one of the major first studies by Pron et al., there were 555 women. One hundred and sixty-four expressed desire to have fertility, but at one year, only 35 had reported trying. So the denominator is not very clear.

But essentially they had 24 pregnancies, 18 live births. But among that, they had three abnormal placentations, including two previa and an accreta. These are very uncommon obstetrical conditions. And so to have that many within 24 pregnancies was considered unusual, and it was thought that there was some pattern of complications that occurred with the UAE, and so they are considered more high-risk pregnancies.

However, there's been more recent case series, and I just list one here that was done in 2009, where 23 patients desired fertility. Sixty-one percent had a pregnancy. There were two miscarriages, but 13 went to term without any complications.

And then in a randomized controlled trial of UAE versus myomectomy, UAE had a lower live birth rate and higher spontaneous abortion rates.

Next up is MR-guided focused ultrasound surgery. And this is a procedure where the patient lies prone in an MRI device -- in an MRI machine, and she lays over an ultrasound device which brings the ultrasound waves together into a focal spot where there is high temperature in the focal spot and then a quick drop-off of temperature in the non-target areas. And what that does is it denatures the proteins and it collapses the vessels. So while you may treat a small focal area, you might actually get a treatment that's a little larger.

Now, MRI is used in many of the devices to map the fibroids, to

guide the beam, to monitor the thermal effects, and then afterwards to look at the treatment effect. Candidates for focused ultrasound are similar to UAE, but there's more stress on those who have few large fibroids that are accessible by focused ultrasound.

So as I mentioned, they do lay on their abdomens. The uterus can fall forward. But you want to make sure that there's no bowel in front of the area that needs to be treated. The other major thing is scars. So if there are abdominal scars, you need to treat around them and not through them. So it all goes into the evaluation of the patients preoperatively. Again, there's a relative cutoff of 10 cm in diameter, and you want the patient to have good renal function due to gadolinium use. Anything that is risky for MRI in general is a contraindication. So metal in the pelvis or devices that are not allowed into an MRI machine would be a contraindication.

The details. It's about a three-hour treatment. Most people will need two days in a row. It's done under IV sedation or pain medications. And, generally, most patients have a urinary catheter to keep the uterus still. The bladder can push the uterus back and forth. It's an outpatient procedure. So even if they need two days in a row, they do go home in between, and it really requires minimal pain medication prescriptions to go home with. There are no incisions and, as was mentioned before, there is no radiation.

This demonstrates the treatment effects. On the left, you can see the fibroid preoperatively. Where there's good vascularity, the fibroid

with contrast lights up the same as the rest of the uterus. And afterwards you see that dark center, and that indicates that there's no more vascularity. And that's what we're really looking for, for treatment with focused ultrasound.

The major risks. As I mentioned, skin burns. That has mainly been resolved with procedural changes. And you want to be careful not to treat through scars. You can have inflammation of subcutaneous fat and muscle. This has been asymptomatic in most patients. It's seen on MRI, though. You could have bowel injury if you treat through it. And there has been a DVT, or a deep vein thrombosis, reported before, and we now use the sequential compression devices to reduce that risk because the patients are laying flat for so long.

Lastly, there can be paresthesias. And the guidelines recommend that you don't treat very close to bony structures, because if the bony structure is heated enough, it can injure the nerves that come out. So a lot of patients will report -- I'm sorry. The patients with these will report pain down the back of their legs or loss of sensation. Overall, this is uncommon, and they generally will spontaneously resolve, but it can take months for that to occur.

Symptom relief is good. It's lowest at three months, and we use the symptom severity score, which was decreased by 50%. That's eight questions of the most likely symptoms that patients have. Ninety-one

percent reported symptom relief at 12 months. And, again, looking at reintervention rate, we found that the more volume you treat, the better the outcome. So when originally people were treating 50% of the fibroid tissue, they would have a reintervention rate of 20% at 2 years. But the most recent data that's coming out looks like it's 20% at 4 years if you have unrestricted treatment.

Fertility sparing option. But these are only observational studies. There has not been a completed randomized controlled trial. But in the largest case series, there were 54 pregnancies, a high vaginal delivery rate, and no distinct patterns of complications like there was with the UAE. And there's been success with IVF pregnancies after FUS. Basically, the labeling was changed to say that we need to counsel women on the risks that are known with focused ultrasound versus the risks that are unknown and also compare that to the gold standard of myomectomy, where we know there are risks.

And the last topic is percutaneous ultrasound-guided radiofrequency ablation. And that's a laparoscopic procedure done in the operating room as an outpatient under general anesthesia. Two incisions are made, one for the laparoscopic camera to visualize the pelvis and the uterus, and the other is made for the ultrasound, which is actually a device that has the ultrasound on the sides so that it can run along the uterus and map the fibroids. And then once the fibroids are found and the area of treatment is

located, a puncture is made through the skin, and a radiofrequency probe is put into the fibroid itself, and it can either be ablated directly through the probe or seven deployable electrodes can be pushed through to fill the fibroid, and it's treated with monopolar radiofrequency energy. This also has temperature feedback and using an algorithm. It heats that fibroid to the target temperature for a set time in each fibroid.

The three-year results show that there were four pregnancies, and I've only seen one case report of the successful pregnancy. I can't report on the other three. I could not find that information. But there's been greater than 50% reduction in symptom severity score, as well. And 11% at three years had required additional fibroid treatment.

So, in summary, fibroids are common and costly. African-American women are disproportionately affected. Symptomatic fibroids can be treated, but asymptomatic fibroids can be left alone and just watched. And there are many alternatives to hysterectomy that are both durable and effective.

I'd be happy to take any questions.

DR. DIAMOND: Okay, I'd like to thank Dr. Laughlin-Tommaso for her presentation.

And we'll ask the Panel whether they have any clarifying questions. Please remember that the Panel will also be able to ask questions during the Panel deliberations during the afternoon.

Dr. Mattrey.

DR. MATTREY: Thank you for a nice presentation. Just a couple questions. One, you mentioned that UAE is contraindicated in malignancy. Can you please describe that a bit more?

DR. LAUGHLIN-TOMMASO: Well, you want to rule out malignancy before any minimally invasive treatment. And so endometrial biopsy would be appropriate or monitoring the -- doing imaging beforehand. So if you find a uterine malignancy, they don't want to treat with uterine artery embolization. However, there have been cases of leiomyosarcoma which have been treated with UAE, and it delayed the diagnosis of the leiomyosarcoma.

DR. MATTREY: And the second question was related more to my education, which was a long time ago, where we were taught that sarcoma is one of the degenerations of leiomyoma. So leiomyosarcoma comes after the fibroids develop. And I've heard controversies as to leiomyosarcoma begins as a leiomyosarcoma. So is the leiomyosarcoma small islands within a fibroid, or is it leiomyosarcoma throughout?

DR. LAUGHLIN-TOMMASO: That's a good question. And hopefully Dr. Cohen can answer that later. But that's very controversial. So there have been both ways. Do fibroids convert into leiomyosarcomas, or do they start as leiomyosarcomas? And I don't think that we know that yet. There's data in both directions. However, loss of chromosomal 1p is being

investigated because there have also been case reports of what was considered a typical fibroid that went on to have a fatal course, but many, many years later.

So could there be the similarities to borderline tumors, of fibroids? Possibly. But I think that's still really undergoing a lot of investigation. And chromosomal 1p investigations will be very interesting for that. So I can't answer that completely.

DR. DIAMOND: Dr. Brown.

DR. BROWN: I'm Dr. Brown.

Just to clarify, do you have any statistical information for the three noninvasive procedures you presented -- uterine artery embolization, the MRI focused ultrasound, and the ultrasound probe -- about the incidence of undiagnosed cancer in general, and specifically leiomyosarcoma and the outcome of those patients? You mentioned that it resulted in -- you knew of one case. But is there any registry or any published papers about the incidence of unrecognized cancer for these noninvasive treatments of fibroids that you mentioned?

DR. LAUGHLIN-TOMMASO: I have no data on focused ultrasound or the percutaneous RFA procedure. The case reports that I saw for UAE, nobody has quantified a total number of how many in this has occurred, but I saw at least three case reports in the literature for leiomyosarcoma after UAE. And I'll try to get you a better answer this



afternoon on focused ultrasound. But, personally, I haven't heard of any, and it's a fairly small focused ultrasound community so far. But I'll look that up for you.

DR. DIAMOND: Dr. Iglesia.

DR. IGLESIA: Cheryl Iglesia. Thank you again for your presentation.

You know, we want to make the best -- use our best clinical judgment. So do you feel that having reviewed all of this literature and the science, do we have enough currently available evidence to help predict using some type of risk calculator which women are at higher risk, so that they can make some personal decisions as well, to which approach? You know, based on age, race, menopausal status, parity, the appearance of the fibroid on preoperative imaging, obviously biopsies, et cetera. Where are we with that?

DR. LAUGHLIN-TOMMASO: We're pretty limited. So we know some statistics on the epidemiology of leiomyosarcoma, which I think we'll probably go over this afternoon. But endometrial biopsy only picks up about 38% of malignancies of the type of sarcoma -- any type of sarcoma in the uterus. And on MRI it picks up about 50% of them, even in known leiomyosarcomas. So in terms of imaging and biopsies, it's very difficult to be able to predict. And I think that in terms of epidemiology, that will probably be addressed by a later speaker. But could there be a risk calculator? Maybe. And I hope we can get to that point.

DR. DIAMOND: Dr. Simon.

DR. SIMON: This may be something that will be brought up later. When you discussed this sort of heuristic approach to leiomyosarcoma, which is the rate of growth and how that has been sort of debunked -- correct me if I'm wrong -- the data which sort of debunks that idea that you can look at the rate of growth as a way to stratify or pick up this occult malignancy, that's true in premenopausal women; is that correct?

DR. LAUGHLIN-TOMMASO: That is correct.

DR. SIMON: So in postmenopausal woman, trying to detect a leiomyosarcoma, a change in symptoms, whether it's growth or just any alteration, that should indeed raise the issue of a leiomyosarcoma.

DR. LAUGHLIN-TOMMASO: Absolutely. So new onset of symptoms, increasing size of a fibroid, those would all -- after menopause, those would all be indications of something abnormal. Most likely you'd want to rule out a leiomyosarcoma.

DR. SIMON: Are there any studies looking at, in particular, leiomyosarcoma development in postmenopausal women?

DR. LAUGHLIN-TOMMASO: I believe there are, but I did not do that research for this one.

DR. SIMON: Okay.

DR. DIAMOND: Dr. Fisher.

DR. FISHER: First, thank you very much for the presentation. I

have a real quick question on the UAE as an alternate therapy. And I think that you mentioned that there is a reintervention rate of about 28% out at five years.

DR. LAUGHLIN-TOMMASO: Um-hum.

DR. FISHER: And I was wondering if we know if that's a revascularization of an old fibroid, or is that for treatment of new fibroids, and also if that rate is indicative of the general population or if it may change due to race, or if you know.

DR. LAUGHLIN-TOMMASO: That's a great question, and I did forget to mention that. So reintervention rate is a little difficult because obviously younger women who are farther from the time of menopause are more likely to either get new fibroids or have those fibroids begin to grow. UAE usually has more of a global treatment. But especially in focused ultrasound, if you just treat the middle of the fibroid or you don't treat the complete fibroid, there can be revascularization of the other areas. And so growth can recur in those situations or new fibroids can occur. And so reintervention rate is different depending on age and most likely, race.

Now, we have some data for focused ultrasound that shows that the best candidates are really the patients who have multiple fibroids close to the time of menopause, because they have less time that you need to really treat, and they seem to do the best and have the most success, whereas, with young women, most likely they're going to need another

fibroid treatment if they start getting new fibroids or symptoms.

DR. FISHER: So to the other question. Do you know if there's a difference in reintervention rate with race?

DR. LAUGHLIN-TOMMASO: Not off the top of my head.

DR. FISHER: Okay, thank you.

DR. DIAMOND: Dr. Isaacson.

DR. ISAACSON: Keith Isaacson.

Are you familiar, are there any -- have there been deaths reported as a complication of uterine artery embolization?

DR. LAUGHLIN-TOMMASO: I have seen reports of major sepsis requiring emergent hysterectomy, and I did not look at the number of deaths after UAE, though, for that. But those can be very serious emergent cases.

DR. DIAMOND: Dr. Simon.

DR. SIMON: Well, one, I can answer that question on deaths after UAE. The answer is yes, there have been, but it's usually delayed. And that's because of sepsis. And there was one case, when looking at a particular type of embolic agent, where a patient had a shunt and it had embolized to the lungs during the procedure. It was not detected. And that was also an immediate death, which I was pleased that it actually got reported.

DR. DIAMOND: Okay. Other questions from the Panel?

Dr. Simon again.

DR. SIMON: One last question. You gave data: 600,000 hysterectomies per year; 40% of those are for fibroids. And then you spoke of some of these other alternative procedures, the focused ultrasound, RF ablation, and uterine artery embolization. Do you have any data on how many of those procedures are done each year, as a juxtaposition to 600,000 hysterectomies?

DR. LAUGHLIN-TOMMASO: We have seen that the rate of hysterectomy is declining over time. So I quoted that number because that had the numbers from that study, the cost data from that study. But one of the more recent numbers I have seen is down below 500,000. And over time, there has been increasing uterine artery embolization and focused ultrasound. There are new data coming out about that, about how many are done in the U.S., but I can't give you an exact number right now. They are increasing over time, and it's actually regional. So what has been seen is that in certain areas of the country, hysterectomy is more likely to occur versus a uterine artery embolization or focused ultrasound.

DR. SIMON: But do you even have -- it's hard to say -- just a rough sense of what percent of patients are getting, say, a focused -- or being offered a focused ultrasound procedure or receiving a focused ultrasound procedure?

DR. LAUGHLIN-TOMMASO: That's good. I don't know that we have a denominator for that. I know in areas that are offered the UAE and

focused ultrasound, if a hospital offers it, they're more likely to get it. I know that we get referrals from all over the country because our institution does do the focused ultrasound. And UAE is much more common. So I don't have a denominator for what percent of patients would have that. But, overall, it's fairly lower. It's much lower than hysterectomy.

DR. SIMON: Thank you.

DR. DIAMOND: Other questions?

(No response.)

DR. DIAMOND: Not seeing any, we thank you very much --

DR. LAUGHLIN-TOMMASO: Thank you.

DR. DIAMOND: -- for your presentation and answering the questions.

And we will ask FDA's Elaine Blyskun to again introduce a speaker. This will be our second invited speaker, Craig Sobolewski, on the agenda topic of surgical options for fibroids.

MS. BLYSKUN: Thank you.

Dr. Craig Sobolewski is an Assistant Professor and Chief, Division of Minimally Invasive Gynecologic Surgery at Duke University. He received his M.D. from The Ohio State University College of Medicine. He completed his residency in obstetrics and gynecology at Lehigh Valley Hospital/Penn State University and stayed on as faculty. His responsibilities there included eventually serving as the OB/GYN Residency Program Director

and Chief of Gynecology.

He joined the faculty at Duke University in 2003. His clinical experience lies in advanced laparoscopic and hysteroscopic surgical procedures. Dr. Sobolewski has received several awards for his skills as an educator, including the Duke University Distinguished Faculty Award, the APGO Excellence in Teaching Award, and the CREOG National Faculty Award. He has authored or co-authored several peer-reviewed publications and book chapters. He was elected to serve on the board of trustees of the AAGL and was honored to serve in that role from 2010 to 2012.

Dr. Sobolewski will be presenting a review of the surgical options for the treatment of symptomatic uterine fibroids.

Dr. Sobolewski.

DR. SOBOLEWSKI: I would like to thank the Panel for the honor of being invited to give this presentation. Let me see if I can find it and pull it up here. Well, if I could find the mouse. There it is. And I'm going to do my best to stay within the 20-minute allotted time. I'm feeling a little bit better that we're ahead of schedule, so hopefully I will stay within that time limit. But I feel a lot less stressed about that.

So I've been asked to discuss the surgical treatment options. I do have two disclosures. I am a consultant and speaker for Covidien, which is a company that manufactures and distributes surgical devices used in laparoscopic surgery. They do not, however, make an electromechanical or

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other morcellating device. They do make specimen retrieval bags, for which I do no consulting or speaking. And I am a consultant and hold stock options in a company called TransEnterix, which likewise does not manufacture any morcellating devices and is a robotic platform for single-incision minimally invasive surgery.

So, briefly, I'm going to speak about surgical options specifically related to the treatment of uterine fibroids, and these include both uterine-sparing procedures and definitive procedures that involve removal of the uterus, either sparing procedures or myomectomy. And these can be performed via three general approaches: abdominal or open; laparoscopic, which we can refer to as traditional laparoscopic as well as computer assisted, frequently referred to as robotic laparoscopic procedures; and then hysteroscopic procedures, which as mentioned at the onset of this meeting is not felt to be at issue with the current problem related to the electromechanical morcellators.

Hysterectomy traditionally was performed via two approaches, either abdominal or vaginal. And within the abdominal approach, it can be further subdivided into either total or subtotal approaches.

And then we heard about some of the alternative approaches, two of which are not really surgical. But the radiofrequency volumetric thermal ablation procedure is done laparoscopically and technically probably does fall under a surgical option.



So abdominal myomectomy is performed through an open abdominal incision. And this is a photo from one of my personal patients that I chose specifically to demonstrate some of the difficulties when dealing with this disease burden. It's been suggested that perhaps preoperative biopsy could be useful as a tool to help to differentiate malignant potential. And very commonly, fibroids are quite large, as can be seen from this one particular specimen, and multiple. And so it really makes it difficult to determine where a biopsy should be performed and sometimes difficult to access the individual myomas to perform that biopsy.

It can also be performed laparoscopically or robotically. In this procedure there is a large predominantly subserosal fibroid on the posterior fundal aspect of the uterus. In order to accomplish this, an incision needs to be made overlying the fibroid and the mass nucleated and then repaired.

And then hysteroscopic myomectomy can be performed via a traditional resection type of procedure, not unlike a resectoscopic prostatectomy, or with hysteroscopic morcellating devices. Hysterectomy involves the removal of either the entire uterus or a portion of it and can be performed either from a top-down approach or a bottom-up approach.

The uterus has several attachments. Its vascular supply, major vascular supply, the uterine artery, is at the neck of the cervix. And so with an abdominal approach, the attachments of the uterus are detached, beginning at the top of the uterus, working down toward the cervix,

controlling the vascular blood supply and then ultimately making an incision where the cervix attaches to the vagina and then removing the specimen and then repairing the top of that vaginal cylinder that is created during that process.

So as we can see here, on the left is a drawing or depiction of a vaginal hysterectomy, whereas the procedure is begun from the cervix, beginning by making that vaginal opening and working up towards the top of the uterus, as compared to the upper right-hand photo, where an abdominal incision is made and the procedure is begun at the top of the uterus and work our way down towards the vascular supply and complete the procedure by separating it from its vaginal attachments. And then down in the bottom right-hand corner are images from my operating room, depicting both robotic and laparoscopic procedures.

Now, as I mentioned before, hysterectomy, when performed abdominally, can be divided into both total and subtotal procedures. So a total hysterectomy involves removal of the entire body of the uterus as well as the cervix, and at the completion of the procedure, the vaginal cylinder is closed with a series of sutures. And that is referred to as a vaginal cuff.

In contrast, a subtotal hysterectomy involves only the removal of the upper portion or body of the uterus and the cervix remains. So that line of sutures at the apex or top of the vagina is not necessary.

There have been nine randomized controlled trials comparing

total versus supracervical hysterectomy with endpoints of bowel function, bladder function, and sexual function, and none of those RCTs have shown any difference between outcomes in those three domains. Nor have there been any discernible differences in complication rates between total and subtotal hysterectomy. However, it's clear that leaving the cervix behind would negate the potential for complications related to the vaginal cuff. So vaginal cuff dehiscence is not a potential risk if the cervix is left in situ.

Moreover, with certain pelvic reconstructive procedures where vaginal mesh is attached to the sacral promontory and used to suspend a prolapsed vagina, leaving the cervix in place negates the potential for erosion of that synthetic mesh into the upper portion of the vagina.

So there may be advantages to the supracervical approach that are not addressed in any of those nine randomized controlled trials.

Hysterectomy by indication. It was alluded to the fact that hysterectomy rates are declining. And, in fact, in this publication from 2013, it does demonstrate that.

Hysterectomy by indication. Fibroids have traditionally and continue to remain a leading indication for this procedure, and it still is approximately 40% of hysterectomies that are done for an indication of symptomatic uterine fibroids.

When we look at hysterectomy by route, again, abdominal hysterectomy, seen here in red, is the leading method by which this

procedure is performed, accounting for about 54% of hysterectomies based on this data from 2010. And you can see that that number has declined slightly, and it had reached a peak in the early 2000s in excess of 60% and now it is down to 54%. Laparoscopic procedures in this data accounted for about 8.5% of procedures.

Now, it's important to recognize where this data comes from. So this data source is the Nationwide Inpatient Sample, and the Nationwide Inpatient Sample is a random sample of 20% of discharges from all hospitals in the United States. And it's important to stress the fact that this is only inpatient procedures. And, in fact, there is no similar database that's available to track outpatient surgical procedures, and that would include patients who are discharged from the hospital setting in less than 24 hours.

That's an important distinction to be made, as can be seen by this peer-reviewed publication out of the Kaiser Permanente in Northern California system, during which in their three-year evaluation of transitioning laparoscopic procedures to a same-day procedure, they were able to accomplish sending 80% of patients home on the same day of their laparoscopic hysterectomy. And I would venture to guess that this is not an unusual phenomenon across the nation. But unfortunately all that I can do is venture to guess, because there is no reliable data source from which to extract the number of hysterectomies performed annually in this country that are sent home prior to 24 hours.

So let's transition over to outcomes. So we'll focus first on hysterectomy. Laparoscopic hysterectomy was first described in 1989, and there have been a multitude of publications demonstrating the technique as well as its effectiveness, many of which are randomized controlled trials.

This slide summarizes, in large part, a paper from the Cochrane database that looked at 34 randomized controlled trials studying about 4500 patients. And it shows that the laparoscopic approach, when compared to the total abdominal approach, has the following advantages, including speedier return to normal activities, fewer infections or febrile episodes, less wound complications, including infection, less blood loss, shorter length of stay, and less pain. And those advantages are obtained at the cost of increased urinary tract injuries and increased operative time.

When comparing vaginal hysterectomy to open abdominal hysterectomy -- so as a minimally invasive surgeon, we typically pool together vaginal hysterectomy and laparoscopic or robotic hysterectomy together and consider those all to be minimally invasive surgical approaches. When looking at vaginal hysterectomy as a minimally invasive surgical approach and comparing it to total abdominal hysterectomy, we see the following advantages, also from that same systematic review from Cochrane which shows quicker return to normal activities, fewer febrile episodes, decreased length of stay, and less pain.

But, unfortunately, in the hands of all surgeons especially, the

vaginal approach may not be technically feasible for all indications. In fact, the study authors from the Cochrane Review stated that the vaginal approach is the preferred approach, when technically feasible, over either a laparoscopic approach or an abdominal approach. And as we heard from Dr. Lawrence earlier, that is the stance of ACOG as well as AAGL and other societies.

I think it's important to look at quality of life. When we're talking about performing the surgical options for the primary indication of hysterectomy, hysterectomy is clearly a more invasive and potentially more risky option as compared in this study to myomectomy or uterine artery embolization. And at 12 months, the hysterectomy group scored significantly lower symptoms and better health-related quality of life than the other two therapies. So although there may be adverse effects on quality of life in the short term, when we look at long-term quality of life, hysterectomy is a very effective treatment for women who have symptomatic uterine fibroids.

So let's shift gear and move over to myomectomy. So let's look at outcomes versus -- in myomectomy, laparoscopic versus open procedures. There's a fairly large meta-analysis comparing these two approaches and found that the laparoscopic group, as compared to the open group, not unlike the hysterectomy data, had less drop in hemoglobin, less intraoperative blood loss, a quicker return to normal activities by postop day 15, and less pain. And those advantages were achieved at the cost of a longer operative

time.

There was a little bit of discussion with this during the previous presentation, and that is the issue of recurrence. Now, the issue of recurrence is essentially a non-issue if fertility is the primary concern. There is no other option but to leave the uterus intact if you want to have a baby in the future. But it's important that we counsel our patients as to the risk of these uterine-sparing procedures as it relates to recurrence.

This data comes from the REST trial, and this is five-year follow-up of a randomized controlled trial looking at hysterectomy or myomectomy together as the surgical arm of that trial versus uterine artery embolization. And there was a high recurrence rate in the myomectomy group: 60% of patients had recurrence versus only 7% recurrence in the uterine artery embolization group. However, there was a 0% reintervention rate in the surgical group and a 33% reintervention rate in the uterine artery group.

Now, of course, one limitation of this study is that there were only eight patients that were part of the myomectomy group that were within the surgical treatment arm.

Now, the primary reason for doing these procedures is for fertility. And one of the things that gynecologists struggle with is the patient who is asymptomatic with fibroids and the question that they may have as it relates to their future fertility: What is the impact that my fibroids may have on my future fertility? And even though I'm not having symptoms, is there

benefit to me to have those fibroids removed, as it relates specifically to fertility? And, honestly, there's insufficient evidence to help us to answer that question, insufficient evidence at least from randomized controlled trials.

There's one RCT that looked at clinical pregnancy or miscarriage rate as an endpoint, and then there are another two RCTs that looked at the technique and its impact on fertility between a laparoscopic myomectomy versus an open myomectomy. And none of these RCTs demonstrated any outcomes benefit.

Now, when you look at the non-randomized controlled trial literature, there are some cohort studies that suggest that the presence of a cavity-distorting myoma, a submucosal myoma, may adversely impact fertility. And so a hysteroscopic myomectomy may be appropriate for those patients.

And again, just briefly, when we look at hysteroscopy, there have been sporadic case reports of an after-the-fact diagnosis of leiomyosarcoma following a hysteroscopic myomectomy. But in those sporadic case reports, there have been no reports of intraperitoneal spread and no women that have succumbed to their disease following that resection.

And then, finally, I'll finish up with briefly discussing morcellation techniques.

There are three options for specimen retrieval when dealing



with fibroids: electromechanical morcellation; vaginal morcellation, which can be performed either through a colpotomy incision at the completion of a hysterectomy or a specifically created incision culdotomy at the time of a uterine-sparing procedure; and then abdominal morcellation, which can be performed through the umbilical port site during a laparoscopic procedure or through a mini-laparotomy created at a site distant or a de novo site unrelated to the laparoscopic port site incisions. Each of these procedures have been described in the literature, being performed within a bag, but there are very few such reports.

Electromechanical morcellation is performed laparoscopically, as we heard at the onset of this meeting, with a device that's designed to fragment the tissue into retrievable-sized specimens. It was first approved in 1995. It uses a spinning circular blade. And there's one device, as mentioned, that uses radiofrequency energy. And when looking at safety outside of the issue of dissemination of tissue, there are multiple studies that demonstrate the safety and efficiency of this when performed by experienced surgeons.

However, as with all technologies and procedures, there are potential complications. This is a very recent study by Milad that was just published in the May issue of the *Journal of Minimally Invasive Gynecologic Surgery* that reports on a review of the medical device reporting in the Manufacturer and User facility Device Experience, frequently referred to as

the MAUDE database. And it may be difficult to read, especially in the back of the room, but there were 55 reports identified in the review of the literature over a 15-year time frame.

Now, we all know that the limitation of the MAUDE database is that it's a voluntary reporting system, and so clearly the incidence is probably much higher than that. However, when looking at those 55 cases that were voluntarily reported, the most common complication reported was a visceral injury related to the bowel, predominantly to the large bowel, and there were also vascular injuries to a variety of vascular structures. There are also reports of retained and parasitic tissues as well as six deaths that were reported to the MAUDE database.

Vaginal morcellation is a technique that has been done for decades and decades. This is a commonly performed technique performed traditionally during vaginal hysterectomy. And then, with the advent of laparoscopically assisted vaginal hysterectomy or total laparoscopic hysterectomy where the specimen is too large to simply pull through the vaginal tube, it's now performed in concert with minimally invasive surgical approaches as well. It's performed with a scalpel and generally uses coring or bivalving techniques. These techniques tend to leave the majority of the outer covering or serosa of the uterus intact and, perhaps importantly, is performed outside of the peritoneal cavity in the vagina.

However, it's unclear whether or not this confers any safety

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advantage as it relates to the dissemination of tissue. And as highlighted by the presentation about the incidence -- potential incidence, many of the studies that talk about leiomyosarcoma identified at the time of morcellation do not distinguish or clarify very carefully by what route those specimens were morcellated. So we really don't know whether or not this technique confers any safety or is devoid of risk.

And then, finally, mini-laparotomy morcellation. Again, this is essentially the same technique that's used when vaginally morcellating, but done through an abdominal incision. So in an effort to reduce the morbidity associated with large abdominal incisions, a smaller incision is made. Frequently, a circumferential wound retractor is placed into that incision so the abdominal wall itself is protected from the specimen. And then similar coring techniques or bivalving techniques which leave the serosa intact are employed in order to remove large specimens through small incisions. And, again, there's no data specifically related to the risk of dissemination with this technique either.

So hopefully, well within my 20-minute allotment, I'd like to summarize by saying that minimally invasive surgical approaches to gynecologic surgery have multiple well-established advantages over laparotomy. Hysteroscopy remains an appropriate manner to remove symptomatic submucosal fibroids. In procedures that require it, morcellation can be safely performed by experienced surgeons. And there are risks to

morcellation, including visceral or vascular injury and dissemination of tissue fragments.

Thank you. And I'm happy to field any questions.

DR. DIAMOND: Okay, I would like to thank Dr. Sobolewski for his presentation.

And will be asking the Panel if they have any clarifying questions, remembering again that we will have an opportunity to ask questions during the deliberations this afternoon.

Before I open the floor to questions, though, perhaps you could describe, for some members of the Panel that are not physicians, who have not seen the morcellation device, how the tissue is actually removed from the abdominal cavity with the use of the morcellation device.

DR. SOBOLEWSKI: Yes. So the morcellators are an outer cannula tube with an inner tube, the end of which is sharpened similar to a scalpel. So it's a hollow circular scalpel. Under direct laparoscopic visualization through another port, this tube, cannula, and circular scalpel is inserted through an abdominal incision. Through the center of that cylinder a grasping instrument is passed, the specimen is grasped, brought up to that circular scalpel or circular blade, a foot pedal or a trigger is activated, and the blade spins as you withdraw the specimen into the tube. So, long cylindrical pieces of tissues are removed with this process.

DR. DIAMOND: Thank you.

I saw a question. Dr. Brown.

DR. BROWN: So in the MAUDE database, where you showed the data about visceral injuries as well as six deaths, what is the denominator in terms of the number of cases? So there were six deaths out of how many patients in that database?

DR. SOBOLEWSKI: All right. So the MAUDE database, again, is just a voluntary reporting of complications potentially related to a device.

DR. BROWN: Correct.

DR. SOBOLEWSKI: So the hospital or surgeon has to report it. I don't think we know what the denominator is. So there were 55 events related to morcellation that were reported to the MAUDE database, including six deaths.

DR. BROWN: Do we have any -- can you make any estimate of the denominator? So how many morcellating -- you know, or knowledge of how often this is used. Can we get any estimate about the incidence of those deaths?

DR. SOBOLEWSKI: I think that's an excellent question. You know, the gentleman from Ethicon had quoted 50,000 procedures annually, but I don't know where that comes from. There is no CPT or ICD-9 code to identify the use of a morcellator. I would venture to guess close to all laparoscopically performed supracervical hysterectomy patients are discharged to home prior to 24 hours. So trying to get the denominator is a

critically important aspect of trying to get our arms around this issue, and I don't know that I or anyone else really has the answer of how to do that.

DR. DIAMOND: Do you have information on those six deaths? Do you recall that?

DR. SOBOLEWSKI: So as I recall, I do have the study in my laptop, which I can review to make sure and I'll clarify this afternoon. But I believe that they were all related to vascular injury.

DR. DIAMOND: Okay, thank you.

Let's see.

DR. YUSTEIN: Dr. Diamond, if I can just make a comment on follow-up to Dr. Brown's question.

Dr. Brown, in my talk this afternoon, I'll be talking a little bit more about the MDR database, and one of my take-home messages is that we shouldn't even be attempting to use those numbers to calculate any incidence or rates of any event due to significant limitations with a passive surveillance system. So I would probably stay away from that.

DR. SOBOLEWSKI: That's an excellent point.

DR. DIAMOND: Okay, thank you.

Dr. Talamini.

DR. TALAMINI: Hi. Talamini.

This morning, as we saw, Ralph Clayman's initial description of using a morcellator was with a bag, and it's obvious that we've migrated from

that. Can you tell me why you think we've migrated away from the use of a bag? Number one. And, number two, if you were to estimate now what percentage of cases actually do use a bag in some manner, what that number would be, what would you guess?

DR. SOBOLEWSKI: I think, since April, that number is much higher. I think it was probably a miniscule amount previously in the benign gynecology community. In the gynecologic oncology community, it's not uncommon for laparoscopic and known endometrial cancer patients to have the specimen put into a bag and morcellated transvaginally within a bag.

I think that there are two reasons that we've gone away from the initial description "within a bag." One is the variable size of the specimens that we're dealing with. So trying to place a uterus that is the equivalent of a four-month gestational age into a bag is difficult, if not impossible at times. And having a system, such as the one that was shown earlier, that really doesn't require us to fit something inside of something but rather protects the whole abdominal cavity might be a very novel approach to that problem.

Secondly, I think that even when it's in a bag, being able to visualize the spinning blade is encumbered because you're looking at the outside of the bag with a laparoscope, and it's disconcerting, to say the least, to have a spinning scalpel inside of something without being able to directly visualize it.

So since this issue has come to light, there have been a variety of techniques described that involve using smaller bags to put the specimen into it, puncturing or perforating that bag with a trocar that has a balloon on the end of it in an attempt to kind of seal the puncture that you've just created, and putting the laparoscope through that trocar on the side of the bag so that you can watch yourself as you morcellated it.

So I think that one very positive outcome of this is that there will clearly be innovation around this problem and one that will hopefully enable us to continue to offer a beneficial approach to this problem to patients while simultaneously mitigating the risk that's identified in terms of tissue extraction.

DR. DIAMOND: Dr. Wentzensen.

DR. WENTZENSEN: Nicolas Wentzensen, NCI.

You showed kind of the adverse events of conventional hysterectomy. I didn't see any numbers on deaths, and those are probably extremely rare. Can you attempt to quantify that or to say it's at least -- it's certainly below a certain -- like one in number. And the related question is, do you think that the population that is currently preferentially treated with morcellation has a somewhat higher risk of adverse events than conventional hysterectomy?

DR. SOBOLEWSKI: Let me start with the first question. So I debated quite profusely -- if that's the right word -- about whether or not to



include a study that has been included in some of the statements from our specialty societies. And this is a study that was a large retrospective cohort using the inpatient data sampling that did find a difference in mortality between abdominal and laparoscopic patients. The problem is that there were some errors in one table of that publication.

I spoke to the study author. They have submitted an erratum to the publisher, and that erratum did not affect the p-values and statistical significance of their conclusions. But because that was not publicly available and something that could also be opined by the members of this Committee, I felt it was probably inappropriate for me to include that as part of the presentation.

So having said that, if the erratum was published and it was felt to be a sufficient conclusion, then the difference would be an odds ratio of about 0.49. So laparoscopic procedures -- the mortality favors a laparoscopic procedure with an odds ratio of 0.49.

There is a study out of the *British Medical Journal* from 2004. It's called the VALUE study. The VALUE study did not specifically comment on mortality, but it did report that there were 14 mortalities in that cohort. It was a prospective cohort study. And there's a statement in the study that says, "And there were no mortalities in the laparoscopic group." So one could assume that those 14 mortalities were in the abdominal group, and that results in an almost 4 per 1,000 mortality rate -- abdominal. But, again, that

probably wasn't powered to find that difference.

DR. WENTZENSEN: And the question of whether --

DR. SOBOLEWSKI: Oh, sorry. Yes.

DR. WENTZENSEN: -- morcellation group has a higher risk of adverse events or not, in your opinion.

DR. SOBOLEWSKI: So that same VALUE study did look at -- actually, it may not have been that study. There's another prospective study that -- oh, it was a thromboembolic event study. It's a Finnish study that looked at the incidence -- the appropriate use of pharmacological thromboembolic prophylaxis and found that patients whose indication was fibroids actually had a higher incidence of complications. And I think that, as is true of any surgery, as the anatomy changes and becomes more challenging and more difficult, then the potential for complication increases.

Not all fibroids are the same. I know that this Panel looked at the EVALUATE trial, specifically at thromboembolic events, and there was no difference between abdominal or laparoscopic in that study. But they excluded patients with uteruses greater than 12 weeks. So that's not the population that we're typically dealing with.

So as the anatomy increases, as the difficulty of the surgery increases, I suspect that there is a greater risk for complications in general.

DR. DIAMOND: Dr. Mattrey.

DR. MATTREY: Thank you for the descriptions.

I'm not a surgeon, so I'm imagining what is happening. For a morcellator to be used, I assume that the organ has already been dissected away from its blood supply and everything else and placed in a bag, if one is using a bag.

DR. SOBOLEWSKI: Correct.

DR. MATTREY: Okay. So the opportunity for hematologic spread is not real.

DR. SOBOLEWSKI: So the opportunity for iatrogenic hematologic spread would not be present directly related to the morcellation.

DR. MATTREY: Right.

DR. SOBOLEWSKI: If anything would have caused hematologic spread, it would have been the dissection that was done prior to the morcellation.

DR. MATTREY: So there was also data presented that doing morcellization through a hysteroscope also had no risk for spread. And I don't remember who presented data, but there was like a 2% or 3% spread with hysterectomies without morcellization. So I'm assuming, is hematologic spread also a risk? Because the reports are all intraperitoneal recurrences, not pulmonary nodules like we used to see in the old days, a rare case of diffuse fibroids in the lungs.

DR. SOBOLEWSKI: Yes. I think that, traditionally, I know from my early education, my understanding was that the predominant mechanism

of metastases of sarcoma was via a hematologic route of spread. But I think that is clearly -- I'll defer to Dr. Cohen and his presentation. But the fact that the few case reports that are out there describing the incidence or upstaging of leiomyosarcoma following morcellation, as you mentioned, typically describe localized spread, intraperitoneal spread, I don't know that the hematologic route -- that we could conclude that the hematologic route is involved. But I certainly don't know the answer to that question -- and perhaps are leiomyoma.

DR. MATTREY: Is there data that talks about the risk for hematologic spread and what that is?

DR. SOBOLEWSKI: I don't know.

DR. DIAMOND: Dr. Hillard.

DR. HILLARD: Thank you for your presentation.

Can you tell me what we know about training, in terms of use of power morcellators? And to resident education in particular, are there any data about -- are all residents being exposed to it or half of residents that are being trained currently? And then, in addition, how would someone, a clinician in practice who wanted to use a power morcellator, learn how to do this technique?

DR. SOBOLEWSKI: To my knowledge, although I used to be a residency program director -- it's been about eight years or so since I've held that esteemed position -- to my knowledge, there is no specific requirement

from CREOG or RRC or any other body that mandates training specific to morcellation as part of a residency training program. So it would be similar to any other technology or surgical instrument that's used. It would be an apprenticeship model of training as opposed to any specific curricula that is required.

DR. HILLARD: So this is not currently being tracked by CREOG, to your awareness?

DR. SOBOLEWSKI: It is absolutely not being tracked by CREOG.

DR. DIAMOND: Ms. Aronson.

MS. ARONSON: I'm Diane Aronson.

I'm not sure if this is the appropriate time to ask this question, but can you speak a bit about the informed consent with these surgical options and if there's any general informed consent that's used or how it's done and when it's done?

DR. SOBOLEWSKI: So informed consent, as you probably know, is not a uniform process that's done via any particular clear set of required guidelines. I think that there are obvious commonsense things that should happen during an informed consent process, but there is no specific requirement by any type of governing or societal body society meeting, ACOG or others, that guide us or remotely mandate that these are the elements that need to be in place for appropriate informed consent during -- when counseling patients.

Now, the AAGL position paper does speak to some extent about informed consent and alludes to some of the important features, including advising the patients of the risk specifically for dissemination of either benign or malignant disease. But to suggest that there's any uniform consensus and that it's happening the same way by gynecologic surgeons across the country is not likely.

DR. DIAMOND: Dr. Iglesia.

DR. IGLESIA: Cheryl Iglesia. Thank you for your presentation.

My question -- you know, and I've read the position statements of AAGL, ACOG, SGO, and I understand that Duke has a recommendation to enhance their informed consent process at your medical center. But at the end of the day, there is shared decision making and surgical judgment. And as an expert gynecologic surgeon, what in your opinion would be scenarios where the risks of laparoscopic morcellation outweigh the benefits? You know, the first picture that you showed was a very large -- it looked a 20-week sized uterus. But do you have, like, guidance?

DR. SOBOLEWSKI: You know, I think that there's clearly interest, and it would not surprise me if there are attempts to create more specific algorithms using a more rigorous evaluation of the science to help us to risk stratify our patients.

The patients that we've already heard, that postmenopausal patient with symptoms that are changing frequently -- at least at our

institution, if we're contemplating a minimally invasive approach to a myomectomy, all of our patients get a preplanning MRI, in part because it's not uncommon for patients to come with an ultrasound that says they've got just a couple of dominant fibroids, and you get an MRI and the radiology report reads "innumerable fibroids" because there are multiple small sub-centimeter fibroids that aren't necessarily detectable on routine ultrasound scanning. And so that helps us to counsel the patient as to the appropriateness for minimally invasive or open approach. And, certainly, if an MRI comes back with any worrisome findings -- so any suspicion of malignancy. And that's stated in both ACOG and AAGL.

But as this Panel has queried and commented upon before, there are no reliable methods, preoperatively, to determine. So I think that the focus probably needs to rely more on how can we make the ability to extract tissue in a minimally invasive way safer and eliminate the risk associated with dissemination.

DR. DIAMOND: Dr. Isaacson.

DR. ISAACSON: Keith Isaacson.

Craig, that was a great presentation. Thank you.

I'm interested in your comment on the postmenopausal patient with symptoms. Would you look at a postmenopausal patient with fibroids who is on hormone replacement therapy versus one who is off hormone replacement therapy? Would you look at them differently when considering

the risk of sarcoma and your method of treating their disease?

DR. SOBOLEWSKI: You know, Keith -- Dr. Isaacson, I think that all of us -- all of our thinking around this issue has changed with this realization. And that is perhaps a shame on us in the past, but certainly, thank goodness, going forward in the future -- and, you know, I think that currently, with the status of things the way that they are, I would look at those patients similarly. I don't know that we have enough data to understand the effect that hormone therapy has on either a benign fibroid or a leiomyosarcoma, to know whether or not that risk stratifies those patients differently.

So I'm very much looking forward to the development of products or techniques that will allow us to offer those two women the same procedure without the fear of disseminating their disease. I'm sorry, that's not a very specific answer to your question.

DR. DIAMOND: Dr. Simon.

DR. SIMON: Thank you for your talk on morcellation for those of us that don't do that procedure.

As we are introduced to some approaches to mitigating risk, bags, in particular, seems to be one thought on it. Can you share with us -- would we find patients where a bag actually could not be used, could not be deployed? And is that something that, for whatever reason, adhesions or whatever scenarios that you can envision -- if you could share those sort of



the top of your head.

And then, along the same thought process, for those patients where a bag could not be used, could you envision a population where that impediment would be something that wouldn't be prescreened, where you would find yourself in a situation where you've committed yourself to a laparoscopic procedure and now cannot deploy the bag and this is not something that would have been foreseen at the outset? I'll let you answer.

Thank you.

DR. SOBOLEWSKI: So, currently, the biggest impediment is there is a relatively limited -- there are relatively limited options in terms of the size of bags that the current manufacturers make. And some of the greatest advantages of laparoscopic procedures are afforded to women who have massively enlarged uteruses, because the alternative is not just an open incision, but it's typically an open vertical incision that extends from the symphysis up above the umbilicus, up above the belly button, so a sternum-to-symphysis type incision. And there are ways to laparoscopically still detach the uterus from its attachments and then, through a small transverse mini-laparotomy incision without a power morcellator, remove that.

And so instead of a several-day hospitalization with a large wound and potential complications related to immobility and all of the other things, you get a patient out in 24 hours and they're ambulating and don't have the same wound complications. And to envision a way to -- again, with

the exception of Dr. Shibley's system -- to figure out a way to put that into a bag is unfathomable at this time.

Adhesions and those sorts of things really are more of an issue as it relates to the initial procedure and not so much with the morcellation. So once the specimen is detached, it's really just a matter of finding a bag that's large enough that you can manipulate it into and then contain it that way.

DR. DIAMOND: I'd like to ask you a question, which is, in your knowledge and in your review for the session here today, did you come across much information which talked about the likelihood of non-malignant fibroids, which have undergone morcellation, having implantation and the likelihood of those causing complications in patients?

DR. SOBOLEWSKI: I'm not sure I understand your question.

DR. DIAMOND: So benign fibroids that then undergo morcellation --

DR. SOBOLEWSKI: Right.

DR. DIAMOND: -- do we know anything about how often they have implantation on peritoneal surfaces and the complications that those cause and the timing over which those complications may occur?

DR. SOBOLEWSKI: So benign leiomyomatosis or peritoneal dissemination of benign disease, such as fibroid fragments or endometriosis tissue. I'm aware of about eight peer-reviewed articles, most of which are

individual case reports. And so it's impossible to reach a conclusion about the incidence of that problem. Again, without something like a registry, it's all voluntary reporting.

So I suspect it happens much more frequently than what's reported in the literature, and what's in the literature is very minimal and sporadic. Again, I came across eight publications with small numbers, some of which were just single case reports.

DR. DIAMOND: And those were related to fibroids or exclude the endometriosis, if you would?

DR. SOBOLEWSKI: Most were related to fibroids, but I can't remember the number off the top of my head. Sorry.

DR. DIAMOND: Thank you.

Dr. Isaacson, you had a question, I believe.

DR. ISAACSON: Not really. I assume we'll get into a discussion on bags, but it was a question about bags, and this may not be the right time for that.

DR. DIAMOND: I'm not sure we have a specific time to talk about bags.

DR. ISAACSON: Then this would be a good time. You know, we've discussed that we all think, intuitively, it's better to put the specimen in a bag. However, I think, as you pointed out, there are no data to suggest that, number one, you have a better outcome if you put it in a bag.

And, number two, I was going to ask you, anecdotally, if you are familiar with any complications that have happened as we've all tried to, in the last six months, put these large specimens into a bag. And complications would include morcellating a portion of the bag, damage to the surrounding viscera, and actually holes in the bag so that the bag is rendered really relatively useless.

So I think if we're going to go down that road, we're going to need to start another MAUDE database with bags and the complications of putting it in, because it really, really is not simple to do. We make it sound simple. And when Dr. Simon brings up the question that this is a very, very technically challenging procedure -- maybe not to Dr. Shibley, who has done so many, but for those of us who are starting out, to put them in a bag. So it was really just asking for your comment on that.

DR. SOBOLEWSKI: No, it's a good question. So as you probably know, your colleague, Dr. Einarsson, published a small sort of feasibility study that reported no complications and is currently involved in a multi-institutional study looking more specifically at the safety and feasibility.

Just from speaking to colleagues and reading on the AHLA listserv and things like that, I've not heard of any complications. But I would echo your sentiment that taking a slippery, round, firm mass using small pincer-like instruments and trying to get it in a bag that doesn't open up on its own is very challenging. And if you weren't a surgeon in the middle of

trying to do it, it would probably almost appear comical to watch the frustrations that we sometimes go through trying to get those specimens into the bags.

DR. DIAMOND: Dr. Snyder.

DR. SNYDER: Dr. Snyder.

I think Dr. Isaacson's question was twofold, too. So, yes, there are just the issues of trying to get the specimen in the bag. But then there's the issue of the ability to safely morcellate in the bag. And beside Dr. Shibley -- you know, the accretion of a separate pneumoperitoneum in there. But I think there's a lot of people on the Panel that need -- would like to hear your anecdotal experience just with the comfort level of not being able to see what you're morcellating if you don't have the scope in the bag with the morcellator.

DR. SOBOLEWSKI: I personally wouldn't do it. If I couldn't directly visualize the end of the scope, I simply wouldn't do it. I do have experience with the technique that Dr. Einarsson described. And I will tell you, it's frustrating to get it set up. But once you have it set up, in many ways it's easier. So once you have the specimen contained within the bag and you're watching from the scope, the specimen can't go anywhere, like it can when you're morcellating outside of a bag.

And so once you're set up, in some regards, it's not only potentially minimizing the risk of dissemination, but may also minimize the

risk of some of the other kinds of complications that were described in the albeit terrible MAUDE database as it relates to visceral injury and other things, because you're contained now.

DR. SNYDER: And just to follow on. You know, again, the suggestion was that we might need a separate MAUDE database. And even though we understand the limitations of that database, of the ones that are there now, those 55 complications, was there any identification of how many of those complications occurred with morcellation in a bag versus not a bag?

DR. SOBOLEWSKI: Not as I recall reading through that paper, no. I now would guess none were in a bag. That would just be my guess.

DR. ISAACSON: Just in the last six months, I'm aware of at least six complications within a bag --

DR. SOBOLEWSKI: Really?

DR. ISAACSON: -- including a bowel injury, two incarcerated hernias, a vascular injury, and then having to go back. And this is only within three institutions. So it's like the MAUDE database, where right now it's probably underreported, we haven't really encouraged people to report those.

DR. DIAMOND: Ms. Aronson.

MS. ARONSON: Diane Aronson.

I was wondering about your comment about an algorithm and usage and also about adhesions that you've mentioned. For women who may

have gone through multiple procedures for infertility, laparotomies, or just a series of tests and exploration surgeries, can you comment a bit about those candidates considering this option?

DR. SOBOLEWSKI: You know, I didn't get into that. There is evidence to support the fact that a laparoscopic approach is associated with less adhesion formation compared to that same operation done through a traditional open incision. And so when patients are coming back in for multiple procedures, in order to avoid further adhesion formation, if feasible, it's preferable to do those operations laparoscopically in order to minimize the risk of subsequent adhesion formation going forward.

Having said that, that's one of those anatomic-distorting situations that increase the potential difficulty and, therefore, risk of the surgery. But as it relates specifically to the use of the electromechanical morcellator, again, all of that anatomic distortion really makes the primary procedure more difficult. Presumably all of that anatomy had to be normalized in order to accomplish your surgery, and now that that's been accomplished, then it's just the task of performing the morcellation. So I don't think that that would specifically result in a contraindication or a recommendation that morcellation not be considered.

DR. DIAMOND: Other questions from the Panel?

(No response.)

DR. DIAMOND: Okay, thank you, Dr. Sobolewski.

DR. SOBOLEWSKI: Thank you.

DR. DIAMOND: So we now have a decision to make, if you'll just give us a couple seconds to do so, whether to try to put in another presentation or go to lunch.

LCDR ANDERSON: We're going to go to lunch.

DR. DIAMOND: We're going to go to lunch. And we'll reconvene, then, rather than at the prescheduled time -- lunch was scheduled for 45 minutes -- I would say 12:45. Does that sound reasonable?

LCDR ANDERSON: Let's do an hour. At one o'clock.

DR. DIAMOND: You want to do an hour, at one o'clock? All right. All right. So we will reconvene at 1:00 pm. Thank you.

Let me just say one other thing, which is that, Panel members, please remember to not discuss the meeting topic during the lunch amongst yourselves or with any members of the audience. And we also ask that all the Panel members return on time. Please take personal belongings with you at this time, as you will not be able to get back into the room until we reconvene.

(Whereupon, at 11:58 a.m., a lunch recess was taken.)



AFTERNOON SESSION

(1:04 p.m.)

DR. DIAMOND: All right, it is now about 1:04, and I would like to resume the Panel meeting.

We will now proceed with our third invited speaker. I'll invite FDA's Elaine Blyskun to now introduce our third invited speaker, Dr. Susan Ascher, on the agenda topic of radiological considerations in uterine fibroid disease.

MS. BLYSKUN: Thank you.

Dr. Susan M. Ascher is a Professor of Radiology at Georgetown University School of Medicine and the Co-Director of Abdominal Imaging at the Georgetown University Hospital. Dr. Ascher graduated from the Weill Cornell Medical College and did her diagnostic radiology residency at Yale-New Haven Hospital. After completing an abdominal imaging fellowship at Georgetown University Hospital, she joined the radiology department. Her clinical duties and research efforts have focused on gynecologic imaging. Dr. Ascher has served as a medical advisor in the United States Office on Women's Health in the Department of Health and Human Services. In that capacity, she helped further development and promotion of breast MRI. She is also a fellow of the ISMRM and has been both a panelist and moderator of the RNSA Sunday Unknown Film Panel.

Dr. Ascher was a member of the Reproductive Endocrinology

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Committee that formulated the new American Board of Radiology Core Curriculum Exam. She recently completed her term as the Women's Imaging Editor for *RadioGraphics*, where she chaired their Women's Imaging Educational Exhibit Committee. Dr. Ascher was a co-editor of the 2012 *RadioGraphics* Monograph: Gynecologic Imaging Across the Life Span. Her current society roles include board member of the Society for Computed Body Tomography/MR, and Chair, Collaborative Committee ACR-SAR-SPR Practice Guideline for the Performance of Magnetic Resonance Imaging of Soft-Tissue Components of the Pelvis.

Dr. Ascher will be reviewing information related to the imaging of uterine leiomyomas and leiomyosarcomas.

Dr. Ascher.

DR. ASCHER: Good afternoon. In the next half an hour or so, I'm going to be speaking about the imaging of leiomyomas or fibroids and leiomyosarcomas.

As a disclosure, my spouse has a professional relationship with Johnson & Johnson which is unrelated to the devices under discussion today.

I'm an imager, so a picture is worth a thousand words. And so if you'll bear with me, I'm going to show you some cases just to illustrate what we're talking about today.

You have three images in front of you. These are MRI images of the uterus in three different patients. On your left is the normal uterus, in

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the middle is a patient with a fibroid, and the right is a patient with a leiomyosarcoma.

Now, the middle patient, I hope the lights aren't really that low and I hope you can appreciate it, but there's a well-circumscribed low signal intensity or dark mass in the uterus, and it's very well circumscribed, and we can see it quite easily versus the patient on the right that has an irregular heterogeneous mass. And I would submit that looking at these two cases, you might not know the diagnosis, but you do know that they're different entities. So that's your tutorial. Here's the quiz.

On your left, we see a well-circumscribed dark mass in the uterus, and on your right, we see a heterogeneous mass in the uterus. If you had to decide which one was a fibroid and which one was a sarcoma, I think many of us would get this correct, and we'd say fibroid on the left and sarcoma on your right.

Similarly, we have a sagittal T2-weighted sequence of the uterus on your left, with a well-circumscribed dark mass, and on your right, we see a very heterogeneous irregular mass. Again, it's fibroid on your left, sarcoma on your right.

But it gets more complicated. And on your left, we see another patient and she has an ovoid mass that's heterogeneous in her cervix, and on the right is a different patient that also has a heterogeneous mass, and it's somewhat irregular. If you had to come down on what these were, you might

be tempted to say that it was a fibroid on the left and a sarcoma on the right, but you'd be wrong. In fact, it's a sarcoma on the left and it's a fibroid on the right. And therein lies the challenge of trying to distinguish degenerated fibroids from leiomyosarcomas.

If we look at the imaging modalities available to imagers and radiologists and ultrasound -- rather gynecologists -- often ultrasound is the initial modality to evaluate a patient in the pelvis. But it suffers from decreased contrast and spatial resolution, it is clearly operator dependent, and it's limited by a patient's body habitus.

CT does not have the contrast resolution necessary to be able to distinguish between the different types of masses in the uterus, and it has ionizing radiation.

Certainly P-E-T, or PET, is a promising modality for confirmation of a suspected mass. It can also identify metastases and recurrent leiomyosarcomas, but it is not widespread in availability, and there are known false positives.

So that really leaves us with MRI, and it's certainly the most promising modality we have to date, but the accuracy, sensitivity, specificity, positive predictive value, and negative predictive value for distinguishing fibroids from sarcomas have not been established in a large multi-center trial.

These are the usual features of a typical, what I call usual, leiomyoma or un-degenerated fibroid. And we know that they're composed

of whirls of smooth muscle cells with intervening collagen. And on your left is a T1-weighted sequence, and you really can't make out the fibroids because the fibroid has the same color, if you will, as the rest of the uterus.

But what we're looking for is a well-defined mass that is low in signal on this T2-weighted sequence. And there's another little fibroid anteriorly in the myometrium. Moreover, when we give contrast, which is part of our usual imaging armamentarium, fibroids are viable and they enhance. So that's the normal.

We also recently added, in our imaging armamentarium, diffusion-weighted imaging, and that exploits the Brownian motion or the random motion of water molecules. And it's really a function of intact cell membranes and cellular density. As a radiologist, we have a picture which we call the diffusion-weighted picture, and then we have a quantitative ADC map. And what we're looking for in malignancy is that the high cells or the increased number of cells in a malignancy impede that random motion of water. As such, we can image that on imaging, and we also can get a quantitative value, which we call the ADC map. Unfortunately, diffusion-weighted imaging, while promising, does have overlap with benign fibrosis, abscess, and cytotoxic edema.

So here I'm trying to show you an image using diffusion-weighted imaging. On your left, you have a uterus. I'm pointing those yellow arrows to two fibroids. And then on your right are these dark holes in the

uterus. On the top is the diffusion-weighted image, and on the bottom is the ADC map. And that blackout sign where it's dark on both of those images tells me there's no restricted diffusion; hence it's unlikely to be a malignancy.

But the challenge really is the degenerated fibroids. We're really good at finding usual fibroids. But fibroids like to degenerate, especially when they get larger. And typically they outgrow their blood supply for a whole host of reasons. And the type of degeneration depends on the degree and the rapidity of that vascular insufficiency. The main types of degeneration we talk about on imaging are hyaline; cystic; myxoid; or red or carneous degeneration, although there is hemorrhagic degeneration, calcific degeneration, coagulative necrosis; and as was alluded to earlier, whether or not there is true sarcomatous degeneration of a fibroid.

Another type of fibroid, while not typically degenerated but is sort of atypical in its appearance, is the cellular fibroid, which is composed of smooth muscle cells with little or no intervening collagen. And that can often be mistaken or occasionally be mistaken for a sarcoma.

I tried to put together a chart of the different imaging features of the different types of fibroids, going from usual all the way down to sarcomatous. And while it's nice to put things in boxes, it's really a convention and it's somewhat contrived because not every type of fibroid fits into a nice conventional imaging protocol.

This is a degenerated or a fibroid that's undergone red or

carneous degeneration, and it has a very specific imaging feature. On your right, you'll see that I have a T1 FS. That's a T1-weighted fat-suppressed technique, and it shows a bright rim around the fibroid. That rim is low on different sequences. This fibroid does not enhance following contrast. And on the diffusion-weighted imaging there's not a full -- there's not a lot of restricted diffusion. This is a very classic red degenerated fibroid.

This is another type of fibroid, again, not classically degenerated, but the cellular or an atypical fibroid. And it's hard to see, but it is well circumscribed, though it has the same color or the same signal intensity as the rest of the myometrium. That's what other usual fibroids look like; they're dark in signal as opposed to this cellular fibroid, which is bright. We don't see it on the T1-weighted sequence, which is common.

But I draw your attention to the two lower panels. On your left is the diffusion-weighted image, with the corresponding ADC map on the right. And you'll see that that arrow is pointing to a bright thing on the left, which falls in signal on the right. And that is classic for restrictive diffusion, even though we know that this is a cellular fibroid and not a sarcoma. Moreover, this fibroid enhances markedly. It's very hypervascular, which is another thing that has been associated with sarcomas but is not only specific to sarcomas.

This is the case I showed you earlier. I showed you the image on your left. And I would say, if this came across my PAC station any day of

the week, I would read it the same way. It is an irregular heterogeneous mass on T2-weighted sequences. And while it doesn't have any blood in it, it has very variable enhancement. That's the panel on your right. And when this patient went to hysterectomy, there was no sarcoma. There was coagulative necrosis and carneous degeneration. And I've also included the diffusion-weighted imaging and ADC map, which in an imager's mind would say that there was some restricted diffusion. Again, many worrisome features, but at hysterectomy, no sarcoma was found.

So distinguishing degenerated fibroids from sarcoma is challenging. And, unfortunately, there are no large prospective studies to look at this, and there are no large retrospective studies to look at it.

And if you look at all the studies going from 1998 forward, I found about 60 cases in total of leiomyosarcomas, but these sarcomas -- these leiomyosarcomas were grouped with other sarcomas in most of the studies. And between these nine studies that I'm going to speak about, there were different imaging protocols in terms of magnet strength, sequences performed, and whether or not IV contrast was given to the patient, how it was given, and when the patient was imaged after the injection of contrast. Moreover, these studies assessed different parameters. So there's really no uniformity even within studies nor between studies.

And this is just a chronologic view showing you what the study was, how many patients were in it in terms of leiomyosarcomas, the criteria



and the findings, and then any data or any statistics that were provided. And the earliest one was in 1998, where they looked at 45 patients who had either four leiomyosarcomas or some other complicated or uncomplicated fibroid. And they found only a 69% chance -- or accuracy, rather, for overall identification of subtype.

In 2001 they tried describing sarcomas. There was a mixed population of sarcomas, and the overwhelming findings were that they were heterogeneous with variable signal intensity and that they enhanced.

The only prospective study that I found was Goto et al. in 2002, that looked at conventional imaging, contrast-enhanced imaging, and then combined that with LDH serum values. And in that study, whereby there were 10 leiomyosarcomas and 130 degenerated fibroids that were not sarcomatous, you can see the accuracy, sensitivity, specificity, et cetera, listed. That was followed by Tanaka et al. in 2004, who, looking at a combination of imaging features, had an 88% accuracy for diagnosing sarcomas.

Again I apologize. I know these are somewhat cumbersome but trying to get a lot of data. But as we go from 2008 downward, we're seeing the addition of functional imaging, that diffusion-weighted imaging and ADC map that I spoke about. And it looks as though, if you look at the two final studies, the Thomassin-Naggara study and the Sato et al. study, by looking at diffusion-weighted imaging, whether something is bright or not on the

diffusion-weighted image, corresponding that with the ADC map, whether that's low or high, they were able to stratify patients in terms of whether they were high risk or low risk and whether or not they had sarcoma. And as you can see, the accuracies are 92.4% and 94.6%; a sensitivity in that last paper that recently came out, I guess, in April or May, of 100%; and, again, negative predictive value of 100%, positive predictive value of only 66.7%, and a specificity of 94%.

And, again, that's a lot of words, so I'm trying to illustrate this more schematically. This is from the Thomassin-Naggara group. This is their partition model, which was trying to differentiate between benign fibroids from either unknown malignant potential tumors or frankly malignant tumors. And they only looked at patients that had a single lesion. They didn't have multiple presumed fibroids. They just had one lesion.

So they had a single myometrial tumor, and if that tumor had high signal intensity in what we call a diffusion-weighted image, they looked then at the T2-weighted signal intensity. And if that signal intensity in that T2-weighted image was intermediate or high, then they looked at this thing called the ADC value. And if that ADC value was low, suggesting that this had restricted diffusion, they were able to correctly classify 28 out of 32 tumors. They did have two false negatives -- one was a recurrent sarcoma and one was a stromal cell sarcoma -- and two false positives that were degenerated fibroids.

This is that most recent paper, Sato et al., and based on the signal intensity of a lesion on the diffusion-weighted image, plus its ADC value, they were able to classify patients according to a high-risk group or a low-risk group. In the low-risk group they had no sarcomas. So they had true negatives, but they had no false negatives. In the high-risk group, of the 15 lesions that were considered high risk, 10 were leiomyosarcomas. Their false positives were these cellular fibroids, again, not classically degenerated but an usual sarcoma -- I mean a rather unusual fibroid -- and they also had one atypical leiomyoma. So in their classification scheme they were able not to have any false negatives.

I'm just going to leave you with a few more slides. Again, a picture is worth a thousand words. I showed the image on the left initially, and you can see the corresponding images. This is a very florid leiomyosarcoma. It is heterogeneous in signal intensity. It has areas of hemorrhage and it has areas of necrosis.

This is an image also of the patient that I showed you, and you can see multiple T2-weighted sequences on the left -- on the top, rather. On the bottom -- again, I apologize, they were supposed to cut the lights a tad more -- you can see that it's a heterogeneous mass that has areas that are not viable following contrast.

And this last case is from Thomassin-Naggara's article, the top panel showing you conventional imaging, the T2-weighted sequence, which

shows a heterogeneous mass; the T1-weighted sequence, which says there is hemorrhage and blood in this lesion; the last, the underlying row on your left, showing that this lesion is viable in parts and it has restricted diffusion according to the diffusion-weighted image and the ADC map.

So where does that leave us? Well, I think, as we've heard today, some potential questions that we can pose may be -- or potential areas of research in terms of the need for a registry of some sort, maybe an imaging library. As radiologists, we probably need an imaging lexicon so that when we describe a lesion, we're all speaking about the same thing. And maybe even assign something, a fibroid score, whether we know it's a definite usual fibroid versus something that we're more worried about and could be a sarcoma. And, clearly, when overlooking all the trials that have been done, we really do need a large multi-center prospective trial with uniform exam parameters.

So, in conclusion, I hope I've given you a brief overview to show you that the features of usual leiomyomas are well established. Florid leiomyosarcomas are routinely detected because they are ill defined, heterogeneous, necrotic, hemorrhagic, have restricted diffusion, and can have serum elevations of the LDH. Unfortunately, there is an overlap between degenerated leiomyomas and leiomyosarcomas.

As a radiologist and as a representative of the radiology community, we certainly have to give measured, balanced interpretations.

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And I think, most of all, there needs to be close collaboration between patients, radiologists, and referring and treating physicians.

Thank you for your time.

DR. DIAMOND: Thank you, Dr. Ascher.

We'll now open this to the Panel for any clarifying questions.

Dr. Neuman.

DR. NEUMAN: Mike Neuman. It was a very interesting talk.

Thank you very much.

I'm wondering if perhaps this is outside of radiology, whether some of the visible light imaging techniques have been used. For example, optical coherence tomography has a limited depth, but it could certainly work with submucosal fibroids.

DR. ASCHER: I know a little bit about that from breast imaging, but I don't know of any studies in particular related to fibroids. But you're right, if it was superficial, you could place it next to the lesion. But I think you'd be very limited in the types of fibroids you could interrogate.

DR. DIAMOND: Other questions?

DR. WENTZENSEN: Nicolas Wentzensen, NCI. Thanks for the talk.

Do you think that the data you presented kind of include those incidental leiomyosarcomas that we are mostly talking about today? Like is this representative? Are they covered there or is that a different -- even

more hard to distinguish a population?

And related to that, do you think, based on what you showed -- I mean, I know that you're trying to make a very accurate decision, but could there be a lower threshold where you could say, okay, with this low threshold it would be very inclusive? We couldn't say for sure all the leiomyosarcomas are included in that group, and the women that don't have those changes, they're safe of not having those, or is it impossible to make that?

DR. ASCHER: I mean, I think it is a continuum, but I think you probably could have threshold imaging parameters combined with other parameters to probably get at that, sort of a risk stratification. One of the papers used age in their formula and that seemed to help them. I'm not sure I have the numbers exactly right, but if a lesion had certain characteristics and the patient was over a certain age, 77% of the time, that was going to be a sarcoma.

The challenges with a lot of the data are that they don't separate out age or don't tell you enough about age. And we're talking about four leiomyosarcomas in amongst eight other types of sarcomas. So it's a little hard to tease that all out, although as an imager, I would think we could come up with some sort of algorithm combined with clinical information.

DR. TALAMINI: This is Talamini. Thank you very much for a clear presentation.

I'm not sure that you'll know the answer to this, but is it

currently -- how much is it protocol currently for women to have an MRI prior to surgical treatment or invasive treatment for fibroids? Number one. And number two, how long has that been the case? And the sense of my question is to try and determine how much MRI data has played into the numbers that we're beginning to see and think about for this.

DR. ASCHER: I can't speak for the country, and I can really speak mostly to uterine artery embolization. I don't have familiarity with HIFU or morcellation, but before uterine artery embolization, most patients would get an MRI. In the early days of UAE, that probably was not the case. It was ultrasound. But as we learned size, number, and location affected outcomes, we needed better imaging tools.

So I would say the broad -- the vast majority of women getting UAE go to MRI. I don't think that's the same, necessarily, with hysterectomy or myomectomy or the other modalities. Clearly, HIFU would have MR, but I don't know that for sure about the others.

DR. TALAMINI: This is Talamini again, just to follow up.

Over how long has that been the case, 1 year, 5 years, 10 years?

DR. ASCHER: The Georgetown experience, we've been doing now UAE probably 15 years. I'd say for the last 12 years. I think if you went to most centers that do a lot of minimally invasive therapy, an MRI would be often performed. I don't know how generalizable that is into the community

hospital and at different levels. I don't have that knowledge. I don't know if anybody has that knowledge.

DR. DIAMOND: Dr. Afifi.

DR. AFIFI: I want of follow up on the question I asked earlier. So I guess what we're looking for is to have the negative predictive value equal to 100%, right?

DR. ASCHER: Um-hum.

DR. AFIFI: And was your answer that you would need to combine several criteria to reach that?

DR. ASCHER: I think it's going to be a combination -- speaking from the imaging perspective, a combination of imaging parameters assessed. I think it's going to be a multi-parametric evaluation, sort of how we are approaching prostate cancer screening these days, so multi-parametric imaging parameters and, I would imagine, coupled with epidemiologic factors as well.

DR. AFIFI: And is such an algorithm now known, or is that something you think should be developed?

DR. ASCHER: Well, the last two studies I showed you, the Thomassin-Naggara and the Sato et al., they do -- those last two slides I showed of the research that they had performed, their studies, was trying to get at an algorithm, albeit they were just concentrating on three imaging features.



I think, in 2014, if we really want to try to have no false negatives -- and obviously that's what we're trying to do here -- I mean, I think you'd have to do conventional imaging techniques and add on diffusion-weighted imaging with an ADC map or an ADC coefficient. But I think that would still have to be taken in light of other epidemiologic factors, age, et cetera.

DR. DIAMOND: Let me ask a question. The type of magnet that's being used for the results that you showed, is that a typical 1T magnet that most hospitals would have, or are you using a 3T magnet for your studies?

DR. ASCHER: Of the nine studies I showed you, eight were at 1.5T and one was at 3T.

DR. DIAMOND: Okay.

DR. ASCHER: So I would say 95% of the literature out there is going to be on 1.5T.

DR. DIAMOND: Okay.

Dr. Mattrey.

DR. MATTREY: Susan, thank you. That was excellent.

So just to see if I can conclude from your presentation, because there was a lot of crossover with the degenerated fibroid, if you see a dark mass on T2 that's well demarcated, that's a benign fibroid, with no question.

DR. ASCHER: Yes.

DR. MATTREY: And that's why the high true negative rate. But the problem comes when they degenerate. So that says, if a lesion has bright signal on T2, is heterogeneous, may be irregular in contour, it is possible or higher probability that that can be a sarcoma.

DR. ASCHER: Yes.

DR. MATTREY: So if we have dividing line, the gray zone is the degenerated fibroid. In my experience, it's somewhere maybe 30% of the time -- I don't know what yours is -- of a degenerated fibroid.

DR. ASCHER: And we see different -- some degenerations I think we're very good at. I think red or carneous degeneration, autoinfarcted fibroids, which we see as women age, the cellular fibroids, I think we're very good at picking up. So I would agree that we're very good at usual leiomyomas, and I think radiologists get that right all the time. I think many degenerated fibroids we get right, but then there is the subset that overlaps with sarcoma.

DR. DIAMOND: Dr. Iglesia.

DR. IGLESIA: Cheryl Iglesia.

I have another practical question because, while most people undergoing UFE, pre-UFE will have an MRI, most undergoing surgery have an exam of ultrasound. And I guess on a practical level, what would you say would be the indication to proceed with the MRI based on ultrasound findings? Because I don't know if it's necessary for everybody undergoing

hysterectomy to get an MRI. It seems rather impractical. But maybe there are some signs where -- you know, other indications where maybe we should proceed with that.

DR. ASCHER: Well, I would agree that it would be impractical and cost prohibitive for everyone to get an MRI before a hysterectomy, given the numbers that have been shown today. My own personal opinion is that if someone's getting a minimally invasive procedure, that an MRI would be a good choice. Ultrasound can be great in some people's hands, but with a large patient and large body habitus and operator dependency, we know -- I mean, the data does say that MRI is a better technology to do the size, number, and location of fibroids. So if that's important to the interventional person, whether they are doing a hysterectomy, I guess, or a UFE, et cetera, MRI is a better roadmap than ultrasound. And that's been borne out in a lot of data.

DR. DIAMOND: Dr. Isaacson.

DR. ISAACSON: Keith Isaacson.

I'm curious. Since you've been doing this at Georgetown, and you guys did so many uterine artery embolizations for the last 15 years, do you have feedback from the surgeons for the ones that you're suspicious that might have a sarcoma and you don't do a uterine artery embolization? What's been the predictive value in your hands?

DR. ASCHER: We haven't had a lot of patients. I know of two

patients in the last probably 15 years that have had sarcomas. One is the one I showed you who did not undergo a uterine artery embolization. The patient came in, and she had her pre-UAE workup. We saw features that were worrisome for sarcoma. She went to a gynecologic oncologist and got taken care of.

I do have one case -- and I show it to all the residents and could find it on my computer -- of a patient that, in our early experience -- I think it was our first or second year after doing this -- that inadvertently got embolized and had a sarcoma. That's two in -- I believe we've hit over 1,000 patients to date. Those are the two I know of.

DR. ISAACSON: And they're all premenopausal, correct?

DR. ASCHER: Yes, both of those cases were premenopausal.

DR. DIAMOND: Dr. Mattrey.

DR. MATTREY: Bob Mattrey.

So what happened to that patient? So what if she got embolized?

DR. ASCHER: Well, actually -- right. Well, she got embolized, which sometimes is normally done if the surgeon -- and gynecologists can correct me -- if they expect a lot of bleeding in the field, they'll sometimes send a patient for uterine artery embolization to shrink the tumor to make the surgery easier. And that would have been great if we had picked it up. But that one case, we didn't pick it up. So when she finally came back into

medical care, she already had advanced disease.

DR. DIAMOND: Dr. Snyder.

DR. SNYDER: What was the time frame in that one case that you're talking about?

DR. ASCHER: It was early in our experience, which meant that we imaged patients before UAE, we imaged them three months after UAE, and then we imaged them at a year. And, again, I think I have it on my computer. She had a pre-uterine artery embolization, and she had a fibroid that was a little heterogeneous. At the time, it didn't strike me as that unusual. She came back for her three-month follow-up. The fibroid had shrunk -- or the "fibroid" had shrunk, but it was heterogeneous still. And then she came back a year later, and it was markedly larger and she had progressed.

DR. DIAMOND: To ask you, perhaps, one last question, most of your presentation has been about leiomyosarcomas and how some fibroids can look -- some benign fibroids can look like a leiomyosarcoma. Is there are a group -- and you've answered this to some degree, but a little more specifically -- are there certain fibroids that -- patients with fibroids that you feel comfortable definitively saying they do not have a leiomyosarcoma or other type of uterine malignancy, that we can identify a subpopulation where that would not be a risk? In your experience, what percentage of patients does that occur in?

DR. ASCHER: If I'm understanding you correctly, what percentage of patients do I look at their MR imaging features and feel very comfortable that they're not sarcomas?

DR. DIAMOND: Correct.

DR. ASCHER: I would say probably 85% of the time I'm comfortable. Again, it's a dialogue between myself and the referring clinician and the interventionalist, but I'd say about 85% of the time there's no question. If I think it's an odd-looking lesion, I'll get on the phone and speak to the referring clinician and/or the interventionalist.

DR. DIAMOND: And do you have any idea what percentage of the patients that those physicians are seeing they are sending to you? Are they only sending the ones to you that they have, for whatever reason, their own clinical suspicions about, or are they sending routinely their fibroid patients to you for MRI imaging?

DR. ASCHER: The bulk of our practice is pre-UAE imaging, so that's what I'm seeing, either referred directly from the interventionalist or from the gynecologist who is having his patient worked up -- their patient worked up for UAE.

DR. DIAMOND: Okay.

Any final questions from the Panel?

(No response.)

DR. DIAMOND: Not seeing any, thank you very much.

We would now like to invite FDA's Elaine Blyskun to come and introduce our fourth invited speaker, Dr. Carmel Cohen, the agenda topic of overview of uterine sarcomas.

MS. BLYSKUN: Thank you.

Dr. Carmel J. Cohen currently serves as Professor of Obstetrics and Gynecology in the Division of Gynecologic Oncology and in the Ruttenberg Cancer Center at the Mount Sinai Medical Center. He founded the Division of Gynecologic Oncology at Mount Sinai in 1967 and was its director for more than 25 years.

He has authored 290 publications and lectured widely.

Dr. Cohen has served in multiple capacities for many of his specialty's academic and service organizations, resulting in his presidency of the New York Obstetrical Society, the Society of Gynecologic Oncology, the Society of Pelvic Surgeons, and the Eastern Division of the American Cancer Society. He was a founding member of the International Society of Gynecologic Oncology, a founding member of the GOG, a founding member of the Ovarian Cancer Research Fund and its scientific director, national board member of the American Cancer Society and chair of the Gynecologic Cancer Advisory Committee as well as the Outcomes Committee.

Dr. Cohen will be providing an overview of uterine sarcomas, including epidemiology, staging, and treatment.

DR. COHEN: While we're setting up, let me just tell you that I

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make this presentation from the point of view a clinician who happens to be a gynecologic oncologist. And I'm really flattered to be invited, first, to be in this colloquy today. And, secondly, I really was awed by the scholarship of the other invited consultants. And in terms of the last speaker, who thought that a picture was worth a thousand words, I have been trained in discourse and colloquy, so for me, a thousand words is worth one picture. I'll try to limit myself.

I had an assignment which was a little more robust than what was just announced. I was invited to talk about the cellular biology and physiology of sarcomas, whether a sarcoma arises from fibroids, the epidemiology, trans-risk factors, racial disparities of leiomyosarcomas, and the presentation, diagnosis, diagnostic evaluations, staging, clinical management, prognosis, and outcomes. That's more than a thousand words. I'm going to do this in summary.

I will tell you in advance that I haven't cited all of my declarations in this peroration, but I can tell you also that in my view, the single most important compendium on soft tissue sarcomas was published last year from Memorial Sloan Kettering Cancer Center. And I will give you the reference for that. I've referenced some of the contentious declarations, but this is an amalgam and a summary of lots of different studies, some of which have been alluded to earlier.

I have no conflict of interests.

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And I will approach this first, in terms of setting the stage for sarcomas by a historical review. It's important only because sarcomas were really defined more recently. From the Greek days until now, they were just the "others." What had been classically described in ancient days were cancers that were carcinomas, primarily. The only sarcomas were those which could be visualized, surface sarcomas, or limbs that had begun to express penetrations through the skin. And the ancients knew that those were different from the other cancers and they stayed away from them, wisely, for lots of reasons.

So the defining characteristics can be inferred from Galen, back in 130 to 200, who avoided these diseases. And since then, over the last 2,000 years, numerous reports by anatomists and surgeons have occurred. But it was Charles Bell, who lived in 1772 to 1842, who distinguished formally sarcoma from carcinoma. And Stout, previous chair of pathology at Memorial Hospital, published a monograph in 1932 on the pathology and treatment of sarcoma.

There was a reasonably small overall prevalence which is not different from today. There were widely disparate microscopic descriptions of non-carcinomatous lesions, often lethal disorders that had either been surgically excised or discovered at autopsy, and all of this obscured the commonality of these lesions as a class. Published reports were mostly anecdotal, until centers built libraries of pathologic material and created

databases.

And I would remind you that the Mayo Clinic was organized about 1900. Memorial Hospital really didn't get started until the turn of that century. The Mount Sinai Hospital in New York is 200 years old.

All of this started late. And because everybody was looking at one or two cases and reporting these anecdotally, there was no real information.

James Ewing, who lived 1866 to 1943, was the first Professor of Pathology at Cornell. Look when he lived and he was their first Professor of Pathology. He was Chief of Pathology at Memorial in 1899 at the age 33. And in his classic monograph entitled *Neoplastic Diseases* in 1919, there was an original description of soft tissue sarcoma and defined sarcoma as a malignant tumor composed of cells of the connective tissue type. That means it was the "other."

At Memorial Hospital, the pathologists developed a tradition of studying soft tissue sarcoma. And I make a big deal about this because it was their interest and a continuum of description of new sarcomas that began to bring some order to this whole field.

Stout, who was Chair of Pathology, published with Ackerman in 1947, describing leiomyosarcomas of soft tissue. So until 1947, there was no leiomyosarcoma.

And you can begin to appreciate the heterogeneity of all of

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these observations, which interfered with the capacity to get them together in one place and in any kind of a registry.

This impetus and attraction led to the establishment of a database from 1982 to the present at Memorial, which includes 8,000 completely annotated patients over the age of 16 years, leading to the publication of the book *Management of Soft Tissue Sarcoma* by Murray Brennan, who was chief of surgery; Antonescu, who was a pathologist; and Bob Maki, who was a specialist in clinical management of sarcoma. Maki is now at Mount Sinai and brought that tradition to that hospital.

So let's look now at the classification of soft tissue sarcomas. These are distinguished from sarcoma of the bone: fibrosarcoma, malignant fibrous histiocytoma, undifferentiated spindle cell sarcoma, leiomyosarcoma. There are, in fact, seven more than that list that I pointed out. And we'll go back for one minute. You will see that rhabdomyosarcoma comes from muscles. There are three major types. We have our own leiomyosarcoma; malignant peripheral nerve sheath tumor -- every time an investigator, usually a pathologist, but often clinicians, felt that there was a sarcoma that was a little different in some way, that became a newly classified sarcoma; angiosarcoma from blood vessels; hemangiopericytomas. Now, there were seven more than I listed, but there are new subcategories in process of being redefined even now.

Among the uterine sarcomas, you can see that leiomyosarcoma occurs with a prevalence of 6.4 million per year.

Malignant mixed Mullerian tumor -- whose name has been changed within this last year -- which is the most prevalent uterine sarcoma, it exceeds leiomyosarcoma by a lot: 8.2 million per year. It was known as the MMMT. Now these are called carcinosarcomas of Mullerian origin, Mullerian being the embryonal source of the development of these tissues which are based on connective tissue moieties.

And then endometrial stromal sarcoma: 1.8 million per year. And these are confined to the endometrium itself, and therefore they have a completely different set of symptoms and presentations. They are not in the muscle of the uterus, and they can be or should be diagnosed very simply.

And, of course, there's always an unclassified category.

Getting to the tumor biology. For all soft tissue sarcomas, there are three dominant variables that reflect the tumor biology. First, there's the histopathology. How does it look under the microscope and what is its origin? Endometrial stromal sarcoma is a relatively responsive sarcoma. Malignant tumors of the Mullerian type, carcinosarcomas, are virulent. Leiomyosarcomas, when detected early, are curable; ones that are Stages III and IV are invariably fatal.

So the type that appears under the microscope is important, and differentiation is critical. But the other variables are not only the

histopathology, but the site and the tumor size.

Analysis of gene profiles have now been completed for 20 types of sarcoma. They have certain common gene patterns which give a suggestion that there is a genetic commonality which can be exploited, perhaps pharmacologically. But, to date, some of these patterns which look like being associated with tumor virulence are proving to be better classified. But all of these studies are performed after surgical intervention. They don't help us in any way in terms of assigning virulence preoperatively.

Now the classifications of uterine sarcomas. There is the mixed homologous Mullerian sarcoma -- this used to be the MMMT -- and mixed heterologous Mullerian sarcoma. Both of those used to be one category.

Homologous means that the elements of the sarcoma are indigenous or local to the uterus. Heterologous means other extrauterine components are there, probably growing from vascular or connective tissue moieties. The example is you may have carcinoma and sarcoma together in the homologous phase. But you may also find bone, cartilage, and other elements which are not inherently uterine, and that's the heterologous Mullerian sarcoma, and those are much more virulent. Then the leiomyosarcoma and then endometrial stromal sarcoma.

Now, this classification is one of very many, but it has been formulated by the Gynecologic Oncology Group, which is a group of trialists. About 35 institutions are usually the principal investigators with all of their

networks, and the GOG has been the primary organization for clinical trials and for other experiments in treating and diagnosing gynecologic cancers.

I was asked to talk about staging. There are two staging systems. One is the TNM system, which is appropriate to most cancers in the United States and elsewhere. And then there is the FIGO system, the International Federation for Gynecologic Oncology, and that staging system is what most gynecologic oncologists employ routinely. And I've matched these two side by side so that there won't be difficulty in understanding their different philosophies.

The purpose of staging is really to compare treatment outcomes and from the stage, perhaps based on previous experiences, to design therapies that will be appropriate for achieving cure within stage. And you see on your left, under the TNM category, they talk about T for tumor, N for nodes, and M for metastasis. And each category is assigned a value and a point in numeric assignment for the presence or absence of those features.

So what you see is here, under the TNM category, whether there is tumor present or not. Here, under the FIGO system, when tumor is not present, meaning if the biopsy removed the tumor completely and there's no tumor in the organ, that is not mentioned separately here. Here it's designated. If there's no evidence of primary tumor because of previous therapy or because there is no record, then this is not mentioned. It's not staged or entered into the system. Here it becomes a T0. And so you go

through the whole staging circumstance.

This system of staging is not the usual FIGO stage for uterine cancer. They created a special staging system for sarcomas. And I will call your attention to the fact that, here, a tumor of 5 cm or less in greatest dimension is IA. A tumor more than 5 cm is IB. A tumor under the other system, which extends beyond the uterus, within the pelvis, is T2. And in the FIGO system it's all Stage II. Stage IIA involves the adnexa. Stage IIB involves other pelvic tissues. Stage III, the tumor infiltrates abdominal tissues. Stage IIIA, it's one site. Stage IIIB, it's more than one site. Stage IVA, it invades bladder or rectum. And here, regional lymph node metastasis is back in Stage III. So it's quite different from the TNM system.

Now risk factors. African Americans have this disease two to three times more frequently than Caucasians.

Previous tamoxifen therapy -- this is just an observation made by those who include risk. Previous tamoxifen therapy gives a prevalence of 17 per 100,000. That's remarkable because that's probably higher than the tamoxifen risk for endometrial cancer. And why that should be is curious. It may be true, true, and unrelated.

However, previous pelvic radiation is agreed to be a causative factor for leiomyosarcoma of the uterus; history of childhood retinoblastoma and history of leiomyomatosis and renal cell carcinoma, which is a peculiar genetic observation based on an identified gene profile.

A single uterine myometrial mass. And we saw that in the elegant presentation that we just heard, in terms of the pictures and the accuracy of MRI. If you have a single myometrial mass in a woman who is postmenopausal and the rest of the uterus looks normal, I think you could take that as a predictive feature and you would find that 1 in 500, with a range between 352 to 1,000, would have a leiomyosarcoma anyway, irrespective of the radiographic pictures.

Presenting symptoms. They're often absent. They're frequently or usually diagnosed during or after surgery. The uterine leiomyosarcoma occurs at a younger age than do the mixed sarcomas: between ages 40 and 60. They usually present with vaginal bleeding and may have pelvic or abdominal pain, depending on the size of the tumor and whether it spreads to other areas.

Otherwise unexplained foul uterine discharge, especially in a postmenopausal woman, suggests that she has some neoplasia that involves the uterine cavity. And that should be investigated early and not just treated with local measures.

Less frequent are these presentations: weight loss, weakness, lethargy, fever.

That can happen absent all of these other symptoms or presentations. And when a patient has unexplained difficulty of that sort, she should have radiographic testing earlier rather than later.



As far as diagnosis is concerned, pathologic inspection of a specimen is really required. Noninvasive diagnostic radiology is helpful. Looking at it from the point of a view of a simple clinician, you really can't dependably distinguish sarcoma from benign or cellular or atypical leiomyomas.

And I would remind you that the elegant presentation that preceded this one was made by a person who has devoted herself to scholarship in this area, and who has chosen to present to us similarly inclined scholars who have measured very, very carefully with techniques, mostly MRI. And the accuracy of that in the neighborhood, so to speak, is reported to be between 40% and 100%, the 100% being the kind of elegance we heard presented.

But I can tell you, as a person who works in a center where diagnoses are made elsewhere and referred in, that the average radiologist does not have the gift or the time or the equipment to do what's being done in Georgetown and lots of other places. And I worry that we will ever be able to set up algorithms that will enable that to be overcome. All of the particular techniques can diagnose sarcomas and mix them up with fibroids, and vice versa.

The histologic diagnosis has some essential elements. First of all, there has to be a correct identification of histologic type; mitotic count is essential; size of the lesion and differentiation. Conventionally, we feel that

mitoses 0 to 5 per 10 high-power fields is critical and indicates that the lesion is benign. I'm talking about lesions in the wall of the uterus. If there are 5 to 10, we consider that borderline, or it can be called a smooth muscle tumor of uncertain malignant potential, or STUMP. More than 10 per 10 high-power fields should be considered a sarcoma. And if this has been surgically removed and there's a question about whether or not to treat, regardless of what is decided, the patient should be carried as a person who will have a higher risk for recurrent disease than other smooth muscle lesions.

Additional cellular features. Immuno-histochemical stains will show ER, PR, desmin, smooth muscle actin, and caldesmon. And karyotypes. More than 50% of these sarcomas have profound structural aberrations such as the deletions which were previously cited. And these are not only in chromosome 1, where testing perhaps can now be done, but 13, 14, 16, 18, and 22. And the frequency of any specific aberration is less than 20%. So you won't find the same aberration more than 20% in different sarcomas.

Leiomyosarcomas have different patterns. But while there's some overlap, I think -- I shouldn't say I. I have been persuaded by the literature that leiomyosarcoma does not come from a degenerated fibroid. It is a different problem.

Therapy. Ideally, the therapy should be complete removal of all grossly identified tumor, with all that that implies. This results in improved survival compared with patients having disease remaining. Now,

that's a pregnant paragraph, and I leave it to your consideration based on what you've heard until now.

Women who are peri- or postmenopausal should have bilateral salpingo-oophorectomy after appropriate counseling, although there is no data to prove that survival is improved by this maneuver alone because most usually, when the diagnosis is made and the opportunity is available, the adnexa are removed at the same time. And what contribution that makes to cure is not known, and I don't think that's going to be done in a prospective randomized fashion.

While metastasis to pelvic nodes in leiomyosarcomas of the uterus is rare, without having metastasis to other sites, most experts remove the nodes if they're palpable or if there's abdominal disease, meaning Stage I and III, which is amenable to resection. So if there's tumor which has already left the uterus but is resectable, in an effort to remove all visible tumor, which improves prognosis, the nodes should be removed. If the disease is not resectable, extensive surgery will not improve survival, but it may in certain patients relieve symptoms and improve quality of life.

So if during the course of business there are Rice Krispies all over the surface of the peritoneum and the liver has a lump in it, there's no merit in chasing all of that with the knife because that patient is not going to survive as a result of that cytoreduction. If it can all be removed, that's marvelous. But if one is leaving significant disease, a lymphadenectomy is

not important except to reduce bulk.

Pelvic radiation, while it reduces local recurrence, doesn't improve survival in patients who have had complete cytoreduction.

Therefore, if the patient has had complete cytoreduction, the option is now for cytotoxic chemotherapy or other treatments, but not radiation therapy. If they recur, such patients will recur because of distant mets, not because of local recurrence.

Now, for chemotherapy, there are useful chemotherapeutic regimens, but there's sparse robust evidence from large randomized studies clarifying the role of chemotherapy after complete cytoreduction in early disease. Currently, there's an international collaborative comparing SARC 05 protocol to observation in patients with FIGO Stage I completely resected. That was started as a GOG 277 protocol.

At Memorial, they did a different thing: 25 patients completely resected for leiomyosarcoma. And they gave a fixed dose rate of gemcitabine, 900 mg/m<sup>2</sup> on days 1 and 8, plus docetaxel, which has been demonstrated to be a useful protocol, 75 mg/m<sup>2</sup>. And the results from that -- these were Stage I and II high grade -- 59% progression-free survival at three years. At median follow-up of 49 months, two years progression-free survival. This was for all comers, not just for this particular group cited in the first sentence. At the follow-up at 49 months, there was a two-year progression-free survival at 45 months, and median PFS was 13 months for

the whole group. That's Martina Hensley's data.

And from that, an international study was done, which added doxorubicin after docetaxel and gemcitabine for four cycles. This was reported at ASCO, and what it showed was that 89% of the patients were able to receive all eight cycles, which is wonderful. Three-year PFS was 57%. Median time to recurrence was 27 months. So this was completely resected disease.

There are many different chemotherapeutic agents that have been tested, and there are others which are certainly active, such as ifosfamide, cyclophosphamide, and there are others. I won't burden you with all of that. It was just a question of proof of principle.

Now, a question that I was asked to answer almost yesterday as I was leaving: Do women with disseminated or advanced sarcoma following morcellation have different prognoses and/or treatment considerations compared to those who did present at the same stage and who did not have morcellation? Now, I've sort of botched up that question, but you get the gist. What is the role of morcellation in terms of advancing stage?

First of all, the first part of the question has to be answered yes, meaning it does have an impact and a direction for treatment, alternating treatment. Frequently, this diagnosis is made only after the operation is over and sometimes after the pathologists have taken their time to do various stains and tests to see whether there really is sarcoma here in

the morcellated specimen. And sometimes the patient has gone home and gone back to their state of origin. And at Memorial, when this data was examined in their series, the mean time to second operation was 63 days.

So the question is, what was the stage of the patient when she was considered for surgery the first time? Well, one has to assume that either she had no preoperative investigation which would have given some suggestion that there was a malignant process, otherwise the morcellation wouldn't have occurred, or that there was some workup that did not show disease outside of the uterus. And if that's the case, one can infer either that she was Stage I or that she had a different stage that was not very bulky in appearance.

In addition, one would have to assume that the person who was doing the surgery looked around and saw something, although when one reads op notes, that's not always the case.

So this is what I have found. There are no published prospective studies. Of course. The distinction between leiomyoma and leiomyosarcoma is impossible without tissue sampling. Prevalence is very low. So if you take all of that into account, if such a study were tactically possible, it would never be allowed. Nobody is going to randomize a person with a sarcoma of the uterus to be morcellated or not and then follow the course.

Several small retrospective studies suggest that reoperation

after the diagnosis is made leads to upstaging. It is not responsible for upstaging but requires the patient to be upstaged, especially in sarcoma. And I say sarcoma because frequently these reports include carcinomas of the endometrium or carcinomas of the ovary that have metastasized to the uterus. So we're talking now only about sarcoma, that washings are negative even when there is advanced disease in the second look, and that in sarcomas, the survival is diminished in those people who were upstaged. Since the second surgery is often delayed by 40 to 60 days in some reports, the original stage is usually unknown.

So I don't think I've contributed to the solution of that problem, except to suggest that, as all of us would probably concede here, inappropriate surgery for sarcomas of the uterus and inappropriate surgery of any kind are to be avoided. And I leave to you and the Panel the job of setting algorithms for helping all of us avoid it.

Thank you.

(Applause.)

DR. DIAMOND: Thank you, Dr. Cohen.

Are there questions from the Panel to Dr. Cohen?

Dr. Talamini, please.

DR. TALAMINI: Professor, thank you very much for a clear presentation.

Is there any chance we could get one of his slides back up, the

first slide that said therapy on it, because I had a question.

DR. COHEN: The first therapy slide?

DR. TALAMINI: The first slide that had the title "Therapy." So my question is, based on the results that you showed us following chemotherapy -- this is obviously a dismal tumor, unfortunately. But in these two statements, I couldn't quite reconcile the two together and perhaps you can help me.

DR. COHEN: Sure.

DR. TALAMINI: The first statement says initial therapy should be complete removal of all grossly identified tumor which results in improved survival; and then the second, that there's no data to prove that survival is improved by that second maneuver.

So what is the data that speaks to what improvement you really get with resection in these patients, given that this is a dismal tumor, from the chemotherapy results that you showed us? How do we know that surgical extirpation actually improves the outcome?

DR. COHEN: I have confused your inference. I mean, you were guided to make that inference. But what I was talking about in the second paragraph here is that women who are peri or postmenopausal, when they have removal of all their disease, should have bilateral salpingo-oophorectomy, because some people feel that these are young women, they should keep their ovaries, they should have the benefit of estrogen



production. There are data that suggest, after oophorectomy, women die prematurely. There are all kinds of meta-analyses that impact on this and confuse the field.

So when one does the second operation to remove all of the disease, we would recommend including removal of both tubes and ovaries. That, in itself, cannot be awarded a major role in cure, simply because we don't know what its contribution is. But we do know that there have been recurrences in the ovary after less surgery is done. And since these people are talking about life, we think they should have their tubes and ovaries removed at the time that all the other disease is being cleaned up.

DR. TALAMINI: Thank you.

DR. COHEN: And the bottom line of the reoperation is that no matter how far advanced it appears, if you surgically can remove it all, the prognosis is better in terms of progression-free interval and quality of life.

DR. DIAMOND: Dr. Mattrey.

DR. MATTREY: I just want to make sure I understood it clearly. From your perspective, if a leiomyosarcoma was discovered de novo with peritoneal implants versus there were no peritoneal implants, but there were implants made mechanically through the intervention, that the disease is identical even though it's likely that the biology of the tumor that spread by itself to the peritoneum seems more aggressive. In other words, is that Stage IV disease when the tumor did it on its own versus Stage IV disease

simply because it happens to be in the peritoneal cavity, speaks of the same tumor property?

DR. COHEN: If it's implanted and growing, it's the same disease. Well, we don't know how it got there, but it has to be staged as an advanced-stage disease.

The real difficulty is speaking, for example, to simple fibroids. There are reports in the literature of fibroids, simple, unadorned, non-cancerous fibroids, growing in the port sites after minimally invasive myomectomy. I'm not arguing for or against using minimally invasive surgery. I think it should be used. There are a couple of reports of leiomyomatosis, as has been mentioned, with so-called metastatic fibroids. And when you go back into the belly, what you see are little potatoes all over the abdomen, but histologically they're benign. And that can occur after incomplete removal of fibroids with spill. So the notion of spill is sort of anathema to preserving the integrity after any surgical procedure removing an organ. If you can avoid it, it should be done.

DR. DIAMOND: Dr. Brown.

DR. BROWN: Carol Brown. Thank you, Dr. Cohen.

Two questions. One is, is it known whether the predominant mode of metastasis of leiomyosarcoma is hematogenous or by direct spread? And, two, do we have any sense of women who do succumb to metastatic or recurrent leiomyosarcomas? Is that usually caused by intra-abdominal or a

distant metastasis?

DR. COHEN: The answer to the first question is -- you asked predominant -- yes, vascular spread is predominant. And that's why recurrence is -- that's why it is not recommended to radiate the pelvis prophylactically after a complete resection of a Stage I or II lesion, because if those people die, they'll die because of pulmonary mets, which is without any recurrence in the abdomen, so that we know that it can be transmitted vascularly.

As far as the second question is concerned?

DR. BROWN: Just what is the most common cause of women who have -- who do die of metastatic leiomyosarcoma? Are they usually passing away from local or abdominal pelvic recurrence, or is it distant metastasis that's usually the cause?

DR. COHEN: One of the problems is that when they recur in the abdomen, they usually recur in the lungs. And the mode of death is going to be obstruction, wasting, or pulmonary difficulties. I don't know the answer to the question because it's described as widespread with pulmonary mets.

I think that the problem that we have is that the prevalence is so low, I don't know how you'd organize any kind of a registry except the one that is at Memorial right now, which was done really out of intense interest by Murray Brennan and the people that followed. And there's no place that I know that has a single collection of 8,000 completely followed persons with

all the parameters that you'd want to look at in terms of looking at the problem of prognosis and predictability and diagnosis and biology.

So I can't answer your question other than to say that widespread abdominal recurrence is bad, pulmonary recurrence happens very frequently, and the mode of egress, I can't tell you about it with precision.

DR. DIAMOND: Dr. Isaacson.

DR. ISAACSON: Keith Isaacson.

When this disease is diagnosed in a postmenopausal patient who has an exploratory laparotomy and a hysterectomy in the standard fashion, what percentage is diagnosed in the early stages versus the later stages, Stage I-II versus III-IV?

DR. COHEN: Well, most of them are diagnosed without evidence of spread. However, the issue is who looked and where did they look. None of those patients had lymphadenectomies done that I know of. And washings are uniformly negative, even in the face of widespread disease. So looking around and feeling around won't really necessarily stage it as a Stage I. And I think the presumption is that that's okay.

And if the uterus were to have been removed and the patient is postoperatively staged by the elegant techniques of radiographic survey and all of that is unremarkable, most of us would not go back into the belly because that's a complete operation. It's not a cut-through. And if there's disease outside, it should be noticed with a PET scan. And then one can go

immediately to cytotoxic chemotherapy and then, if necessary, do a second look and remove the nodes and make sure that everything's clean.

DR. ISAACSON: And the second question is more theoretical. We've known about disseminated leiomyomatosis long before we had laparoscopy and morcellation.

DR. COHEN: True.

DR. ISAACSON: This happened when we were doing open myomectomies for years.

DR. COHEN: Right.

DR. ISAACSON: And, clearly, you don't intentionally leave any type of tissue behind when you're doing it openly or with the laparoscope. Do you think that there may be potentially another mechanism that a certain small percentage of patients get this disseminated disease other than leaving tissue behind?

DR. COHEN: Well, I'm sure that you're correct. I was offering that as proof of principle, that leaving behind bits of tissue can allow implantation of that tissue and flourishing under certain circumstances. We can see this with all the theories about endometriosis, as you well know, and the manipulations that went on to prove that it wasn't retrograde spill through the fallopian tubes and implantation and in all of that era of thinking about contamination from a primary specimen. I think some of that was probably true, and I think that if we can remove all of the tissue, it's better.

DR. DIAMOND: Dr. Cohen, needle biopsy you haven't mentioned. Do you think there is a role for needle biopsy of masses which are thought to be fibroids which may be suspicious for a sarcoma, either going transcervically or transabdominally in order to do such a needle biopsy?

DR. COHEN: When you say transcervically, you mean into the endometrial cavity or through the endometrial -- through the myometrium into the abdominal cavity?

DR. DIAMOND: Really endometrial cavity into the fibroid.

DR. COHEN: Oh, into the --

DR. DIAMOND: Presumed fibroid or --

DR. COHEN: Yeah.

DR. DIAMOND: -- transperitoneally under ultrasound imaging or some of other form of imaging as a means of getting a diagnosis if it's a suspicious looking fibroid.

DR. COHEN: Well, I think two things. I think that if you have to go to that length, unless you're going to do it routinely on everybody, I don't think it's going to be useful. And doing it routinely on everybody is likely to lead to more trouble than benefit. I don't have a problem about putting a needle through a loop of bowel to get into something else, for complicated reasons that we don't have time for here. But the yield from that is going to be very small.

If you buy a cantaloupe and it looks good and it smells good

and you knock on it and it's good and you put a needle into it and it tastes good, that doesn't mean there isn't a worm at the other end of the cantaloupe. And I don't know how you can do that.

With radiographic guidance, you can get to the worst part of it. And I think that if that develops, then that would be terrific. Right now I'm not sure we're there, but it's certainly an opportunity to do this. And since a lot of people are going to have myomectomies and there are other cancers which can be present that are morcellatable, it might not be a bad idea to do it. It doesn't have to be randomized on a limited number of volunteers.

DR. DIAMOND: Okay.

DR. COHEN: Yes.

DR. MOORE: Lisa Moore.

I'm trying to understand the natural history, so I want to give you two scenarios. The first is a woman who has an undiagnosed sarcoma and she has a hysterectomy, but the uterus is removed intact. What would be expected to be her survival or what would happen to that lady from that point? Or, in the second case, if it's a woman who has an undiagnosed sarcoma, but there's nothing done at all about it, what would be expected to happen to her?

DR. COHEN: All right. So there are two women who have had hysterectomies.

DR. MOORE: No, the first one had a hysterectomy, but the

uterus was removed intact and they found, incidentally on pathology --

DR. COHEN: I see.

DR. MOORE: -- that she had a sarcoma.

DR. COHEN: Okay.

DR. MOORE: And the second one is a woman who has a sarcoma but doesn't know it --

DR. COHEN: Okay.

DR. MOORE: -- and has not had a hysterectomy.

DR. COHEN: All right. So in the first case, the woman who had the hysterectomy with a sarcoma in it, if that patient has been completely resected, if the doctor at the time did a frozen section and knew there was a sarcoma there and either performed him- or herself or called someone in who could help and they staged this patient and there was no disease remaining, that person should be left alone and followed. There's no evidence yet. Unless she gets into a study, there's no evidence to give these chemotherapeutic regimens automatically to that woman. She should be in a study.

The one who has a sarcoma and doesn't know it, if nobody intercedes, we'll have an advanced cancer from which she'll die.

DR. MOORE: How quickly?

DR. COHEN: How quickly? It depends on the histology, it depends on the size, it depends on whether it's a leiomyosarcoma or a mixed



Mullerian tumor or an endometrial stromal sarcoma or any one of a number of other sarcomas.

DR. MOORE: Well, let's say it's a leiomyosarcoma. And what I'm trying to figure out is, what's the difference in this woman and the woman who actually got morcellated? And the survival.

DR. COHEN: Well, the morcellated woman has had her lesion removed, and if she hasn't had vascular spread by this time, then that will be prevented. The woman who keeps her uterus is going to get vascular spread sooner or later. It may not necessarily be abdominal spread. It can go directly from her uterus to her lungs without passing "go" in between.

DR. DIAMOND: Dr. Isaacson.

DR. ISAACSON: Real quick. Just a follow-up on a comment that you just made. What is the value of the frozen section for the leiomyosarcoma, since it's a random section almost like a biopsy? Preop. Is there a value for a frozen section?

DR. COHEN: Well, right now nobody has done any histologic examination of this lesion, this fibroid, presuming it's a fibroid. Now, if the fibroid is cut and there seems to be some liquid formation or it has a discoloration or it doesn't look typically like a fibroid, somebody there is going to say this is a spindle cell tumor -- if they're not going to do a frozen section, this is a spindle cell tumor awaiting a final pathology report. If you demand that there be a frozen section of the ugliest-looking part and they

find a cancer there, then you can go ahead and stage her and perhaps save her some trouble. Otherwise, it may well be that she has disease in her nodes which is unknown, and we're not going to go back and do the nodes unless they are very much enlarged on noninvasive radiographic staging after it's all over.

DR. ISAACSON: So the recommendation is to look at the tumor grossly, and if you see something abnormal, then to send it for a frozen section, but not necessarily routinely send all fibroids for a frozen section.

DR. COHEN: I personally send up uteri to the pathologist. If there is a reason for my having done the procedure to begin with, this woman had some pathology, because I frankly observe fibroids. I don't operate on them unless there's a clear indication. I'm not an endocrine person. I don't deal with infertility. If someone comes to me at the age of 45 with fibroids which aren't growing rapidly and from which she's not bleeding and there's no compression of other adjacent organs, I tell her to be followed with noninvasive radiographic follow-up and watch her. I don't use that as an excuse for a hysterectomy or a myomectomy. I certainly wouldn't do a myomectomy on a lady of that age. And there are all of these other ways of controlling fibroids, if she wants to be proactive, without putting a knife to her belly.

DR. DIAMOND: All right, before we -- Dr. Fisher.

DR. FISHER: Just one quick question. And I apologize if I

missed this.

DR. COHEN: No, go ahead.

DR. FISHER: It has to do with vascular spread.

DR. COHEN: Yes.

DR. FISHER: Is there a difference between vascular spread of LMS with tissues that are taken en bloc and tissue that is morcellated?

DR. COHEN: No, I don't -- do you mean, is there a difference in prevalence and frequency?

DR. FISHER: In frequency.

DR. COHEN: No, I think it's just a matter -- I have no evidence that morcellation increases the risk of vascular spread because the patient has been disconnected from the tumor. And the vascular spread is just a statistical fluke that it's going to happen at some time in that patient. So the longer the patient is exposed to the cancer, the greater is the opportunity for vascular spread to occur and to go to the lung.

DR. FISHER: Okay, thank you.

DR. COHEN: Strictly, it's a statistical exercise.

DR. FISHER: Okay, thank you.

DR. DIAMOND: All right. Before we go on to the FDA presentation, I would like to ask the Panel, now that we've heard all four of the presentations, if they have any questions of any four of the invited speakers before we go any further.

Dr. Mattrey.

DR. MATTREY: Yes, just a question. I mean, we heard there are hundreds of thousands of hysterectomies done either for fibroids or other reasons. There has got to be pathology on those. How often is leiomyosarcoma found in those 600,000 interventions? Does anybody know the answer to that one?

DR. DIAMOND: Do any of our invited speakers wish to answer that question? Dr. Cohen looks like he's coming back.

DR. COHEN: I showed you the prevalence figures here. I can tell you that in the 2014 facts and figures from the American Cancer Society, which is the group that's supposed to be answering questions like the ones you've just put, there's no information.

DR. DIAMOND: Okay.

DR. MATTREY: Every piece of tissue goes to a pathologist. This is Dr. Mattrey. I can't imagine that data is not available.

DR. COHEN: Well, I think you'd have to survey each department of pathology, because it's not mandated that they discriminate between leiomyosarcoma. They talk about uterine sarcomas, but you've seen that there are four of them, of which leiomyosarcoma is the second least frequent. And the others are dominant, relatively, mixed Mullerian tumors.

DR. SOBOLEWSKI: So I'll just add or stress a comment that I made during my presentation earlier, and that is not only --

DR. DIAMOND: Could you use the microphone, please? And just indicate who you are for the record, please.

DR. SOBOLEWSKI: I'm sorry. It's Craig Sobolewski.

And just again to reiterate a comment that I made earlier. Not only is it difficult to understand the incidence, I would agree that we ought to be able to, in some fashion, get our arms wrapped around the number of leiomyosarcomas diagnosed. Unless we understand fully what the denominator is, we really can't make sense of the prevalence. And we don't know honestly how many hysterectomies are done. There is no database that can accurately determine the numbers of hysterectomies done because, as I mentioned, a substantial number of minimally invasive procedures, vaginal hysterectomy and laparoscopic included, go home in less than 24 hours. So all of the publicly available data is for inpatient hysterectomies.

Thank you.

DR. DIAMOND: Dr. Sobolewski, I have one question also for you or other members of the other invited speakers.

Do we know the patients who have had -- who were thought to have uterine fibroids and ultimately were identified to have leiomyosarcomas? Do we have any idea of the size of those tumors that were morcellated that resulted in dissemination?

DR. SOBOLEWSKI: To my knowledge, after reviewing the papers, it's just numbers that are given and the characteristics of the

individual leiomyomas are not reported.

DR. DIAMOND: Okay.

DR. GALLAGHER: This is Colleen Gallagher. I have a question for Dr. Ascher.

DR. DIAMOND: Dr. Ascher, please come back to the microphone.

DR. GALLAGHER: So I realize that you are doing the MRIs predominantly for UAE procedures. But I'm wondering, when you go to do those, do you do all four of the types that you were talking about, including the diffusion-weighted and the ADC mapping automatically as a part of that -- an algorithm for your own practice -- or is that something that has to be specifically ordered and requested by the physician who is going to be doing the UAE?

DR. ASCHER: Susan Ascher.

In our practice, it is automatic. In all neuro applications, diffusion-weighted imaging is part of the usual armamentarium of imaging. That has migrated into the body more and more. I don't know, I think it's often in the liver. I don't know if it's done in the uterus everywhere, but that is something that's clearly being spoken about more in our literature. But it's not a knee-jerk response like it is in the head and neck. But in our practice, we do it for every patient, and we also do it for all known gynecologic malignancies.

DR. GALLAGHER: Okay. And you also talked about ADC mapping. Is that --

DR. ASCHER: Yes. That's a diffusion coefficient that you get from your diffusion-weighted imaging. It's a logarithmic phenomena. It can be projected as a map, and there are also quantitative values. But you get it from doing your diffusion-weighted imaging.

DR. DIAMOND: Thank you.

All right, we will now proceed with the FDA's presentation. I would 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.

FDA, you may now begin your presentation.

And for the Panel, our intent will be to go through the entire FDA presentation and then open it up for questions of the FDA at that point in time.

DR. JONES: Good afternoon. My name is Chris Jones. I serve as senior advisor in the Office of Policy and Planning in the Office of the Commissioner at FDA. And I'll start off FDA's presentations this afternoon with an overview of an assessment that we did, looking at the quantitative assessment of risk of uterine power morcellation.

We had two specific research questions that we wanted to answer in our assessment. The first question was, what is the prevalence of

unsuspected sarcoma and leiomyosarcoma specifically among women undergoing a hysterectomy or myomectomy for presumed benign leiomyoma?

The second research question was, what is the probability of seeding an unsuspected sarcoma by morcellation, and what is the impact of morcellation of an unsuspected sarcoma on clinical outcome?

I'll first talk about our first research question. And essentially we were exploring generating a prevalence estimate. We knew from previous studies that individual studies had looked at a specific patient population and attempted to make some statement or estimate around prevalence among that population. However, really no one had used a meta-analytic approach to generate a prevalence estimate.

This slide outlines our search criteria. And we first searched PubMed, Web of Science, and EMBASE for papers that were specifically exploring unsuspected uterine sarcoma among patients who were undergoing gynecologic procedures. We initially identified 41 papers through our search, and we predetermined that we would use a cutoff year of 1980, as far as when procedures were performed -- not that the study necessarily was published after that point, but when procedures were performed -- for our literature review. And we felt that this would help maintain some consistency among the patient population and help reduce some variability and study when we were generating the estimate.



So there were two studies that were identified that were published where procedures were conducted before 1980. That left us with 39 studies for review. We then looked at those studies to see if they were applicable to our research question, and the vast majority of those were not. We also did look at the references. By hand, we looked at the references of those particular studies to see if there were additional papers that would be relevant.

So that left 11 specific papers that looked at incidence of occult leiomyosarcoma or sarcoma -- generally, uterine sarcoma -- among our original 41 citations. During data abstraction, as we were reviewing the references of the literature, we found an additional seven publications. So that left us with a total of 18 that were relevant to our research question.

Then we set out, looking at the particular 18 studies, to see how could we best define the population that we were interested in, specifically people who were undergoing hysterectomy or myomectomy for presumed fibroids, of benign fibroids. And we essentially landed on nine studies that included that particular patient population that were included in our primary analysis. And we felt that this was an important way -- we wanted to identify those studies that were really looking at identifying the prevalence or incidence of cancer in their patient population, as opposed to a broader patient population where the procedures were done, but they may or may not have been specifically looking for cases of cancer.

There were an additional nine citations that we included in a secondary analysis that we added to the primary nine that we included in our primary analysis. Two of those studies did look at patients with fibroids. However, one of them was a reply to a letter to the editor, and we just felt there wasn't sufficient information to include that study. And the second was a non-English language study, and we had already predetermined that we would include English language studies only.

The seven additional citations that were not included in the primary analysis were looking at a broader patient population, patients who were undergoing hysterectomy for prolapse or multiple conditions. They were undergoing hysterectomy. And it wasn't feasible to try to tease out the particular patients who were only being seen for fibroid surgery.

And I think it is important that there were cases of sarcoma identified in those studies. However, all of the sarcomas that were identified in those studies were in patients who also had fibroids. So we didn't want to make it murky as far as patients with other gynecologic issues. We were really looking at that patient population that had fibroids.

It's also important to point out that of those seven studies, a high percentage of many of those studies, the patients also had fibroids. So not surprisingly, the cancers would have been found on those patients.

So this slide depicts the nine studies that we included in our primary analysis, and we've laid out the year the study was published. You

can see they were published between 1990 and 2012. The particular study years, you can see some in relatively recent years and some covering longer periods of time, the particular procedures that were done and the indications. Of course, all of these were for presumed benign leiomyoma.

You can see the country that the study was conducted in. The majority of them were in the U.S., the total patient population again ranging from 104 to close to 1450 patients. And we also have the number of uterine sarcomas, so including the broader group which you've heard about today and their associated rates and 95% confidence intervals for the specific study, as well as cases of leiomyosarcoma specifically and their associated rates and 95% confidence intervals. These were the nine studies that were included in the primary analysis.

This is a similar formatted slide, which is the additional nine citations that were not included in the primary, but were added into a secondary analysis. It's the same setup. But you can see here again, the indications for surgery were different. Some of them had multiple indications for surgery. And, again, you can see study years spanned 1996 through 2014; and, again, the number of uterine sarcomas and the number of leiomyosarcomas and their rates and associated 95% confidence intervals. I hope that you brought your reading glasses. I know that's not an easy slide to make sense of.

So once we had identified which particular studies we would

include in our analyses, we ran a couple of different models to see where would we land on the prevalence estimate. So the first that we ran, we both ran it for uterine sarcoma as well as leiomyosarcoma specifically. And the first model was just a simple pooling of the data. If you just looked at the patient population total and the cases of sarcoma or leiomyosarcoma, these would be the rates that you got. And we converted them, the proportions, to rates per 1,000 women.

We ran two additional models, both of them random effects models. We felt like random effects was a better fit than a fixed effects model. And you can see here the rates and 95% confidence intervals for those models. And, ultimately, the SAS procedure was the most robust model, and that's what we have in your Executive Summary. The numbers that are reported there are drawn from that particular model. And you see here, for uterine sarcoma, a rate of 2.8 per 1,000 women, and for leiomyosarcoma in the primary analysis, 2 per 1,000.

And you can see here similar models were run for the secondary analyses, slightly lower rates and a little bit tighter confidence intervals. Not unexpected because of the larger number of patients in the rest of the studies. But, generally, there is consistency among the rates.

And this slide is simply looking at the reciprocal of the proportion in sort of a number that might make it easier to have a conversation about, of one and X number of women. And this is typically the

number that's been cited. You've heard a couple of different citations throughout the day.

Again, drawing from the SAS procedure, which we viewed as the most robust procedure, we estimate 1 in 352 women with a uterine sarcoma who were undergoing hysterectomy or myomectomy for presumed fibroids. You can see there the confidence interval between 224 and 552. And for LMS specifically, it was 1 in 498. Again, the confidence interval is a little bit wider. There were fewer events, so 262 and 943.

Similar to the previous slide, the secondary analysis has slightly lower numbers -- or higher numbers in this case, and you can see here what those are. But, again, across the board, using various models, you get a relatively consistent number.

And this slide just depicts the individual studies that were included in the primary analysis using their rate, which are the diamonds, and then their confidence intervals. And compared to the combined estimate using the SAS procedure, here you can see 2.8 per 1,000 and you can see where the studies line up and the confidence intervals for those studies. And this one is just specific to leiomyosarcoma. Again, using the same format, a rate of 2.0 per 1,000 women and the associated studies.

There are several limitations that are certainly worth noting with respect to our prevalence estimate analysis. The first was that we relied on the published literature, and the majority of studies that we looked at

were studies that were conducted at large academic centers. And so there is certainly the possibility for publication selection and referral bias based on our review of the literature and how we identified cases. We also attempted to control for this in our modeling and also in our selection.

So for selection bias, we attempted to pick as similar a patient population as we could, and we decided not to include that broader patient population. But to really understand among these studies and among this population of women who were undergoing surgery where the clinician felt they had fibroids, what was the risk that they were subsequently diagnosed with a sarcoma or a leiomyosarcoma specifically? And we felt like really controlling that group would help us develop a robust estimate. And we also used random effects modeling to help to control for some of the differences across the studies.

It is worth pointing out that in many of these studies, an index case may have spurred their analysis, so that has the potential to impact the results. And none of the studies were randomized. They were retrospective studies.

And I think an important point is that we relied on the published literature, and we didn't have access to the raw data, and we were not able to stratify our estimates by age. And as you've heard, there are certain risk factors, age being one of those, that may increase or decrease your risk, and we were not able to do that. So it's a general estimate of 1 in

352 or 1 in 498 among the population. But the ages among the studies varied quite significantly as far as the age range of women included.

Our second research question was looking at the probability of seeding an unsuspected sarcoma by morcellation. And then if this was done, what was the impact on clinical outcomes?

We used a similar search strategy, which you can see is outlined here. We initially identified 196 studies. We looked through those studies to see if they were relevant. Forty-four of those were conducted and published before 1980 or without full text. They were not included. And we go through the 152 remaining studies to see if they were relevant. Again, the vast majority of those were not. One hundred and eight were excluded. And many of those simply asked different questions than what we were looking at and were not relevant to our particular research question for looking at impact on outcome or dissemination.

We reviewed the abstracts, 44 papers, to see if they would fit. Thirty-nine of those did not. And the vast majority of those were case studies, small cases studies or single case reports where somebody had been morcellated and they had found some dissemination or some impact. But we really couldn't make sense if we're trying to compare that to patients who are morcellated versus patients who are not. So those studies were excluded. These are the last five studies.

We also identified an additional study as we were going

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through the references of the studies that we had identified, and there was one study that was in press, which subsequently has been published now, that we included. So there were seven total studies that were relevant to our research question.

Again, here, this slide just depicts those particular studies that we looked at. You can see again the study years; the patient populations -- relatively small sample sizes for those; the procedures, morcellation versus no morcellation and then some for specific types of hysterectomy that were conducted; the particular cancers or neoplasms that the researchers were looking at -- some of them had a bit of a broader question, but they looked at sarcoma as part of their research question; follow-up mean and median times; and then the particular outcomes that they were looking at. And you can see here that most of the studies were looking at more than one outcome, so dissemination, recurrence, disease-free survival, and overall survival.

I think it is important to note that the bottom three studies, Seidman, Oduyebo, and George, were conducted by sort of an overlap of researchers at overlapping institutions during overlapping periods of time. They asked slightly different questions, but I think it is important to take that in a context that some of the numbers represented in each of those individual studies may have also been a patient that was included in the other studies.

So the first question that we were looking at was looking at risk



of peritoneal dissemination, and there were two studies that provided some information on that, the Seidman study and the Oduyebo study.

In Seidman, they had 64% or 9 of the 14 cases had pathological evidence of dissemination. And of those 14, there were 7 LMS cases, and among those 7, 57% showed evidence of dissemination. And in the Oduyebo study, 2 of 7 or 28% of the LMS cases had disseminated disease that was detected after immediate surgical re-exploration. So out of the seven studies, really only two of those provided some information on that particular outcome of interest.

The next few slides discuss four of the seven studies that had comparator groups. And the first question we wanted to ask among those four studies was looking at local and any recurrence following morcellation compared to non-morcellation.

So you can see here two of the studies included only patients with LMS. One of the studies, the Park study, included patients who had endometrial stromal sarcoma. And in the Morice study, they included all types of uterine sarcoma. Again, you can see here the total number of patients that were included, as well as the counts and percents of both local recurrence and any recurrence among the study population.

In general, the four studies found that there were increased rates of both local and any recurrence in patients who underwent morcellation compared to those who had not been morcellated. In the Park

study, as an example, 44% of morcellated patients who had LMS had local recurrence compared to non-morcellated patients. And 52% had any recurrence in that study, compared to 22.6% among non-morcellated patients.

We also looked at the odds ratios. And I'll point out that the majority of the odds ratios were presented in the publications themselves. We did calculate for some based on the numbers that were included, and we present the odds ratios as well as their 95% confidence intervals. And three of the four studies found a statistically significant increase in the odds of local sarcoma recurrence in morcellated patients, and the odds ratios ranged from 5.3 to 9.4. In the Morice study, there was no statistically significant difference for local recurrence.

When we look at any recurrence, the Park LMS study found a statistically significant increase, although the George and Park ESS studies both pointed in the direction of increased odds, although it did not reach statistical significance. In the Morice study, they did not report odds ratios or even percents and counts of any recurrence. They were looking at only local recurrence.

And the last two outcomes that we were looking at were disease-free survival and overall survival. Again, we looked from the same four studies, the local and any recurrence studies, and disease-free survival was defined as essentially time to recurrence of disease.

Again, here are the same number of patients. You can see the follow-up time for the various studies. Two of the studies did not provide follow-up time for morcellated versus non-morcellated patients. And when we look at disease-free survival, three studies, the George LMS study and the two Park studies, found a statistically significant increase in odds of poorer survival for patients who were morcellated compared to patients who were not morcellated. And I'll say that the George study was a hazards ratio and the other two were odds ratios.

In the Morice study, looking at all types of uterine sarcoma, they found that there was no difference. But they actually didn't report the hazard ratios in the study. They reported the graphs and described that there was no difference, but we don't actually have the specific numbers.

When we look at overall survival, again, three studies pointed in the direction of poorer overall survival among morcellated patients compared to non-morcellated patients. However, only the Park LMS study reached statistical significance for overall survival being poorer in patients who were morcellated compared to those who were not.

Again, there are several limitations that are worth discussing. The first, again, is publication bias and referral bias. We based our review on the published literature, and so obviously it has its inherent limitations. Again, these studies were not randomized, so there is the potential possibility that there were underlying differences among patients who were morcellated

versus those who weren't that are not accounted for in the outcomes that we've presented -- not controlled for in the outcomes that we've presented. Again, an index case may have spurred the study researchers to look at this particular issue among their patient population.

And it's also important to point out again, similar to the prevalence estimate, it's not clear and, even in some of the studies, not possible that power morcellation was what was done to these particular patients considering the study years, some dating back to the '80s, prior to power morcellators being available. And in some cases they specifically say that scalpel morcellation was done in some of the cases or it wasn't specifically mentioned in the studies. And again a relatively small number of studies and a relatively small sample size.

And so when you start looking at statistical significance, it's not surprising, a little bit of underpowered studies for some of this. But, again, there is consistency in the direction for both local and any recurrence, as well as disease-free and overall survival, that point to poor outcomes among patients who were morcellated compared to those who were not.

So based on our assessment, our quantitative assessment, of the risk of power morcellation, looking across the literature, among patients who are undergoing a hysterectomy or a myomectomy for presumed fibroids, we estimate a prevalence of 1 in 352 women for uterine sarcoma and 1 in 498 for LMS specifically.

Among the studies that did provide information on peritoneal dissemination or cancer upstaging following a morcellation, they reported that this occurred in approximately 25% to 64% of cases, again, pretty small numbers of those studies, but that's the information that's available at this time.

Looking at the particular outcomes of patients, both local recurrence and any recurrence, the studies show that those who were morcellated have significantly higher risk for both local and any recurrence compared to those who did not undergo morcellation. And, generally, the trend was for poorer disease-free and overall survival among patients who were morcellated compared to those who were not.

And I think there certainly has been a very robust discussion today, and you've heard some different prevalence estimates from a variety of the speakers in the morning, and using slightly different data sources. So I think as we try to understand the limitations of the current data and the strengths of the current data, there are certain things that are worth pointing out. And I've gone through our assessment here and sort of the reasons as to why we structured our literature review the way we did, why we included the studies that we did, and I think it's important to realize that estimates may differ because there are differing search terms.

Looking at different study periods, we felt that a cutoff date of 1980 made a lot of sense to try to keep as consistent a patient population as

possible.

Looking at primary purpose of the study, we really, in our primary analysis, included those studies that had as a research objective to identify cases of occult sarcoma in patients that were undergoing hysterectomy or myomectomy for presumed fibroids. And we felt that that was really the best way to ascertain the outcome, that they needed to be looking for it. Even if it was retrospective, they needed to be looking for it as opposed to simply just looking at patients who underwent a hysterectomy, even if it was for fibroids, but it never crossed the researcher's mind to look for cancer. So it's possible that that would bias our results towards a higher number or higher risk, but we felt that was the best way to get at the best possible ascertainment of the outcome.

It's also important that we looked at two different estimates, sarcoma -- the broader group of sarcoma, which is 1 in 352, and for LMS specifically, which is 1 in 498. And I think sometimes it may get confused as far as what particular estimate people are discussing.

It's also important to look to the confidence intervals. So of course, using a random effects model, we're going to have slightly wider confidence intervals. But even across the various estimates that we generated, they all fall within the same confidence interval, although the individual point estimates are slightly different.

And I think it's also important to consider the number of cases

driving the estimates. In absolute terms, it's a relatively rare outcome. We had 26 cases of uterine sarcoma in our primary analysis and 19 cases of leiomyosarcoma in our primary analysis, out of about 9600 patients. But, again, when you look at the reciprocal of the proportion, you get 1 in 352 and 1 in 498.

So thank you very much. And I think I'll move to the next speaker.

DR. DIAMOND: We're going to take questions for all of the FDA speakers at the conclusion of their presentation.

DR. YUSTEIN: Thank you, Dr. Jones.

Again, my name is Ron Yustein, and I'm going to spend a few minutes summarizing some of the additional information in your Panel package. What I'm going to do is I'm going to spend about the next 15 to 20 minutes, and I'm going to be touching on several different topics.

I'll first briefly describe and discuss MDRs in general, to put those into perspective. And then I'll summarize those that we've received related to the current issue related to the laparoscopic morcellators and the dissemination of malignancy. Then I'll present some basic information related to laparoscopic specimen bags, in terms of their regulation and review by FDA, as well as some data from the literature related to permeability and integrity of bags, followed by a brief discussion of the MDRs for laparoscopic specimen bags. And then I'll end with a very short discussion

about variations to morcellation techniques.

In terms of medical device reports, or MDRs, Section 519 of the Food, Drug and Cosmetic Act grants FDA the authority to require mandatory reporting of adverse events from manufacturers, importers, and device user facilities. And the Code of Federal Regulation, 21 C.F.R. Part 803, establishes the reporting requirements for those entities.

To start, I wanted to clarify that, from the regulatory standpoint, an event is considered reportable as an MDR if the device may have caused or contributed to a death or serious injury. And then certain malfunctions of a device are also reportable, namely, if a device fails to meet its specifications or perform as intended and it is likely to cause or contribute to death or serious injury if that malfunction were to recur. I wanted to point out that this requirement does not differ based on device classification. And for clarification for the Panel, if a device may have contributed to or have been a factor in spreading a contained malignancy, FDA would consider that type of event to be MDR reportable.

This chart summarizes reporting requirements at a high level. In general, device manufacturers are required to report deaths and serious injuries and reportable malfunctions to FDA within 30 calendar days of becoming aware of the event.

User facilities such as hospitals and ambulatory surgery centers are required to report device-related deaths to both FDA and the



manufacturer within 10 days, and they should report device-related serious injuries to the manufacturer in that same time frame.

Although requirements to manufacturers, importers, and user facilities exist, any person may submit a voluntary report to FDA at any time. About 95% of the MDRs we receive are from manufacturers.

Before getting into the actual numbers, I wanted to make sure that the Panel understood some of the limitations of the MDR system, which is a passive surveillance system. There are many, but I'm going to highlight the more important ones for your discussions.

1. There is an underreporting of events to CDRH. We know that. This may be due to the end users of devices being unfamiliar with MDR requirements or even knowing that FDA regulates medical devices. In addition, at times, the clinical injury which may have resulted may not be readily apparent, or passage of time may make it less likely for people to make the connection between the device and the event.

2. MDRs often lack critical or sufficient information. Details regarding the patient, their clinical history, concomitant medications and procedures and outcomes may be missing. Sometimes the actual device may not even be known when the MDR is provided.

3. The fact that an MDR is reported does not mean the device definitively caused the death or injury. We need to take into account the natural history of the patient's disease, comorbidities, concomitant

medications, and devices or procedures, all of which can confound the ability to draw a direct cause-and-effect relationship.

4. Because the system is passive in nature and because of underreporting and the inability to accurately determine the number of device uses, MDRs should not be used to calculate any rates of events.

5. Trying to draw definitive conclusions from trends in MDRs over time can be difficult. Changes in numbers for an individual product can be impacted as the device or procedure gains or loses popularity in the clinical community. A recent recall, recent news media or public attention, or manufacturer inspection, among other items, can affect MDR reporting. Comparing numbers between companies is also not practical, as this is influenced by factors such as market share.

The major utility of MDRs in general is that they can provide a qualitative snapshot of a device's adverse event profile during real-world use. Review and analysis of MDRs may provide information on the types of events being seen along with their severity, clinical consequences, and treatments needed to address the issue. Changes in these parameters may be noted, and signals may be generated. MDRs submitted by manufacturers also include their evaluation of the event, which at times may include assessment and testing of a returned product.

A review of our MDR database reveals 21 reports, which have been received by FDA, related to laparoscopic power morcellators and the

dissemination of malignancy through June 22nd of this year. The numbers in my next few slides differ from those in the Executive Summary because we performed an additional look at the reports after we produced that document.

Although we have received 21 reports, it is possible and even likely that some are duplicate reports. However, it is hard to make that statement with absolute certainty because of the limited information provided in some of the reports.

As mentioned in my timeline from this morning's presentation, the first related MDR report describing dissemination of malignant tissue associated with a laparoscopic power morcellator was a voluntary report received by FDA in late December of 2013.

All 21 reports have been received in the past six to seven months. However, the events they describe took place as far back as 2006. As I mentioned a couple of minutes ago, it is not uncommon for FDA to receive an influx of MDRs when a specific type of device or event receives public attention.

The table on this slide illustrates the year of events, not the year the MDR was received. Again, due to significant issues with underreporting, these should not be interpreted to represent all of the events which took place during those years nationwide. However, they are the only ones reported to FDA.

Patient age was reported in 16 of the 21 reports. And for that group, the mean and median age of the women was about 50 to 51 years. None of the reports specifically mention the woman's menopause status. The majority were voluntary reports from individual patients or family members, and most of the reports involved U.S. cases, although we have received one report from Japan.

Seven of the 21 reports noted events where the patient ultimately expired. The table on this slide provides a summary of the information from those seven reports. The last two MDRs contain the exact same verbiage and may represent duplicate reports. Three of the seven were submitted as voluntary reports. One of the seven reports noted a formal stage for the disease after reevaluation and restaging, and that was IIIB, while several others described disseminated or metastatic disease being present. Four of the reports provided a brief timeline of events, and in those four cases the time to death was an average of 11.5 months following the index procedure.

This slide summarizes additional information provided for the remaining 14 reports. The majority of these cited leiomyosarcoma as the malignancy diagnosed after morcellation. In one way or another, most described dissemination of tissue. A handful of reports described treatments which the patient underwent subsequent to the diagnosis of the disseminated disease, including debulking surgeries, systemic chemotherapy,

and local radiation therapy.

In summary, CDRH has received 21 MDR reports related to the issue we're here to discuss this week. All have been received since December of 2013, although some report events as far back as 2006. There is limited information provided in those reports, and some may actually be duplicates. Leiomyosarcoma was the most frequently reported malignancy, and many of the reports received did describe dissemination or advanced stage disease, seven reporting patient death.

I want to switch gears now and summarize for you some of the information in your Executive Summary regarding laparoscopic specimen bags.

As the safety issue we are here this week to discuss has moved to the forefront, there has been significant interest and mention of the use of specimen bags as a potential means to contain fragmented tissue during morcellation. You have heard several presentations this morning to that effect, and the Panel will be asked to discuss the use of bags as a potential mitigating strategy tomorrow.

Laparoscopic specimen bags are medical devices that are usually single-use, disposable plastic receptacles on appropriate delivery accessories which are used for collection and extraction of tissue during laparoscopic surgical procedures. These devices are also Class II products regulated as 510(k)s. This slide lists the type of performance data which is

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typically provided to and reviewed by FDA in the 510(k) submissions for specimens bags. Clinical data is not submitted to support substantial equivalence in these submissions.

The indications for use for these products are broad, although some may make mention to the specific types of tissues or organs which can be collected with the device. These devices are not reviewed, cleared, or indicated specifically for the reduction of risk posed by malignant tissue.

The labeling for specimen bags, with respect to use with morcellators, varies from manufacturer to manufacturer. Several manufacturers have chosen to include a contraindication for their product, in terms of use with a morcellator. Several have chosen to include a warning or precaution in their labeling which advises the physician to avoid contact of the bag with sharp instruments, including morcellators. Several products do mention morcellation in the instructions for use, although not always specific for power morcellation. The labeling for many, however, is silent in terms of use with laparoscopic power morcellators.

Specimen bags were designed and intended to collect and contain tissue specimen and to aid in the extraction during surgery. Certainly, there is plenty of documentation and experience that these devices can be used successfully and effectively to perform those functions during laparoscopic surgeries.

However, the use of a power morcellating device within a

specimen bag introduces several questions regarding the bag. Two of the major questions might be (1) is the bag impermeable to small tissue fragments in particular, down to the level of cancer cells? And (2) how resistant is the bag to tearing or rupturing in different settings, including with the concurrent use of a power morcellator? Both of these factors may be relevant to the ability to contain worrisome material during the extraction process.

Unfortunately, to date, it appears that little specific data is available to speak to these points. Permeability data is not typically evaluated as part of FDA 510(k) submissions for specimen bags. And although hydrostatic leak testing, burst testing, and puncture testing may be part of such submissions, testing with power morcellators is not.

I wanted to summarize some of the information in your Executive Summary based on published literature. Some of the literature is decades old, and the results have not necessarily been replicated. I wanted to start by briefly mentioning the issue of bag permeability.

A study by Urban et al., published in 1993, is consistently quoted in the literature as the landmark study which demonstrated that at least one marketed specimen bag, the Cook LapSac bag, is impermeable to cancer cells. I wanted to describe that study in more detail for you.

The investigators collected 24 bags after they had been used once for power morcellation during a laparoscopy course. Four of the 24

bags demonstrated leakage and had visible pinholes and were excluded from the rest of the study. Of the remaining 20 bags, 18 were divided into six separate groups, and one of those groups of six was where the bags were filled with a suspension of mouse bladder tumor cells, and that bag was then suspended in a four-liter beaker of water for three hours and agitated every 30 minutes. Samples from the beaker were taken at one and three hours for analysis.

At the end, one of the six beakers had a single cell visible on the grid at both readings, indicating, according to the authors, that the concentration of cells in dialysate was  $1 \times 10^4$  cells. While the article did not say the unit specifically, we might assume that this is  $10^4$  cells per milliliter.

That bag showed no visible leakage or pinholes on inspection. The authors speculated that if there had been a true leak or perforation, there should have been an increase in concentration from the one- to three-hour reading, but it was constant. This led them to conclude that contamination of dialysate likely occurred at the onset, although no sample was taken at time zero for comparison to confirm that.

It should be noted that one of the investigators during the study was the co-inventor of the product and was receiving royalties at the time.

Rassweiler published results of an in vitro test with a variety of available specimen bags from different manufacturers in 1998. Among the



fluids tested was a tumor cell suspension. The fluid-filled bags had digital manipulation performed to simulate morcellation, and the lower part of the bag was then rinsed in normal saline and the eluate was examined microscopically.

The authors concluded that all bags, except those from one manufacturer, proved to be impermeable to tumor cells before and after manipulation. However, we are uncertain as to the exact methodology and adequacy from the report.

Moving to bag integrity, there are two published in vitro studies which evaluated the forces required to disrupt specimen bags on a bench and are shown in this slide. The Eichel study evaluated bursting tension of different bags by using a 25 mm ball placed at the bottom of the bag, which was then pulled through a 20 mm hole in a Lucite plate. As you can see, some products were disrupted with as little as 30 pounds and others required up to 133 pounds.

Puncture pressure was measured by sandwiching a monolayer sheet into a stretcher block of Lucite with a hole through the middle. A 16.5 mm Kelly clamp and a pair of ring forceps attached to a strain gauge were individually depressed into the material until a puncture pressure for each instrument was obtained. The table on this slide depicts the results, again demonstrating some variation between products.

Rassweiler evaluated tear forces needed to cause bag rupture.

Bags were cannulated, closed by staples, and then filled with water, continuously monitoring until rupture. The filling pressure was used to calculate resistance in  $\text{N/mm}^2$ , and the span in results is shown in the table on the slide.

Also, both of these studies are 10 or more years old, and it should be noted that some of the products tested are no longer marketed, and many of the products currently marketed were not tested.

This slide points out some key components of two additional in vitro studies looking at bag integrity, but this time in conjunction with the use of a power morcellator.

Cai et al. evaluated LapSacs while performing in vitro morcellation of porcine kidneys in a pelvic trainer under three different scenarios. Group 1, consisting of 10 samples, was one where power morcellation was performed within fluid-filled bags under direct visualization with the aid of a nephroscope placed within the bag. Group 2, again a sample size of 10, was power morcellation performed within fluid-filled sacs monitored by laparoscopic visualization outside the bag. And then the third group was manual morcellation using ring forceps after the mouth of the bag was brought to the body surface through a port site and monitoring via laparoscopic camera.

In Groups 1 and 2, the authors kept a constant flow of irrigant into the sac during morcellation, both to cool the blades and keep the bag

expanded.

The bags were assessed after each trial. One pinhole perforation was noted in Group 1, nine perforations in Group 2, including five large and four pinholes, and none in Group 3.

It should be noted that the morcellator used in this study was a prostate morcellator not indicated for gynecological use and intended for use specifically in a fluid median.

Parekh et al. also performed in vitro evaluations of tissue morcellation within bags using the Steiner morcellator. The kidneys injected with methylene blue were morcellated within either a dry or fluid-filled LapSac. This was a very small study, but no perforations were noted within the fluid-filled bags, but eight perforations were seen in one of the two dry bags, leading to gross tissue spillage.

Cohen recently described an in vitro study using indigo carmine-dyed beef tongue specimens which were placed in one of two types of bags and then inside an enclosed laparoscopic box trainer. The opening of the bag was brought out through a defect and a trocar inserted into the bag. The bag was insufflated and an LPM was inserted. Morcellation was performed under laparoscopic visualization, and four trials were performed with each bag type using a multi-port approach. There was no gross spillage of tissue chips. One bag had a single puncture site. All others were visually intact. Blue dye spillage did occur in one of the trials. In this case, spillage

was noted from a seam of a bag prior to morcellating, but after insufflation. Cytological examination of the box washings revealed muscle cells in this case. Washings for the other ones were negative.

The authors concluded that the use of larger bags and continuous laparoscopic monitoring may provide additional safety measures, and that containment systems may effectively decrease or potentially eradicate tissue spillage as compared to traditional open morcellation technique.

Certainly, the blades of a morcellator can disrupt a specimen bag which is made from plastic materials. As mentioned before, many bags were not designed, tested, or intended to be used with an instrument like a power morcellator. Beside the morcellator blades causing tears in specimen bags, the frictional heat and/or mechanical pressure exerted by the instrument may also possibly cause bag damage or rupture, as can generic sharp instruments used during typical surgical procedures and the act of pulling a closed, filled bag through a narrow trocar or incision.

Switching now quickly to the medical device reports received for laparoscopic specimen bags, the reports include a variety of different laparoscopic procedures from different specialties, not just gynecological ones. We took a look back over the last 10 years and, in fact, the majority of reports we have for specimen bags relate to procedures involving cholecystectomies and appendectomies. Others included uterine, kidneys,

adrenal glands, spleen, lung lobes, ovaries, bowel, and prostate.

The most common type of event reported to FDA in these MDRs was the disruption or breakage of the bag, often during withdrawal of the bag and its contents through the trocar or incision. Some reports noted prolonged procedure time to retrieve the tissue or bag fragments. In these cases, additional steps may have been required to complete the procedure, including expanding the length of the port incision. Other events included difficulties opening, deploying, or closing the bag, bag disconnections from the supporting handle, and the bag getting stuck in the trocar.

Only three specimen bag MDRs in the past 10 years specifically mentioned morcellation. In all three, morcellation of a spleen within a bag was being performed and resulted in the morcellator damaging the bag, followed by injury to local vascular structures and/or bowel.

Four other bag MDRs specifically mentioned malignancy in the event description. In all four reports, the bag malfunctioned during retrieval of the specimen. In two of the four reports, this resulted in release of the contents into the abdominal cavity. No further patient outcome data was available in those reports. However, it should be noted that none of those four reports noted whether morcellation had been performed or not.

The last topic I wanted to touch on for a few minutes relates to variations to morcellation. Not alternatives to laparoscopic surgery or performing laparoscopic surgery without morcellation, but rather how some

have described various techniques to perform morcellation associated with laparoscopic surgeries.

This is certainly not an all-inclusive discussion, as evidenced by some of the information you heard earlier today from various speakers, including Dr. Sobolewski. However, FDA will be asking the Panel tomorrow their thoughts on whether any specific surgical techniques, intraoperatively, can reduce or eliminate the risk of intraperitoneal dissemination of malignancy during morcellation.

Several literature reports describe techniques for the removal of larger uteri during laparoscopic hysterectomy, in which the specimen is too large to be extracted vaginally. In one technique, a specimen bag is inserted through a laparoscopic port and opened intra-abdominally. The specimen is placed in the bag and the port incision is extended, perhaps to 2 cm to 3 cm, so that the edge of the bag can be brought up through the incision. The specimen is then brought above the abdominal incision before it is cut, essentially morcellating extracorporeally. Clinicians who support this technique claim that this reduces the risk for both intra-abdominal injury from morcellator blades as well as intraperitoneal contamination of tissue during extraction.

Other in-bag morcellation techniques which have been advocated to reduce the risk of bag damage, and therefore possibly tissue dissemination, include performing morcellation within the bag under direct

visualization using a smaller laparoscope and/or ensuring that the bag is insufflated sufficiently with either fluid or air.

Finally, transvaginal in-bag extraction and morcellation of a laparoscopically transected specimen has been advocated by some -- and you heard about that earlier today -- as a way to maintain the minimally invasive nature of a procedure and avoid intraperitoneal morcellation.

The Panel will be asked tomorrow to provide FDA with their opinions and recommendations regarding intraoperative strategies which may be used during morcellation which may mitigate the identified risk, including, but not limited to, the use of specimen bags and specific morcellating techniques such as the one I briefly described.

With that, I would like to now hand over the podium to Dr. Julia Corrado from our Office of Device Evaluation who will discuss some issues related to morbidity and mortality associated with the different surgical routes of hysterectomy.

DR. CAREY-CORRADO: Good afternoon, everyone. I thank all Panel members and members of the audience for attending this meeting.

Dr. Sobolewski has already talked about details of various surgical approaches for hysterectomy and myomectomy. I'm going to briefly discuss some quantitative results on clinical outcomes for different approaches to hysterectomy.

The reason for the presentation is that FDA believes that there

will be consequences of increased public awareness of laparoscopic power morcellation for symptomatic fibroids. We believe that based on patient-physician dialogue on the risks and benefits of laparoscopic power morcellation, that some patients may seek to avoid laparoscopic power morcellation for their hysterectomy procedure. And as a consequence to wanting to avoid, potentially, some patients may wish to avoid power morcellation. We think that patient counseling regarding alternative surgical routes for hysterectomy need to be transparent and based on the best evidence.

The synopsis I'm going to present is based almost exclusively on the Cochrane database of systematic reviews by Nieboer et al., published in 2009. The Cochrane Review presents outcomes from randomized controlled trials comparing one surgical approach to hysterectomy with another. Thirty-four studies are included. The total number of patients was approximately 4500. And I have an asterisk so that you can see the distribution of the 4500, what proportion received abdominal versus vaginal versus laparoscopic hysterectomy.

We would note that this review was cited by ACOG in their Committee Opinion Number 444 on the route of hysterectomy for benign disease. And I would also note that the review does not address the risk of cancer dissemination secondary to morcellation.

So, first, I'm going to summarize clinical outcomes for vaginal

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versus abdominal hysterectomy. Dr. Sobolewski has already presented the punch line on this. So what my slide will add possibly is some more quantitative information regarding those outcomes.

I would also say that many outcomes are reported in the Cochrane Review, and this list is not comprehensive, but we attempted to identify some clinically important outcomes. So we'll be again presenting results for return to normal activities; intraoperative visceral injury, specifically urinary tract injury; operative time; hospital stay; the occurrence of febrile episodes or infection; and mean blood loss.

In the column on the far right-hand side you can see the number of randomized controlled trials that contributed to the outcome in the meta-analysis and the total number of subjects.

Regarding return to normal activities, vaginal hysterectomy was associated with approximately a 10-day faster return to normal activities. There was no statistical difference in the occurrence of intraoperative visceral injury or operative time. However, hospital stay was significantly shorter with vaginal versus abdominal hysterectomy, and the odds ratio on the occurrence of febrile episodes or infection favored the vaginal approach. There was no statistical difference in mean blood loss. So the takeaway point is that vaginal hysterectomy provides faster return to normal activities, shorter hospital stays, and fewer febrile episodes or infections compared to abdominal hysterectomy.

The next comparison is laparoscopic versus vaginal hysterectomy. I'll be talking about similar outcomes, that is, return to normal activities, intraoperative visceral injury, other intraoperative complications (that is, not including visceral injury), operative time, duration of hospital stay, and the need for transfusion. And because it's late in the afternoon, I will quickly go to the outcomes for which there was a statistically significant difference.

Laparoscopic hysterectomy was associated with a higher risk of intraoperative complications, longer operating time, and a higher odds ratio for the need for transfusion compared to vaginal hysterectomy. The take-home message is that the vaginal route offers important benefits compared to both abdominal and laparoscopic hysterectomy. And ACOG has recommended -- and other professional organizations -- that the vaginal route for hysterectomy be undertaken when possible. Importantly, however, it is not possible in all cases.

So when vaginal hysterectomy is not an option, it brings us to consider laparoscopic versus abdominal hysterectomy. And we will be speaking about similar outcomes as I have discussed in the prior two slides.

Where you see the checkmark in the far left column, that indicates that there was a statistically significant benefit to the laparoscopic approach. And the middle column gives you an idea of the quantitative nature of that benefit. So for return to normal activities, other intraoperative

complications excluding substantial bleeding, the duration of hospital stay, the occurrence of wound infection, and a mean difference in blood loss, laparoscopic hysterectomy had benefits over abdominal hysterectomy. Regarding intraoperative visceral injury, specifically urinary tract or bladder, and operative time, the advantage went to the abdominal route.

Regarding thromboembolic events, there was no difference based on three randomized controlled trials, with an  $n$  of approximately 1100, a little more than 1100 subjects.

I have to add that, as I mentioned, this is not a comprehensive list of all the outcomes. And a very important outcome that I have not listed here, which may be intuitively obvious, but I wanted to call out, is the occurrence of pain or the need for postoperative analgesia. And that overwhelmingly favored the laparoscopic approach.

So laparoscopic hysterectomy provides faster return to normal activities, fewer intraoperative complications excluding urinary tract injuries and substantial bleeding, shorter hospital stays, less wound infection, and less blood loss compared to abdominal hysterectomy, whereas abdominal hysterectomy was associated with fewer intraoperative urinary tract injuries and shorter operative time compared to laparoscopic.

I want to spend a little bit more time discussing thromboembolic events, as they do have the potential to contribute to severe morbidity and even mortality.

There are varying interpretations of the available evidence and literature on this topic, that is, the comparative risk of venous thromboembolic events for laparoscopic versus abdominal hysterectomy. We think it's worthwhile to discuss it here because we believe that patient counseling regarding the risk of venous thromboembolism does have potential to impact a patient's decision regarding the surgical route of hysterectomy.

So going back to our Cochrane authors, the risk of thromboembolic event was evaluated in three randomized controlled trials that are included in the Cochrane Review. You can see those three trials.

Incidentally, the Garry et al. (2004), that was relatively a large study compared to other studies and is an important study in the Cochrane Review. It was the EVALUATE study. This was a study where there were two parallel RCTs that were undertaken at the same time, one comparing laparoscopic and abdominal and one comparing laparoscopic versus vaginal hysterectomy. It's important to point out that the investigators decided the initial allocation to the two different studies, possibly because vaginal hysterectomy is simply not an option for some patients and it would have been inappropriate to randomize. But that is my speculation. I do not know.

So the point that this slide is attempting to make is that the odds ratio on the risk of thromboembolic event for laparoscopic versus abdominal hysterectomy showed that there were no statistically significant

differences in the occurrence of this event for these two routes of hysterectomy. And the meta-analysis of those three studies concluded the same thing. So, again, there are different interpretations of available literature for this endpoint.

The last topic I briefly wanted to touch on is what we know about the risk of mortality for laparoscopic versus abdominal hysterectomy. Again, we think this is going to be potentially important in patient counseling, and what we would like to say about it is there is limited comparative outcomes data. As Dr. Sobolewski indicated this morning, there is currently information in the public domain that points to an increased risk of mortality for the abdominal approach versus the laparoscopic approach. He discussed some of the issues around that information.

This was a retrospective cohort study using Health Cost and Utilization Project Nationwide Inpatient sampling between 2002 and 2008 study. We believe that it should be transparently communicated that there are limitations to the study, including the following:

- The study captured in-hospital events only;
- The severity of the fibroid disease is unknown as that information is not gettable;
- Coding precludes identification of conversion from laparoscopy to laparotomy; and
- There's no information available on certain confounding

variables, such as body habitus, that may impact this outcome.

Also, this information does not consider the risk of morcellation of an occult malignancy and how this might contribute further to this outcome.

So our conclusion is that patient counseling regarding alternative routes of hysterectomy should be based on transparent and high-quality evidence.

Next, Veronica Price, biomedical engineer, will discuss how FDA regulates laparoscopic power morcellators.

Thank you.

MS. PRICE: Good afternoon, distinguished members of the Panel. My name is Veronica Price. As Julia said, I'm an engineer within the Obstetrics and Gynecology Devices Branch within the Office of Device Evaluation in CDRH. I can also tell you the good news, that I am the last presenter. So I'll try to speak quickly.

The focus of my talk today is on the regulation of laparoscopic power morcellators. The following is an outline for my presentation this afternoon. I'll begin with a very brief introduction to medical device regulation.

Laparoscopic power morcellators are Class II devices. Medical devices are classified into one of three classes (Class I, II, or III) based on the

level of control needed to provide adequate assurance of safety and effectiveness.

Class I devices are those devices that need only general controls to provide a reasonable assurance of safety and effectiveness. General controls include things such as prohibition against adulterated or misbranded devices, good manufacturing practices, registration of facilities, a listing of device types, et cetera.

Class II devices, such as laparoscopic power morcellators, are devices that cannot be classified into Class I because general controls are insufficient to provide a reasonable assurance of the safety and effectiveness of such a device, and for which there is sufficient information to establish special controls to provide such assurance. Class II devices typically require premarket notification to FDA -- that is called a 510(k) -- prior to being marketed.

Special controls, if promulgated by FDA regulation, are applied to all devices within a specific product category. They may include one or more of the following: physician/patient labeling; premarket studies; performance standards; guidance documents, et cetera.

For those devices with special controls, device manufacturers must provide evidence in their 510(k) submissions of how the special controls were addressed.

In addition to postmarket surveillance as a special control, FDA

also has the authority to require postmarket surveillance under Section 522 of the Food, Drug and Cosmetic Act. Section 522 provides a mechanism by which FDA can obtain additional safety and/or effectiveness data for devices after clearance through the 510(k) process or approval via the PMA process.

In contrast to special controls, which are applied to all devices within a product category, 522 studies can be ordered for individual devices or particular modifications to an individual device.

Class III devices are those devices that cannot be classified into Class II because insufficient information exists to determine that general and special controls are sufficient to provide reasonable assurance of the safety and effectiveness, and the devices are life sustaining and/or life supporting, or of substantial importance in preventing impairment of human health, or presents potential or unreasonable risk of illness or injury. Class III devices require PMA, or premarket approval, prior to being marketed.

I will now provide an overview of the regulatory history and a general overview of laparoscopic power morcellators. Most of this you've already heard, so I'll go through it quickly.

Dr. Yustein mentioned that the first laparoscopic power morcellator was cleared via 510(k) in 1991. It had a general use indication. And the first device that had a gynecologic indication was in 1995.

LPMs are used to cut, core, and extract tissue. Currently marketed laparoscopic power morcellators are either electromechanical or



electrosurgical. They may be electrically powered through AC line current or with a battery. Laparoscopic power morcellators may be single-use disposable, a reusable device, or include a single-use component such as a morcellator blade and a reusable component such as the motor drive.

The basic principle of operation requires that tissue be brought into contact with the cutting edge of the device. This may be accomplished with suction or through use of a grasper passed through the central lumen of the device. Electromechanical morcellators use a spinning blade to cut tissue. The size of the blade and its speed of rotation will vary across device manufacturers. The currently marketed electrosurgical morcellator uses bipolar RF energy to cut tissue.

Depending on the design of the device, morcellators may reduce the size of the tissue by either cutting -- sorry -- by either coring out cylindrical pieces or peeling it away in layers.

The premarket testing of laparoscopic morcellators is driven by the indications for use and the technology. Device manufacturers conduct testing that is relevant to the design of their device and its mechanism of action. Due to differences in design, testing may vary across device manufacturers. However, there are some typical tests that apply to most laparoscopic power morcellators. They include things such as basic safety testing, including electrical safety and electromagnetic compatibility, software evaluation, biocompatibility, sterility, and functional performance.

As previously indicated, laparoscopic power morcellators were initially cleared via 510(k) with a general indication. The initial submissions that included a specific gynecologic indication in the proposed indications for use focused on the technical performance. If the specifications were the same as the marketed device, then the 510(k) for the new specific GYN indication contained additional limited clinical data. The purpose of the clinical data was to show that the device could be used in gynecologic laparoscopic procedures without technical issues, and that the tissue fragments removed through the device were sufficient for histopathologic evaluation. In some cases, there was also some data on the rate of morcellation.

The Panel will be asked tomorrow to comment on whether clinical data, either premarket or postmarket, is necessary to address risks of laparoscopic power morcellators for gynecologic use.

Device manufacturers develop labeling for their devices. Currently marketed laparoscopic power morcellators with a specific gynecologic indication typically include a safety statement in the labeling regarding use of the device in cases of known or suspected malignancy or cancer. Labeling for these devices does not generally include information regarding the risk of undetected uterine sarcoma in women with fibroids.

I'd like to spend the next few minutes reviewing the postmarket signal and providing a high-level overview of risk management.

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With FDA's receipt of the postmarket signal, an analysis of the available information on uterine sarcoma and leiomyosarcoma was undertaken. As discussed earlier this afternoon in detail by Dr. Jones, the analysis revealed that the probability of the risk was higher than previously appreciated. As a result, the risk analysis for these devices must be updated, which includes a reevaluation of risk control, for example, the preclinical testing and the labeling.

Risk management. Device manufacturers systematically manage risks throughout the total product life cycle. There is an accepted international standard that may be used as a tool. The components of risk include the probability of occurrence of harm and the consequence of that harm or the severity.

As part of the risk management process, device manufacturers need to conduct a risk analysis which considers the intended use of the device, and then identify the hazards and estimate the risk for each hazard. The manufacturer then identifies control measures that are appropriate for reducing the risk to an acceptable level.

When developing control measures or mitigations to reduce risk, the first priority is device design. The device, with confirmation through testing, would ideally demonstrate that the device is safe by design. If that is not possible, the second priority is to examine accessory devices or surgical techniques that can be incorporated into the use of the device to

demonstrate that the risk has been reduced to an acceptable level. Finally, information and labeling for the device and/or training may be used in addition to any of the mitigations above or by itself. In addition to its use as a mitigation tool, labeling is also used to provide information on risks.

I'd now like to specifically discuss some potential risk mitigations for spreading undetected uterine sarcoma.

When considering the device design as a risk mitigation for dissemination of malignant tissue, there is a current lack of information on particulate generation and dispersion with the currently marketed laparoscopic power morcellators. None of the currently marketed devices include a method for tissue containment and therefore, as designed, they do not mitigate this risk. FDA encourages innovation in this area.

The Panel will be asked to identify key design/performance features with respect to mitigating this risk. The Panel will also be asked tomorrow for recommendations regarding preclinical testing to evaluate particulate generation.

One example of an accessory that may be used to mitigate the risk of intraperitoneal dissemination is the use of a specimen bag. As previously discussed in detail during Dr. Yustein's presentation, specimen bags may be a mitigation against the risk of tissue fragment dispersion. However, they would need to be evaluated for permeability and integrity when used with a laparoscopic power morcellator. In addition, modifications

to the current morcellation techniques to incorporate bags may need further evaluation.

The Panel will be asked to discuss available information on specimen bags tomorrow, during laparoscopic surgery and whether it supports their use as a mitigation.

There are other surgical techniques for morcellation described in the literature and described earlier by Dr. Yustein and included in your Executive Summary, which have been reported as a potential mechanism to reduce the risk of tissue dissemination. They include in-bag extracorporeal morcellation, in-bag visualization of morcellation, vaginal morcellation with and without specimen bags, adequate draping, and use of atraumatic instruments.

The Panel will be asked whether there are surgical techniques for performing uterine power morcellation that adequately mitigate the risk of intraperitoneal dissemination of tissue.

Some potential ways in which labeling may be used to mitigate this risk include patient selection information; a statement to determine, prior to the procedure, whether a laparoscopic approach with a laparoscopic power morcellator is preferable to an alternative approach in which the uterus/fibroid is removed en bloc; recommendations or use of a specimen bag or other techniques may also be included.

As previously indicated, labeling also serves to inform users of

risks. Labeling for laparoscopic power morcellators generally does not inform users of the following risks: the risk of unsuspected uterine malignancy and the risk of dissemination of unsuspected uterine malignancy with use of the device.

The Panel will be asked to provide labeling recommendations to mitigate risk, including patient selection/screening, directions for use. The Panel will also be asked for recommendations on identifying risks in labeling, including a boxed warning, FDA's strongest type of warning.

Training. FDA does not regulate the practice of medicine and therefore cannot prescribe a particular training regimen. However, we can require it as a special control. Many device manufacturers have successfully worked with professional societies to develop training programs.

The Panel will be asked to provide recommendations on special or additional training.

I would like to now transition from the specific risk of spreading undetected uterine sarcoma to a more comprehensive review of all of the risks associated with laparoscopic power morcellators and consider ways in which they may be mitigated.

As I previously pointed out, Class II devices are those for which there is sufficient information to establish special controls, that is, mitigations. Given this new safety information for laparoscopic power morcellators, it's important to reevaluate all of the risks that have been

known to be associated with these devices and determine whether they can be mitigated.

When considering the risk of laparoscopic power morcellators, they can be categorized as those general risks that are typically associated with powered surgical tools, for example, a device malfunction that might lead to injury, nerve/muscle stimulation in the case of an RF device, electrical shock, electromagnetic interference, adverse tissue reaction, and infection.

We can then consider those risks that are more specific to laparoscopic power morcellators and their use in gynecology, which would include dissemination of unsuspected cancerous tissue beyond the uterus, dissemination of benign tissue, injury to non-target tissue, and inadequate sample to determine pathology.

The Panel will be asked to comment on the completeness and accuracy of the list of risks associated with laparoscopic power morcellators.

The table above is intended to summarize how each of the general risks previously identified might be mitigated. So, for example, for the risk of a device malfunction leading to injury, potential mitigation measures would include things like software verification and validation, non-clinical performance testing, maybe labeling and training and so on.

When we consider the specific risks of laparoscopic power morcellators and their use in gynecology, and we look at that first risk of dissemination of unsuspected cancerous tissue beyond the uterus, potential

mitigation measures might include non-clinical performance testing, including specimen containment system, labeling, and training. In the case of dissemination of benign tissue, we may be looking at similar mitigation measures. For the injury to non-target tissue, similar, and that would be looking at non-clinical performance testing, labeling, and training. And, finally, for the risk of inadequate sample to determine pathology, we might consider non-clinical performance testing.

The Panel will be asked to comment on the completeness of the list of risks and mitigations and whether the risks can be effectively mitigated to an acceptable level.

Labeling mitigations. When considering some of the other specific risks identified with laparoscopic power morcellators which can be mitigated with labeling, the risk of dissemination of benign disease may include recommendations for use of a specimen bag or other techniques for tissue containment. The risk of injury to non-target tissue may include information on the need for direct visualization, maintaining a pneumoperitoneum, and exercising care during insertion and removal of the device.

The Panel will be asked to comment on these proposed labeling mitigations and indicate whether any additional information is necessary.

The utility of clinical data. FDA does not currently include clinical testing in a list of potential mitigations, although in certain



circumstances we can require clinical testing, premarket or postmarket, for devices in Class II. For most risks, non-clinical data provide adequate or superior risk mitigation when compared to clinical data. In some cases, however, premarket clinical data may be necessary in addition to bench testing to demonstrate device performance and/or its effectiveness.

Postmarket clinical data may also be necessary.

510(k) submissions for laparoscopic power morcellators that include similar indications for use and technology do not require clinical data to support a finding of substantial equivalence. In light of the new safety information, FDA is considering whether clinical data may be necessary.

Some of the factors to consider when deciding whether clinical data is necessary for the regulation of laparoscopic power morcellators include:

- What information can be obtained from the clinical data that couldn't be obtained from bench or animal testing?
- What is the question that the clinical study would attempt to answer?
- How would the clinical data be used to address risk?

Just to reiterate what I had said earlier, the Panel will be asked to comment on whether clinical data will be necessary to address risks.

Finally, I will conclude with regulatory decision making.

For the purposes of making a regulatory decision on the

appropriate level of control for laparoscopic power morcellators, FDA considers all risks to health posed by laparoscopic morcellators for gynecologic use, and whether sufficient information exists to establish special controls or mitigations to provide adequate assurance of safety and effectiveness.

FDA has identified potential mitigations for the identified risks, which may serve as special controls and assist in providing sufficient regulatory oversight on these devices, given the postmarket safety signal.

That concludes my presentation. Thank you.

DR. DIAMOND: I'd like to thank all the FDA presenters for their presentation.

I note that we've been going for about three hours straight and we keep on losing individual members of the Panel. And so I think, rather than asking the FDA questions now, we'll probably take our break first for 10 minutes, and then we'll ask questions of all of the FDA presenters when we come back from that break.

(Off the record.)

(On the record.)

DR. DIAMOND: All right, because of some of the questions that have come up during the session today and some of the suggestions from the audience, as well, about possible roles for registry, we've asked FDA to give a brief presentation about registries. And we'll start with that, and then we'll

go to our questions for the FDA, including any we may have on the registry, as well.

(Pause.)

DR. GATSKI: Sorry about that. We're ready.

My name is Megan Gatski from the Division of Epidemiology, and I will present a brief overview of registry studies.

Registries have been described as an organized system for the collection, storage, retrieval, analysis, and dissemination of information on individual persons who have either a particular disease, a condition that predisposes them to the occurrence of a health-related event, or prior exposure to substances or circumstances known or suspected to cause adverse health effects.

A registry is systematic data collection on all exposed patients, a repository of data for analyzing real-world device performance, and ongoing data collection system that can be leveraged for more in-depth studies.

A registry is not a silver bullet that will solve all postmarket surveillance needs or a single-arm study compared to OPC or performance goal.

Steps to consider in the planning phase of a registry include the purpose, appropriateness, stakeholders, feasibility, team, governance, scope, the core data/outcomes/population, and the protocol and project plan.

The key points to consider in a registry include study design,

data sources, patient selection, comparison groups, sampling strategies, and consideration of possible sources of bias and ways to address them to the extent that is practical and achievable.

The types of data to be collected are guided by the registry design and data collection methods. Data sources are classified as primary or secondary based on the relationship of the data to the registry purpose.

In summary, a registry is good for:

- gathering data on devices where exposure can be easily identified or defined;
- evaluating interactions between different medical products;
- hypothesis generation or signal detection;
- index procedure and acute outcomes; and
- defined populations.

Thank you.

DR. DIAMOND: Thank you.

We will now go ahead with questions from the Panel to the FDA based on what are now, I guess, five presentations we've heard.

We'll start with Dr. Hillard.

DR. HILLARD: So, first of all, I'd like to thank the presenters. So far I think there's been lots of important and helpful information that's been presented.

But I do have some general questions, and I would say, at the

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risk or perhaps the benefit of not being asked to serve on subsequent panels, I'm going to go ahead and ask the question or questions, which is, can you tell us -- and I'm not sure to whom I'm directing the question, so you all can decide who best can answer -- but the question is, what was the process that occurred at the FDA prior to issuing the Safety Communication?

And, in particular, why is this meeting where much important information has come out, why is this meeting occurring after that statement was issued?

And then what will the process be after this meeting?

DR. YUSTEIN: I'm Yustein.

So I guess you had three questions there, the first one, what was the process leading up to the Safety Communication. So as I tried to identify in one of my introductory slides in the timeline, we first took on the safety signal back at the end of December, slightly after Christmastime, and we had assembled a team internally to look at the information and certainly refining a signal, gathering additional information can't be done overnight. So from January through February and March was when we were conducting our literature review, and Dr. Jones and his group were conducting their analysis. We were looking at other sources of information, looking through the MDRs, et cetera.

Certainly, pulling together a panel is not something we can do overnight. Putting out a communication is something that we had easier

control over in terms of timing, and we felt that the information that we had gathered and assessed at that point was worthy of putting out at that time and not waiting two to three months to assemble a panel. To gather a group this large with this type of expertise cannot be done overnight. It takes us quite a while to get people cleared for the panel and to set this up.

In terms of where we go after this panel, I think that certainly this safety issue is a very high priority for the Center, and as we move along, anything that we do decide to do will be made public.

DR. HILLARD: Thank you.

DR. DIAMOND: Okay.

Dr. Talamini, please.

DR. TALAMINI: Thank you.

My main question revolves around the statistics on the number that Dr. Jones brought forward. And I think the issue for me, when this number first was made public and I began speaking with busy gynecology colleagues, it just wasn't passing the smell test for many of them who are very busy and might statistically see one of these cases a year, based on that sort of a statistic.

So with that in mind, in generating that number, did the FDA consider looking at other ways to try and corroborate that with large state databases or society databases or other means to sort of cross-check that number? That's one question.

And then my second more-detailed question, you mentioned in one of your slides the possibility of some of the patients being counted more than once in the numerator of the meta-analysis that you all did. And, of course, with numbers this small, that can make a huge difference. Is there any way to look into that in more detail?

DR. JONES: Sure. So the second question is, I think, very straightforward, easy to respond to.

So where I mentioned there was overlap in patients was not part of the prevalence estimate. It was just looking at the outcomes, which we did not use a meta-analytic approach. We just looked at the individual studies and their odds of local recurrence, disease-free survival, overall survival. So in that context, we're not double counting as far as the events that were used to generate the prevalence estimate.

As far as looking at other data sources to corroborate, there's really not a great data source. I mean, there's been some discussion today around could you try to estimate the number of people who are diagnosed each year with LMS or uterine sarcoma and use that as a numerator and then some denominator of how many hysterectomies are performed, and it really didn't seem feasible. You're not looking at the same data source, the same data captured within the same data sources. Certainly, lots of limitations to that.

And we felt that this approach, at least looking at the

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population that we looked at, was the best way to get the estimate because you are looking at -- you know, it's single population that was looked at. You know, cancers were in the patients that the procedures were performed in as opposed to pool from multiple data sources. So we felt that this was a more robust estimate.

But I completely agree with the fact that an individual clinician might see one case a year. I mean, if you look at the number of events and the years of the studies, you know, you see seven cases of LMS in the Leibsohn study from 1983 to 1988. Other studies, you may see even less in that over a longer period of time. So I don't think that that's inconsistent.

And the actual proportion is very small. I think when you start looking at 1 in 352, those types of things just seem like whatever -- every clinician sees 1 out of every 352 patients that they see. And that's, you know, not what is reflected in the actual studies that were included.

DR. TALAMINI: Thanks. I probably wasn't clear. Many of the clinicians that I talked to said the opposite, that they would -- on this statistic, they would expect to see one a year, and they don't.

DR. JONES: Um-hum.

DR. TALAMINI: So that's the smell test that it didn't pass for a number of the busy clinicians that I talked to. But, of course, individual practice is very different from a real study, so thank you.

DR. DIAMOND: Dr. Afifi, I think you were next.



DR. AFIFI: Abdelmonem Afifi.

And also for Dr. Jones. If you could bring up Slide No. 9 of your presentation. I couldn't tell the difference between Slides 9 and 10. They have the same title, but they have different numbers.

DR. JONES: Okay. So Slide 9 is looking at the rate per 100,000 [sic]. And Slide 10 is looking at simply the reciprocal of the proportion.

DR. AFIFI: Okay, good.

So the other question, which is one that you touched on a little bit, how do you explain the differences between your numbers and the other numbers that came up, for example, specifically one of the public contributions this morning about 1 in 7,000-something?

DR. JONES: Well, I can't directly comment on that study. I haven't seen the studies that were included in their analysis. There's some layout of the inclusion and exclusion criteria, et cetera. So I can't comment directly. I will point out that it looks like the number of events that they have in their primary analysis is about 14 cases of LMS among their 38,000 women that were included.

DR. AFIFI: Um-hum.

DR. JONES: We had, in our primary analysis, 19 cases of LMS among -- about 9600. So I think some of it is, you know, the inclusion/exclusion criteria of studies that were included in patient populations, whether or not the studies were particularly looking for cancer

or not looking for cancer.

I do think in the slide where they present their confidence intervals, their estimate of the confidence interval in their primary analysis, in their retrospective -- when they stratify by prospective and retrospective, our confidence intervals actually overlap within the retrospective for LMS in our primary analysis. I think the bottom of their confidence interval was about 860, and ours is 943 or something like that.

So I think you also have to consider, we had pretty tight confidence intervals, which I think reflects somewhat of the analysis and the limitation and inclusion criteria for our studies. They had quite wider confidence intervals, which would suggest some variation or greater variation among their studies or study population. And I think, also, we included different study years, and so it's not clear what influence that may have had.

DR. AFIFI: My last question also for Dr. Jones.

I'm just curious. Who else worked with you on this analysis? Not their names, but what, like, were there statisticians, other physicians, et cetera?

DR. JONES: Two physicians with public health training.

DR. AFIFI: Okay, thank you.

DR. DIAMOND: Dr. Wentzensen.

DR. WENTZENSEN: Nicolas Wentzensen.

A related question, also. I was also struck by the estimate, and

I think one potential bias you mentioned, I think, is very important, the fact that individual cases might have triggered writing a paper or writing a report, because I think the incentive is so much higher to report something. And pretty much all the case numbers in the individual studies were maybe, were around 2, so I mean, zero was always in the confidence intervals. I mean, there's just probably a deficit of studies that haven't seen anything.

And the other, like one of the sniff tests you can do is -- I mean, you could look at the total number of estimated cases from the ACS, which is 1600, and if you take the 1 in 350 and just do a very rough calculation with the hysterectomies performed, I mean, you would get to a pretty close number to that, which, to me, strikes me as far too much because you would expect a lot of the leiomyosarcomas are not identified through that process. So I mean, that's just one way to maybe get at the total number of it.

What's your comment on that?

DR. JONES: Yeah. I mean, I think again, we wanted to study the specific population and events that were identified in patients who underwent the procedure, and so we felt like this was a better way to generate the estimate. I mean, inherently, there are limitations, certainly, and the fact that these were published studies.

I did sensitivity analyses, taking out individual studies and seeing how that would change the estimate. Essentially, everything was in the confidence interval range. And even adding in a broader patient

population where clearly there are fewer events didn't dramatically change the estimate. And I think we're consistent with the previous published literature.

DR. WENTZENSEN: But wouldn't you expect a higher total number of events by the ACS predictions, if that was true? I mean, did you try to reconstitute that?

DR. JONES: We did not. Not directly.

DR. DIAMOND: Let me ask a question following up on that, if I may.

The denominator that you looked at was individuals undergoing hysterectomies or myomectomies for fibroids, or did that include all patients undergoing hysterectomies? Because if you look at the slides where we saw, what? At a minimum now 300,000 hysterectomies a year that are being reported and that excludes those who are going home the same day. With this ratio, the number that we would expect each year would be considerably higher than the 16 that you identify.

DR. JONES: So this was specific for patients who were undergoing hysterectomy or myomectomy for presumed fibroids.

DR. DIAMOND: So it's not all hysterectomies?

DR. JONES: No. And it's not even -- I mean, there were certain studies that patients may have been undergoing hysterectomy for multiple reasons, so prolapse or -- and fibroids. And we did not include those in our

primary analysis.

DR. DIAMOND: So that's --

DR. JONES: And I don't know that -- I mean, Julia might be able to answer that question of the specific number, but I don't know if we have that for fibroids, a really good estimate.

(Off microphone comment.)

DR. JONES: Forty percent, right.

DR. DIAMOND: So that may be part of the sniff test differences.

DR. CAREY-CORRADO: Of all the women who undergo hysterectomy annually, I have seen estimates of approximately 40% who are undergoing hysterectomy for a diagnosis of uterine fibroids.

DR. DIAMOND: Dr. Isaacson.

DR. ISAACSON: This is a little bit different question, I'm just -- on your Research Question 2, What is the probability of seeding an unexpected sarcoma by morcellation and the impact of morcellation -- and then you have four studies that address that. But it looks like all four studies probably compared hysterectomy -- open hysterectomy versus hysterectomy with morcellation.

Did you see any data that compared myomectomy with uterine-sparing myomectomy, open versus myomectomy with a morcellation? So it tries to address the question, if you're going to have local

seeding and it has something to do with the opening the uterus, taking out a fibroid, doesn't really matter how you get the fibroid out, versus getting that fibroid out with a powered morcellator. Did you have any data that would address that?

DR. JONES: I'll have to actually go back and look. Off the top of my head, I'm not sure. I don't think so, but I would have to go back and --

DR. ISAACSON: Yeah. All the ones that you list here just address hysterectomy. They don't address myomectomy. And we're looking at myomectomy in a younger population that we assume has a lower incidence of sarcoma, and we don't really know if morcellation of a fibroid itself has any impact based on the data that you presented.

DR. JONES: Out of these studies, I don't believe there were.

DR. DIAMOND: Dr. Snyder.

DR. SNYDER: My concern about the figure, 40%, are done for fibroids, I don't know if that's what the diagnosis code was or what, but if there's already a prevalence of fibroids, it's twice that. You know, there are a lot of patients that have hysterectomies for abnormal uterine bleeding refractory to medical management, and it most likely is because of fibroids, you know, or sub-mucous fibroid.

There are a lot of patients that are undergoing hysteroscopic resection of sub-mucous leiomyomas or inoculated intracavitary myomas. And those should be included when you're looking at what is the chance of

leiomyosarcoma being in any given fibroid.

DR. DIAMOND: Any comments from anyone on the Panel?

(No response.)

DR. DIAMOND: From the FDA?

(No response.)

DR. DIAMOND: Okay.

Dr. Gallagher.

DR. GALLAGHER: Okay, so I want to change gears just a little bit. As I was listening to you present about regulation, I was struck by the difference between a Class II and a Class III. I wasn't here in 1995 when the decision was made. Thank you to people who reviewed it then.

But I'm looking at it now and seeing that perhaps, especially looking at two specific elements of that, the insufficient information -- because we have all these questions about the differences, so that's kind of caused me to think about that.

And then also, the devices are -- or presents potential or unreasonable risk of illness or injury. Would the information that we have today cause someone in your position to even think about changing this from a Class II to a Class III? Based on what you have today.

MS. PRICE: So I would say that we have, always have, that opportunity to up-classify a device. We can go through a process by which we do that. The goal of today's meeting with the people that we have

assembled in this room was to get the clinical expertise to talk about what are the risks and what are the mitigations, and we can then take that information and look at our regulatory paradigm. And if there is something that needs to be revisited about where it's classified, we can come back, if we needed to, to the Panel. We could do a number of things.

There are things we can do internally with that information, but we would also have the opportunity to come back if we needed to. But we thought that the best use of this expertise was advise us: Do we understand all the risks now? Are there mitigations? You know, what's your best opinions on this with the information that's available in the literature?

DR. GALLAGHER: Thank you.

The only reason I asked the question is because I'm just looking at that one slide, what to do with that. I'm certainly saying we're going to look at all those other questions. I think they're key questions to even knowing what we have or don't have in terms of information, so thank you.

DR. DIAMOND: Thank you, Dr. Gallagher.

Dr. Brown.

DR. BROWN: Yes, this is a question for Dr. Jones.

Dr. Carol Brown. Question for Dr. Jones.

If we could pull up Slide No. 17 from Dr. Jones' presentation, please? This is a slide about the studies that you reviewed to look at risk of peritoneal dissemination, and this was a case where there basically -- the two



studies are the same group of patients.

But in the second bullet, you have that 64% of their cases had pathological evidence of peritoneal dissemination. But I just wanted to clarify, because when I go through that paper, it's not 64% of the cases of leiomyosarcoma. It was actually only 4 out of the 14 total cases where leiomyosarcomas that had dissemination -- so that would actually be, like, at 28%. If you looked at all the people that were explored.

So I just wanted to clarify that that 64% is referring to the majority of those cases where STUMPs and apical lumen wasn't -- okay, thank you.

And then I had another question for --

DR. DIAMOND: Dr. Jones, do you want to respond to that or --

DR. JONES: No, no.

DR. BROWN: No, he was just -- it was just a clarification.

And then I had a question for Dr. Yustein.

So getting back to the issue of -- you presented the data and you cautioned us about the MDRs, and Dr. Sobolewski gave us some information earlier. I was just curious. I understand that the purpose of this meeting was only to look at the issue of safety with regards to the risk of disseminating peritoneal leiomyosarcoma.

However, I was struck, just looking at the whole question of safety of these morcellators, that according to the data we saw, the MDR

report indicates that six women expired directly from probably vascular injury through the morcellators. So I'm wondering, is that a separate panel that would look at that from the standpoint of the morcellator safety, or would we be looking at all of these questions together?

DR. YUSTEIN: Right. So I knew that we were going to be talking about the Milad paper, which is what Dr. Sobolewski referred to, and in your executive summary we also summarized that paper, which was looking at the serious injuries associated with laparoscopic power morcellator MDRs. When that paper was written -- and it just came out, but I'm sure it was written before we received our first set of MDRs for this specific issue, so what I decided to do in looking at the MDRs is we only focused on the dissemination issue because that paper covered the serious injury issues other than that.

Now, certainly if we looked today, would we have more than those 55? Yeah, we might have 57 or we might have 59, but that really doesn't matter; the number doesn't matter. The events are going to be the same. And, yes, there are a bunch of other MDRs for morcellators that are more in the mechanical realm. In fact, the majority of MDRs in this class are for mechanical issues like the blade stops rotating during surgery; that shows up quite a few times. But I wasn't sure that that really was relevant to the issue that we're talking about here today. So I think in terms of malfunction, serious injuries, and the issue that we're dealing with now, I think we covered the important part of that.

So your second part of your question was?

DR. BROWN: Let me restate my question.

So as I understand it, we're being asked to look at the adverse event of death resulting from use of the morcellator in women, ultimately, or in women who have peritoneal dissemination due to the morcellator use. So I guess I'm just saying I saw some information today that I wasn't aware of that shows that women who are having uterine morcellation for, I think, also fibroids in the context of doing procedures died from a mechanical problem. So what I'm saying is are we not to be considering that in terms of our overall consideration?

DR. YUSTEIN: So I think Ms. Price's mitigation chart that we'll be going over tomorrow -- and I think she briefly showed that today -- does talk about one of the risks being -- I don't want to use your exact words, Veronica, but injury to local tissue.

MS. PRICE: Injury to non-target tissue, that was --

DR. YUSTEIN: Right. So that would be injury to vasculature, other organs, anything. And the Milad paper, that's what that's talking about, injury to bowel, injury to vasculature. So we have identified that as a risk that you will be talking about tomorrow.

In terms of the whole risk profile of these devices, yes, we're here mostly to focus on the issue of upstaging an unsuspected malignancy and not just patients who die. I mean, there are several folks out there,

including some people in the audience who are still with us after this event, so we're not necessarily focusing just on death as the outcome, but the fact that this can lead to an upstaging that then subjects them to additional procedures, you know, chemotherapy, other operations.

So I'm not sure if that answers your question. We are including that as a risk to talk about tomorrow, but the main focus of this panel meeting is on this dissemination of unsuspected malignancy.

Does that answer your question? I want to make sure I answered it. Okay.

DR. DIAMOND: Yes, please.

MS. MATTIVI: Hi. Kris Mattivi, the Consumer Representative.

And I'm actually not sure if this is a question for the FDA or if this might be more appropriate for general panel discussion, but Dr. Yustein, you were talking about modifications of the morcellation technique, and it was alluded to from some of our speakers this morning about morcellation -- I understand we're focusing on gynecologic applications of the morcellation at this point, but it's not the only application for power morcellators.

And so I'm wondering, in some of the other applications, say in renal situations, are there other strategies or are there other ways that this tool is used where there is also the possibility for dissemination of material in the abdominal cavity? Are there other strategies used to mitigate that risk in other applications where we could have lessons learned?

DR. YUSTEIN: Yeah, so that is part of the discussion that we'd like to hear from the Panel, and we do have some experts on the Panel who are not necessarily GYN docs. So certainly gaining from experience from them might be useful for us. There is a lot of literature out there in the urology world, but we're really focusing specifically on this for several reasons.

One is this is the signal that has come to us, this is where we're seeing the issue in terms of the numbers of reports in the literature in terms of this type of event happening. You know, also it seems that the gynecological universe seems to be a little unique. We heard earlier today that the gynecological community has moved away from using bags and that also they presume that the lesion is benign because of this prevalence being so low, whereas I think, and I don't want to speak for other surgeons, that in other surgical specialties perhaps a mass is considered malignant until proven otherwise and maybe in this situation it's more to the point where, well, because benign fibroids are much more common, we're assuming it's benign. So I think this offers a special niche in terms of needing to address this. Now, we are looking at morcellators in general, and we will be exploring other areas, but this is something that we felt we had to address sooner rather than later.

DR. DIAMOND: Dr. Hillard.

DR. HILLARD: Not to belabor a point that was brought up

earlier, but I'm still, as well, stuck on this mal test and the numbers, and just for Dr. Jones --

(Off microphone comment.)

DR. HILLARD: So a question for Dr. Jones is that in terms of -- you mentioned the possibility or the probable issue related to publication bias. And if I'm a community physician at a community hospital taking care of basically healthy women, 80% of whom have fibroids, most of which won't need surgery, but low-risk women for having a malignancy, then why would I report anything? Number one.

But, number two, why would I report 500 or 1,000 or 10,000 hysterectomies where there were no leiomyosarcomas or sarcomas? So tell me why you assumed that publication bias is likely to be low.

DR. JONES: I don't think that I made that assumption. I said I think that publication bias is something to consider in interpretation of the estimates that we've generated, and I think certainly, you look at the studies, you know, they were an index case, typically was identified, and then they went back and looked at just all the people who had received a hysterectomy or myomectomy for fibroids to see were there are other cases like this.

So, certainly, you know, those people had some interest in researching that question, and then they ultimately wanted to publish that to share that information. So, certainly, there are probably others who had the experience of never looking at it because they wouldn't have even thought to

be concerned before the last couple of years when this is really becoming more increasingly found in the literature and people were discussing it.

DR. HILLARD: But I think you're hearing from members of the Panel is that the numbers seem very high in terms of prevalence.

DR. YUSTEIN: Dr. Diamond, can I make a quick comment?

DR. DIAMOND: Sure.

DR. YUSTEIN: So I think when we get to the questions, you'll see that our first question, you're basically -- you're starting to actually have the discussion that we want you to have amongst yourselves, which is how reliable is the data that's been used for these estimates, the strengths, the weaknesses, and what's the magnitude of this risk. So we're going to look forward to that discussion amongst yourselves, as well, and hopefully later this afternoon.

DR. DIAMOND: Ms. Aronson, did you have a question?

MS. ARONSON: Yes. I'm struggling, too, with the incidence and all. And as a patient, if it's your mother, your sister, your niece, your aunt, it means whether it's 1 in 352, 1 in 500, 1 in 7,000 -- this meaning.

What I'm wondering about is -- you know, I'm hearing some say it's so rare they never see it. How much information do we have about race as far as clusters of it showing up, where if the research is done from just specific hospitals or locations, is that twisting the data? And geographic locations. And so ethnicity, race. You know, I keep hearing we don't have

enough information, so that's my struggle.

DR. DIAMOND: Does anyone from FDA want to comment?

DR. CAREY-CORRADO: I'll take a shot at responding.

There are SEER data that identify cancers by histology in a regional manner, so you can look at a SEER database. I am not positive, but I believe that the northeastern United States has a relatively higher incidence of leiomyosarcoma, but again, I would just encourage you to look at that database. There's a lot of very valuable information.

DR. DIAMOND: Dr. Brown.

DR. BROWN: Again, just a point of clarification; I keep asking the same thing. But it is a fact that the incidence of leiomyosarcoma is low in general in the population, but there's another cancer that -- which is endometrial cancer, endometrial type, which is much more common. Was your analysis -- I guess this is for you, Dr. Jones -- limited to only looking for studies or reports that talked about unsuspected sarcoma? And if that hasn't been looked at, is that something that we should be looking at in the context of this discussion? Do you have any information about that?

DR. JONES: So we limited our analysis to uterine sarcoma, specifically. So there were studies that were identified that looked at other types of endometrial cancer or even ovarian cancer where patients had had some procedure, a morcellation or hysterectomy. We did not include those in our analysis. Not to say that it's not something that could be looked at; it's



just for the purposes of this particular assessment in this particular issue, we just looked and limited it to sarcoma.

DR. DIAMOND: Dr. Isaacson.

DR. ISAACSON: A question for Veronica Price.

I'm struggling a little bit with the bag issue, and the question you want us to address and to answer, number one, because I saw no data suggesting that morcellation within a bag or a containment system provides a better outcome.

Number two, I'm not sure, when we're talking about leakage, does it make a difference if it's leakage just enough for fluid or a few cells, or does it have to be leakage large enough for significant chips? Because most of what we heard is, you know, you're leaving pieces of uterus behind in the abdominal cavity, and that seems to be obviously something you don't want to do. But just having a bag that might have a leak of fluid, we have no clue if that really is going to present an adverse outcome. So I don't really know what standard -- because we have no data to base this on that we're looking for, for assessing morcellation within a containment system.

MS. PRICE: I'll say that part of that we will put back to you as part of the discussion questions to talk about. Some of the things that have come up, as we've discussed it -- and that's why we're having the discussion questions for you -- is (1) to understand differences, look at morcellators overall. There may be differences among morcellators. Are the size of those

chips, are they the same or different? And if it's smaller, do we worry less, do we worry more? Is it better to have bigger ones because then you can see it?

And then when we talk about containing it, step one is to show that on a bench. You know, you would look at that and say, first of all, was everything contained? And then if for some reason not everything was contained under this design that we would come up with, the industry would somehow affirm, from clinical advisors, what gets out and would that be a problem? Would we be concerned about it? So it's a whole process.

I mean, as we said, first, you would like to know that the bag isn't permeable, then you would want to know that the integrity is maintained when used in the presence of a morcellator. That's your ideal system. But if you had some issue where there was -- you know, it would be part of this whole analysis, if there was some sort of pinhole, is there still a risk to the patient? So we would have to look at all of those things.

DR. ISAACSON: So you're okay with -- basically, we're giving our opinion because we really have no science or data to back up whatever opinion we come up with, at least that I've seen in the literature, number one.

And, number two, it sounds like we should probably exclude myomectomy because, again, we have no data that makes a difference if you're going to do a myomectomy where you have to transect through the serosa in the muscular areas to get a fibroid. For an open myomectomy, is

there any difference whether you morcellate the tissue or whether you extract that tissue within a containment system or intact, because the integrity of the uterus has been opened, so it's not self-contained anymore?

So we really have to look at this. Are we really talking about morcellation just for hysterectomy or are we talking about it with myomectomy? Because, again, there are no data for myomectomy. None of these studies addressed myomectomy. They all addressed -- that's why I asked you if they all addressed hysterectomy when it comes to peritoneal seeding from morcellation. And so I would say that if we can morcellate hysteroscopically and we feel safe about that, then we probably should be able to morcellate a fibroid laparoscopically and feel safe about that because we have no -- because again, the uterus, the integrity of the uterus, has been compromised already, no matter what technique you use.

MS. PRICE: Go ahead.

DR. CAREY-CORRADO: This is Julia Corrado.

I guess I just wanted to butt into this conversation and reply that the integrity of the serosa in the uterine wall may have been breached, but the lesion itself can be resected intact.

DR. ISAACSON: There is a pseudo capsule.

DR. CAREY-CORRADO: Right.

DR. ISAACSON: But there often is not a clear plane.

DR. CAREY-CORRADO: Fair enough, but nevertheless --

DR. ISAACSON: So when you're taking out a fibroid, you're clearly --

DR. CAREY-CORRADO: But nevertheless --

DR. ISAACSON: You're spilling cells when you're doing it open and --

DR. CAREY-CORRADO: But when you take a lesion and you create it, you reduce it to a multiple, many multiple smaller pieces. I think that the Panel should consider the plausibility of whether that would increase the patient's exposure if there's a malignant cell there. So, again, we invited you, as clinical experts, to talk about this. And, certainly, I think it would be great if the clinical thought leaders would, again, prepare algorithms for how to triage patients, whether they're having hysterectomy, and then separately, whether myomectomy is indicated. Certainly the patient's age is going to be lower in the myomectomy population. But we would be looking for the clinical experts to answer these questions.

DR. ISAACSON: And just the last point of that. It got back to the question I asked Dr. Cohen, which was when we did all of these open, you still had incidence of disseminated leiomyomatosis from myomectomies. And that's when you were removing the fibroids intact, not chopping them up. You're just taking them out one by one. So that, again, I think we really need to focus on separating the risks with myomectomy versus the risks with hysterectomy.

MS. PRICE: And I think that's great input, and that's what we need you here for, to help us.

DR. DIAMOND: Other panel questions?

Dr. Simon.

DR. SIMON: Sure. I'm going to give you a homework assignment because I assume we'll see you tomorrow.

In discussing this issue of prevalence -- and Dr. Pritts presented this, 1 in 7,450 and perhaps it's 1 in 342, or if you use the upper confidence interval that was presented, I think, on Slide 10, it's 1 in 840-something. But let's just say it's 1 in 1,000 because it may make the math easier. And we'll have this discussion about mitigating risk and, you know, there are certainly two ways to go about doing that. We could detect the fibroids or detect the leiomyosarcoma before the surgery, if we had a perfect imaging modality -- as per Dr. Ascher -- and everyone could do it, that would be great. If we can't do it, then we could potentially mitigate the risk during the procedure with a bag.

But if we had an imaging modality, let's say, that had a sensitivity and specificity of 99%, which would be quite good, and let's just say we put the prevalence at 1 in 1,000 -- and my homework assignment for you is to say what kind of a study, how many patients would we need to enroll to detect an 80% signal to determine that we indeed have mitigated the risk?

And I think it would be a vast study, and you can tell us what it would be just so we know. And the same goes when we have a discussion regarding mitigating the operative risk. So to reassure the public -- and I'm not sure we're going to be able to, but how large a study would we need to do to detect a signal if we indeed were to dial down the operative risk in a disease where the prevalence is 1 in 1,000? How would we validate? And I'm not sure we can, but how big -- my assignment is to you guys, tell us how big that study would be.

MS. PRICE: Well, I'll jump in and just say just remember, as I walked through -- and we can go through it tomorrow again -- you know, when I talked about risks and mitigations, the proposed first step would actually be a bench test. I mean, we can do a lot more. If you're talking about looking at, again, fragments and containing them, you can come up with models; they've been in the published literature -- Dr. Yustein talked about some of them today -- where you can actually do a very robust design to look and see, can you contain those fragments? And will a bag or containment system or a new design --

DR. SIMON: No, I think -- I mean, I look forward to the discussion tomorrow to try to figure out ways to keep everyone from going down this path, but it's more to make an unknown known as best as we could so when we come up with strategies to say how would we ever know, how would we ever validate these strategies, to know that we actually made a

dent, so three years from now we're not back here saying, you know -- because I think whatever we come up with tomorrow, it is going to be largely based on speculation.

We don't have data to really work off of, and so we're going to try to create an algorithm where one hasn't been done before and figure out how to dial this risk down. But we're not really going to know if we made an effect until some point in the future, but I'm just -- so we all understand how many patients would have to be treated, based on a prevalence of 1 in 1,000, for us to even understand, if we did reach a point where we could measure the effect. That's my question. Or that's my -- I guess for us to know that number would be helpful. I would find it helpful to know.

And here's my last -- also, the other point I have. I don't work for the FDA, but I have to believe that this isn't the first time that a device or even, perhaps, a drug has been released into the market, and then lo and behold, we find ourselves facing, sort of, a spike in an unusual disease that many of us have not seen a lot of, but perhaps now we're seeing 30 cases. And I'm just wondering, in the past --

UNIDENTIFIED SPEAKER: Hundreds.

DR. SIMON: Or hundreds. Well, whatever it is.

In the past, how has the FDA dealt with these sorts of issues from a precedent standpoint? I mean, the only thing that comes to mind to me is when I was much younger, growth hormone was not made through -- it

was made through, I think, real tissue and then there was a spike in Jakob-Creutzfeldt disease at one point, back in the '80s.

I'm just wondering how has this been dealt with when this event takes place, you have an unusual spike in a disease that we're not really experiencing? How has that been handled in the past? Are there any lessons learned that you guys can share with us and the way it's been dealt with?

DR. YUSTEIN: Off the top of my head, unfortunately, I can't. I mean, we take into account -- if you're asking what is our threshold for action? Is that what you're getting at?

DR. SIMON: No, it just seems like we have a device, it's been on the market, and now we're seeing this spike in a disease that, frankly, we don't see that often, you know, disseminated leiomyosarcoma, very aggressive, in a cluster of patients. And so I'm just wondering, not being a student to the FDA, has this happened before in other devices, other drugs? And the only thing that came to mind for me -- and again, I'm not researching it, was I just remember in the past, there was a spike in Jakob-Creutzfeldt disease before, when they were giving growth hormone and it was manufactured through human tissue or through some tissue which exposed people to the Jakob-Creutzfeldt virus.

And so, you know, then suddenly you had this spike in a cluster of rare diseases. I mean, that's what this appears to me, where -- you know, everyone assumed the prevalence of leiomyosarcoma is quite low, so low



that we could morcellate the uterus without regard to the risk. And, suddenly, now we're trying to wrestle with, was that initial assumption correct? And I guess we'll talk about it more tomorrow.

But I'm just thinking, I wonder, this can't be the first time that such an event has taken place, and are there any lessons learned that the FDA has from, well, this is the way we dealt with this issue back in '91 or '78 or whenever some of these have come up for?

DR. YUSTEIN: So there's one example that I can bring to mind, which is, you know, with silicone breast implants and lymphoma, anaplastic cell lymphoma, that was starting to be reported in a couple of cases here and there. Again, hundreds of thousands of breast implants are used a year, and we were seeing a few case reports of that. Maybe Megan can -- is Megan still here? Can talk to that. We actually did work with the professional societies to set up a registry to follow patients, specifically looking for that lymphoma to try to get a better handle on that. I think that's one example.

Ben, you had another one?

DR. FISHER: Yeah. The example that I have goes way back, and this is when I worked with latex. And I think the hardest part was getting everyone to realize that there was such a thing as latex allergy. And then once we realized that there are people out there that are allergic to latex and want to put it out there, there was a tremendous spike in the reporting, and people came forward and said yes. So then how did we handle that?

We tried to work with the professional societies and we tried to work with industry on a variety of levels. One was how could we decrease the amount of protein down to a level where it wouldn't have an adverse effect, and there is no level. And the lessons learned were that -- you know, I think we're still working on it. And I'm hoping that this isn't the same situation with latex. I mean, we've made progress with latex, and people realize it now. There's labeling on things to let people know that there is latex, but it was not something that we changed overnight; it took years to work with the latex thing.

I think in this situation right now, and this goes back to some other questions that we've had, you know, some of the things that I'm interested in is that what I've heard prior to coming in today, and what I've heard even today, is that for gynecological use, that at one time there were containment bags and that we've moved away from it. So some of the questions that I want to put out there and that I'm interested in getting answers for is why? I mean, was it felt like we didn't need it or that it was -- you know, it added time to the procedure or that the bags didn't work?

So I think that some of the things that we're struggling with right now is that if you look at these morcellators, they do what they're supposed to do, and we've gotten to where we are now because we've regulated them on their performance. I mean, they do what they're supposed to do. Something has come to the forefront here, and we recognize

it and we may argue as to what the exact number is. I think the thing that we all agree on is that we have a heightened awareness for this and what we're trying to do is, we're trying to bring to you the questions about some of the risks that we can identify, trying to get your opinion on some of the risks that we may not see, and can we adequately mitigate those risks? I mean, that's going to help us determine what the next step forward is.

So there was a question about up-classifying it, so we're just trying to get our heads around the information that we need to help us prepare to move in that direction. So when Veronica was talking earlier about bags, I guess the question is, you know, does a bag do anything? I'm under the impression that sometimes bags can be used with morcellators to morcellate and get rid of tumors and other specialties. How do they do that? You're talking about lessons learned. How do they do it and take out a known tumor? And would it be applicable to try to apply some of those procedures to take out something where we might be trying to remove a tissue where it's just suspect?

So we're going to asking some questions that -- you know, like what kind of premarket testing? If we decide to go with a bag, what are the concerns that we should be looking at for a bag? You know, maybe a bag isn't the right solution. Maybe there's a containment system out there that we haven't thought about yet, and innovation and industry will help us get there. So it's a complicated question, and I don't mean to be Mr. Teflon, but we're

going to put these questions back on you, you know? What do you guys think?

There are people around the table here that have expertise in areas other than GYN, and we're hoping that if they've used these morcellators for those other fields, that maybe they have a piece of information that can help us out for what we're faced with here.

DR. BROWN: One other question for Dr. Yustein.

So the MDRs that were reported about dissemination of malignancy after morcellation, there were 21. And when I looked at your table, is it correct that you only have pathology on 13 of them? Is that right? Because then one table you have listed, there were 10 leiomyosarcomas, 2 endometrial stromal sarcomas, and 1 STUMP.

DR. YUSTEIN: Can you refer me back to a slide number?

DR. BROWN: I think it's Slide 32 of your presentation. Slide 31 and 32.

DR. YUSTEIN: The chart of the seven deaths?

DR. BROWN: No. It's Slide 32 about the dissemination of malignancy after morcellation.

DR. YUSTEIN: Okay.

DR. BROWN: And just in general --

DR. YUSTEIN: Okay.

DR. BROWN: -- you mentioned in there that you don't have

complete information, but I just wanted to clarify that is it only 13 of those MDRs that actually give you the histologic diagnosis?

DR. YUSTEIN: Oh, okay. Okay.

DR. BROWN: Because that's what it looks like to me, putting it on --

DR. YUSTEIN: Yeah, I'm sorry. My slide numbers are off because we added a slide.

DR. BROWN: Oh, okay.

DR. YUSTEIN: So I'm sorry.

Okay, so that's where it's titled "Remaining MDRs," that one?

DR. BROWN: Yes, um-hum.

DR. YUSTEIN: Okay. So I have 13 listed there. That's because -- so this is the 14 cases that were not deaths, and only 13 of them specifically noted the malignancy that was reported. So, again, incomplete information in MDRs is the rule, not the exception, so --

DR. BROWN: Okay.

DR. YUSTEIN: -- the fact that we actually got the type of malignancy in 13 out of the 14 is pretty unusual. So, in other words, the fourteenth, it didn't say.

DR. BROWN: And do you have the authority or the ability, as the FDA, to contact the people who submitted these MDRs and request or compel more detailed information?

DR. YUSTEIN: Sure. We do. Unfortunately, a lot of these MDRs came in as voluntary reports, which did not necessarily have reporter information in them. But we can go back to individual people if their contact information is provided and they give us -- they have to check a box that gives us the authority to do so. We can go back to people.

DR. BROWN: Thank you.

DR. YUSTEIN: Would that make a difference to have --

DR. BROWN: Well, I think it's -- in order to really assess -- you know, we need a little more information, like detailed information about what was the nature of the first surgery and also some of the histologic findings about the sarcoma, things like that.

DR. YUSTEIN: Yeah. Again --

DR. BROWN: The size, yeah.

DR. YUSTEIN: And as I pointed out, we get what we get, and unfortunately, most MDRs have very limited information.

DR. BROWN: Right.

DR. YUSTEIN: We do often go back to manufacturers and ask them for details because manufacturers are expected to evaluate the events that are reported to them, so it's their duty to go back and evaluate those. We have contacted patients or physicians, individual reporters, as well, to get additional information.

DR. BROWN: But maybe in the context that this has generated

so much increased awareness and it sounds like more reports will probably come in.

DR. YUSTEIN: Right.

DR. BROWN: Maybe we could get that, because I think it's really difficult to answer some of the questions that you've asked about the risk of peritoneal dissemination because we do not have --

DR. YUSTEIN: Right.

DR. BROWN: -- any data, and I think it would be useful to our deliberations to have more data, more details about the cases where this has happened, you know, the pathology, if there was any preoperative imaging, all that would be helpful.

DR. YUSTEIN: Right. I don't disagree with you, and if we had received that information, I would have put it in there, but, unfortunately, a lot of that was missing.

DR. DIAMOND: Dr. Mattrey.

DR. MATTREY: Forgive me for asking such a stupid question. Do you have mechanisms to control false reporting? I mean, you know, we see on Yelp and other reporting and reviews, you know, the owner and their buddies come in and give scores of 5 and one unhappy camper gives it the 1, and I mean, is there some control for this reporting that guarantees their authentication?

DR. YUSTEIN: Well, certainly voluntary reports that come in

from an individual, a family member -- I mean, we don't necessarily have a mechanism to go back and check that. We don't do that regularly. For manufacturers, sometimes when we are out inspecting their facilities, we may look at their complaint files to make sure that what they've submitted is consistent with what they've received. But in general, no. I mean, there is not a strict mechanism by which we would say this one looks like it's not real. We take every MDR on face value.

DR. DIAMOND: Dr. Iglesia.

DR. IGLESIA: Cheryl Iglesia.

I have a question, really, about the registry and about the special controls, because it just seems to me that a device registry isn't going to really provide the kind of guidance that we need for patients, which is -- based on for them to make the most thoughtful decision about the choice of how they're going to treat their bodies and their uteri for patient selection, but you need more of registries specific to fibroids.

Because, you know, you even said it yourself, the problem with this, the number is the population surveyed and age, race -- you know, we know those all play a factor. We don't have all the data that we need, but I just wanted Megan to comment on that in terms of 522 guidance.

Is it about the device or is it about our limited knowledge about women's risks regarding their own fibroids and the treatment that we choose for them based on the specific characteristics?



DR. DIAMOND: Dr. Gatski, do you want to respond to that?

DR. AFIFI: I have to confess that I wasn't paying attention.

DR. DIAMOND: Okay.

(Laughter.)

DR. AFIFI: So could you please repeat the question?

DR. DIAMOND: Well, I was asking actually Dr. Gatski.

DR. AFIFI: Oh, I see.

DR. DIAMOND: Who gave the presentation on registry. Sorry.

DR. FISHER: This is Ben Fisher with --

DR. AFIFI: Off the hook.

DR. IGLESIA: No, I was looking at who was behind you.

DR. FISHER: You know, we're not sure that a registry is the answer and I think that -- I don't know that -- I don't speak for Megan, but I don't know that we've actually sat down and thought about what a registry would look like. I'm not even sure, you know, before we go -- a lot of times we hear, oh, we're going to have a registry.

Well, I think the question behind that is what is the data that you're trying to get, what's the answer that you're trying to get out of the registry? So I think we got into discussions about collecting that type of clinical data. You know, my question to you would be what will we be trying to get out of the registry? You know, what additional -- I mean -- I'll just leave it there.

MS. PRICE: And I'll jump in -- Veronica Price -- because you said 522 specifically.

So that isn't to answer a basic science question or what's the prevalence or something. Those are ordered on a particular device to answer a specific question, so that would not be the mechanism by which to do it. It wouldn't even really be a premarket question for a device manufacturer. If that information doesn't exist, then we have to rely on other groups, societies, you know, to fund that basic research to get that information.

DR. DIAMOND: Yes?

DR. NEUMAN: I'd like to change the subject a little bit and just comment on my impression, not ever having used a morcellator. I'm hearing that you're considering the morcellator as a generic device, yet when I hear examples of it, they range from something that's a mechanical device that cuts things up, to electromagnetic devices, RF devices, hot wires, and probably there are some other things, as well. And these all use a different physical principle for destroying or cutting up the tissue.

And, yet, we're considering it as one device, and I would think some of the things that you're looking at in terms of the particles that are produced, how they are disseminated and what have you, will be different for these different devices. And I'm curious if FDA has taken that into consideration at all, and if so, is it something that they consider to be a significant problem?

MS. PRICE: So this is Veronica Price again, and absolutely. And it is one of your discussion questions tomorrow that we will review.

DR. FISHER: It's actually Question No. 7.

MS. PRICE: Whether it is -- I mean, they are all different, and whether we need to consider it different by either modality or design or anything like that.

DR. DIAMOND: All right. I think we will call this part of the meeting to a close. We thank again the members from the FDA.

And we will go to the questions that the FDA has for us and we'll start with Question No. 1.

DR. BROWN: May I just ask a procedural question? I'm just a little confused. So we are now going to start discussing the questions, but aren't we going to be hearing a whole other day of testimony tomorrow? Or information?

DR. DIAMOND: Tomorrow we will have some additional presentations, public presentations, yes. So comments from societies or from individuals, as we heard first thing this morning. But we will start going through Question No. 1 at this point of time.

DR. BROWN: So would we then have an opportunity to -- will we then revisit these questions after we've heard -- because we may hear additional information tomorrow that might reflect how we answer these or -- I'm confused.

DR. FISHER: Dr. Diamond?

DR. DIAMOND: Yes.

DR. FISHER: If I could? Yes, we weren't able to get --  
Ben Fisher, FDA.

We weren't able to get everybody scheduled for their testimony today, so it is split, and it's my hope that we can probably dwell -- we're not going to go into a lot of questions, just the first one. If there happens to be testimony tomorrow that may impact this question, I would certainly like to try to revisit it to find out if it changes your thoughts.

DR. DIAMOND: All right, would you like to read the first question?

MS. BLYSKUN: Yes, this is Elaine Blyskun.

So, first, I just want to note that these questions have been revised, and they're different from those that are in the handout. They have been revised separately to the Panel members.

DR. DIAMOND: Yes.

MS. BLYSKUN: They're not part of the packet that includes the other information.

DR. TALAMINI: So this is Talamini.

So the ones that you handed out today are the same ones you're going to be reading? Yes?

MS. BLYSKUN: Yes, yes.

DR. TALAMINI: Thank you.

MS. BLYSKUN: Separately from the larger packet.

DR. TALAMINI: Got it. Thank you.

MS. BLYSKUN: So Question 1: FDA conducted analysis of published literature indicating that for women undergoing a hysterectomy or myomectomy for presumed fibroid disease, the risk of having an unsuspected sarcoma is approximately 1 in 350 and for leiomyosarcoma (LMS), specifically, approximately 1 in 500. The analysis also indicates that women who undergo morcellation of an unsuspected malignancy are at higher risk for dissemination and upstaging of their malignancy and disease recurrence, as well as a poorer disease-free and overall survival. With regard to the risk of having an unsuspected sarcoma or a leiomyosarcoma in women undergoing hysterectomy or myomectomy for presumed fibroid disease:

- a. Please discuss the strengths and weaknesses of the information available to assess this risk.
- b. Based on currently available information, please discuss the magnitude of the risk.

DR. DIAMOND: All right. So we will go ahead and start with the (a) portion of this question. Does anyone on the Panel wish to make a comment on strengths or weaknesses of the information available to assess the risk of having an undiagnosed or unrecognized or occult leiomyosarcoma when treating a uterine fibroid?

Dr. Snyder.

DR. SNYDER: One of my mentors used to always ask me to make a distinction between controversy and confusion. And controversy, you know, being many differing opinions related to the facts that exist and confusion being that there really are no facts, and after hearing all of this today, I don't know where we're at with really getting an incidence, and I don't know how to do that if a large portion of our patients with fibroids never get operated on. Now, some of them are going to be the ones that present with advanced disease, and so I'm more confused this afternoon than I have ever been.

DR. DIAMOND: Okay.

Dr. Isaacson.

DR. ISAACSON: I certainly respect Dr. Jones or Mr. Jones, his analysis, but I also respect the analysis by Pritts et al., knowing several of the authors, that they're very -- they are excellent academicians. And you can't just say that, in my mind, I'm not comfortable saying there's an overlap in the confidence interval, so there's really no difference between 1 in 350 or 1 in 500, and 1 in 7,000 and 500. There is a difference. And we've got to figure out which one is closest to being correct.

And understand that the FDA did not have the luxury of reviewing their data in their paper, but I'd like for them to do that and then have them come back and see if they're going to revise their numbers after

they've read this or after it's -- you know, assume it goes through peer review and gets published.

UNIDENTIFIED SPEAKER: Assuming.

DR. ISAACSON: Assuming, yeah.

UNIDENTIFIED SPEAKER: Assuming.

DR. ISAACSON: If it doesn't, then it's a whole -- you're right.

(Off microphone comment.)

DR. ISAACSON: Completely different --

LCDR ANDERSON: I'm going to take a break.

DR. DIAMOND: Sir, we're going to have to ask you to please not speak.

LCDR ANDERSON: We're taking a five-minute break right now.

(Off the record.)

(On the record.)

DR. DIAMOND: So the committee is going to convene inside for just a moment.

(Off the record.)

(On the record.)

DR. DIAMOND: And, Dr. Isaacson, I don't know. Were you saying something?

DR. ISAACSON: Yes. My point was is that I think you have two very, very credible sources or authors that have come up with very, very

different results, and I don't know if the FDA would be willing to reevaluate their data and their numbers if and when the Pritts data becomes published, because again, it's got to influence the numbers because of the dichotomy between 1 in 7,500 and 1 in 500 or so. So it's more of an issue for the FDA, instead of saying assuming on this question that the incidence is 1 in 350 to 1 in 500, that they'd be willing to look at the most recent data, if it gets published in the next three to six months, and then revise their information, should they choose to. That was number one.

And then again, based on this question that we have here, I really would like to again go back and try to separate women undergoing hysterectomy versus myomectomy instead of saying "or myomectomy" because again, all the data that has been presented has been morcellation of an intact uterus versus morcellation of a fibroid that's been extracted from the uterus already. So my suggestion is that we look at those independently as opposed to keeping them together.

DR. DIAMOND: Okay.

Dr. Afifi.

DR. AFIFI: Yes, Abdelmonem Afifi.

I would like first to distinguish between a qualitative aspect of the question and the quantitative part of it. The qualitative part says that there are some undetected sarcomas that could be disseminated into the rest of the body and that presents a danger. And what we're trying to do is to



minimize that risk. That's the qualitative part. And I think that qualitative aspect will be coming up tomorrow in several of the other questions.

Quantitatively, yes, we do have at least two presentations of risks, prevalences actually. And yesterday I remembered that other material had some other estimates going somewhere between 1 in 500 and 1 in 1,500, something like that. All of these have some errors attached to them, and the errors, there are various sources of it; at least three of them are important.

One is how much of the literature has been covered? And, two, was the denominator calculated correctly? And, three, was the numerator calculated correctly?

In terms of the numbers of papers that are covered, we'll never know if all of them have been. My concern with -- let's see -- the Pritts et al. analysis is that they go very far back, 1960. There are so many aspects of medicine that have changed since then. And the identification of the cases, my father used to always say, "Before the invention of the sphygmomanometer, there was no hypertension."

Well, it's a little more complicated than that, but the diagnostic criteria have changed a great deal since then, and I would imagine that that analysis has a lot more in the numerator that has not been counted than the analysis by Dr. Jones and his group. If you're looking for some things, you'll find some of them, but not all.

I believe that the study by Dr. Jones and his group probably

identified a closer number to the true numerator than the study by the Pritts group. So in that sense, then, I tend to believe the number 1-in-whatever, 350 or 352, a lot more than the 1 in 7,000. But, again, going back to the quantitative versus the qualitative, my bigger concern is really with the qualitative aspects of the question.

Thank you.

DR. DIAMOND: Okay.

Dr. Talamini.

DR. TALAMINI: Thank you. This is Mark Talamini.

I think with respect to Question 1a, I think that the data is weak, in summary, and I think it's weak because of the inherent flaws of the meta-analysis technique. And I think the tolerances that we've talked about just -- I mean, we just don't really know what the number is, and I would encourage -- well, I'll back that off. I think there are other potential ways to try and get at the number using big data, large state databases, Medicare databases, the SEER database. It might get us closer to the real number.

Having said that, I think it's both -- in one sense, it's not important, and in another sense, it's very important. I think that number is very important with respect to informing patients about what their risks really are when they're considering their options for treatment. In another sense, though, for the individual patient, obviously it's a huge risk, and there are really two sets of populations that we're trying to serve here. One is the

patients that have unsuspected cancers that are about to face this, and the other is the large set of patients who don't have cancer but are seeking benign treatment. Obviously, we need to do much better with both of those populations of patients.

So I think the second question, based on the currently available information, discuss the magnitude of the risk --

DR. DIAMOND: We haven't gotten to that part yet.

DR. TALAMINI: Oh, we haven't gotten to (b) yet?

DR. DIAMOND: Just 1a.

DR. TALAMINI: Okay. Thank you.

DR. DIAMOND: Sorry.

Dr. Brown.

DR. BROWN: So this is Dr. Brown.

In response to (a), Discuss the strengths and weaknesses of the information available to assess this risk, so if the question is about what is the risk of having an unsuspected sarcoma at the time of what, again, I think there was no data provided about "at the time of myomectomy." I think there is data provided to us that is very weak about the risk of unsuspected sarcoma at the time of hysterectomy, and I think that data that should have been provided for us and that needs to be added to this is the risk of any type of occult malignancy, including cervical and ovarian, tubal, and endometrial in trying to understand the risk of unsuspected malignancy being disseminated.

DR. DIAMOND: Okay. We would like to hear from each member of the Panel, so I'm going to ask everyone who hasn't made a comment -- Mr. Gardner, do you have any comment that you would like to add?

MR. GARDNER: I have really nothing to add to what's already been said, that there is quite a bit of uncertainty in the data. We all know there is some risk, but quantifying it is very, very difficult.

DR. DIAMOND: Ms. Mattivi.

MS. MATTIVI: I would agree that the data themselves are -- there are a lot of questions around the data. But agreeing with Dr. Talamini, as well, that the number really does not make a difference when it comes to that one person.

DR. DIAMOND: Ms. Aronson.

MS. ARONSON: As far as the strengths and weaknesses of the information, you know, if more of these cases are happening and that's why we're hearing more now, we don't know whether it's because they just weren't reported and -- but is there an environmental issue that we don't even know about that's increasing this risk that we need to be cognizant of, as well?

DR. DIAMOND: Okay.

Dr. Simon.

DR. SIMON: Yeah, I think the data is quite relatively weak, and I

don't think it adds anything just to say it probably is somewhere between the 350 and 7,000 incident of prevalence that was quoted. I will say I did a quick calculation, and if we had said there were 130 cases of disseminated leiomyosarcoma and you worked off of the 1 in 7,450 cases that Pritts had presented, that would translate to, I think, 700,000 hysterectomies to get to that number. So I think -- and you can do, you know, just to back into it. So I think the 1 in 7,450 may be inaccurate on the upper end, so -- but I echo what Dr. Talamini has said, as well, for the individual patient. It's really 0 to 100 and that's -- it's a binary question.

DR. DIAMOND: Dr. Gallagher.

DR. GALLAGHER: First of all, I want to say that I agree with the last comments of Dr. Brown, and I want to add to it that one of the things that I would like to know that I haven't seen at all here is the scientific knowledge of how it is that the cells would be able, in the peritoneum, to that quickly move the cancer that fast, just based on this particular methodology being used in comparison to not. You know, what's the difference between finding it without using a power morcellator and how long it takes for the disease to develop compared to when the power morcellator is used. Those kind of things I haven't really heard.

DR. DIAMOND: Okay.

Dr. Mattrey.

DR. MATTREY: So I'll add to the confusion. I think it is a very

confusing issue. I mean, we heard from Dr. Cohen that there are 1.8 cases per million per year. It seems like the numbers are a little bit overestimated, from my perspective. The other is there is no data. Typically, you have a stimulus response that when the morcellator came into being, if it was indeed a risk factor, there should have been a rise in incidence of peritoneal implants from leiomyosarcoma or other uterine sarcomas. I have not seen that data presented so that I can correlate stimulus and response. So it seems like looking at the curves that were shown today, most of them were flat or decreasing despite the introduction of a device that could have made things worse. So that correlation is not made clear in my mind.

DR. DIAMOND: Okay. And just for, I think, a factual correction, maybe Dr. Cohen could address -- I think the numbers he was showing, 1.8 per million people per year.

DR. MATTREY: Correct.

DR. DIAMOND: Is that correct?

DR. MATTREY: That is the number.

DR. COHEN: That was for endometrial stromal tumor --

DR. DIAMOND: Okay, so that --

Dr. COHEN: Leiomyosarcoma is 6.4, and there are others which are more prevalent that were not even mentioned --

DR. DIAMOND: Okay, so Dr. Cohen's comments were that that was correct, that it was 1.8 million per year, but that was for --

UNIDENTIFIED SPEAKERS: Stromal.

DR. DIAMOND: -- endometrial stromal tumor. It was 6.4 for leiomyosarcoma, and mixed mesodermal tumor was slightly more, 8.4 per million per year, and that there are other types that are even more common that were not listed on that slide.

Let's see. Dr. Brown, you've spoken. Do you have any other comments? If not, Dr. Hillard.

DR. HILLARD: So I am concerned about the data we've heard. I don't think we know a real number. I think it's very important, as Dr. Talamini had indicated, it's certainly important for the women who have an undiagnosed malignancy, but it's also important for the 80% of women who have fibroids who may be making a decision to have their fibroids observed. So I think it's a really important question, but I don't think we know the answer. I'm concerned about publication bias.

DR. DIAMOND: Okay.

Dr. Moore.

DR. MOORE: I think there is a broad range between the two numbers, 1 in 300 and 1 in 7,000. But, unfortunately, I think this is something that there can never be a trial of, so we're never going to know those accurate numbers. We may be stuck with quoting that range between 1 in 300 through 1 in 7,000, which is really not useful to the majority of women because you may fall into the 300 or you may fall into the 7,000. But I don't

think that there is anything else that can be done.

And I'm not sure that creating a registry is going to be beneficial because, since this is such a rare disease, we would have to have so many patients included in that registry who had the procedure and then the one that had the sarcoma before, we'd have new data which potentially will take years.

DR. DIAMOND: Dr. Iglesia.

DR. IGLESIA: I agree with everyone so far about the data being confusing and weak, and there are homogeneous populations and interpretation can differ against -- between those who are looking at the data. You know, that being said, Julia Corrado and Dr. Talamini both mentioned this database, and I think it would be useful for us to look at SEER not just for the sarcomas, but also for the other cancers that Carol was saying, because that's real data that we do have. So I think that would be helpful in strengthening the discussion overall.

DR. DIAMOND: Okay.

Dr. Snyder, unless you have a different comment, I'm going to go to Dr. Wentzensen.

DR. WENTZENSEN: Nicolas Wentzensen.

I agree that the data are weak, and I think there's wide agreement, qualitatively, that this happens and that this is bad, but I think the quantitative measure is important because when we think about the



alternative, we want to balance what is the risk in the alternative, what is the risk in what we're doing now. And I think, unfortunately, that the risk measure on the other end is also very poor, that's what we heard, so I think it's a problem.

DR. DIAMOND: All right.

Dr. Shriver.

DR. SHRIVER: Craig Shriver.

So, first, I want to say I'm not representing the Department of Defense; these are all my own personal opinions.

So my perspective on answering these questions over the next day is going to come from a little bit different -- than I think most people. So I'm a cancer surgeon. And Dr. Cohen mentioned the Memorial Sloan Kettering Cancer Center sarcoma database. I trained under Murray Brennan, who started and established that database. So my perspective and principles and philosophy of approaching tumors, masses, is -- turns out it's very different than most people on this Panel, as a cancer surgeon.

And as somebody who comes from the perspective of here's a lump -- and I train my residents in this, I've been a program director in residency training 16 years -- assume the worst and treat it as if it's going to be the worst. So if you come from that --

(Applause.)

DR. SHRIVER: So if you come from that perspective --

LCDR ANDERSON: Excuse me.

Hi. I'd like to note for the record that there is disruptive behavior in this room, and I'm going to ask for the individuals to either cease the behavior or to leave.

Thank you.

DR. SHRIVER: So from that perspective, I think what we can all agree on is if we knew that a patient had a sarcoma, we would not stick a device in it and morcellate it, certainly not in the open abdomen. And there's a lot of important questions being asked here. What's different about the peritoneal cavity? It's an agar plate. It's an environment of support and embryogenesis almost, versus an actual orifice. So when you take a tumor out through the vagina, let's say, you do a removal of a fibroid and bring it out through the vagina -- it's why colon cancer on the right side of the colon, which sheds tumor cells all the time down the colon into the rectum, that we know for sure because there are fecal tests for that. It doesn't cause cancer downstream. It's because in a natural orifice there are mechanisms in the epithelial lining to prevent that, but not the peritoneal surface. That's a supportive environment for cell growth.

So when I look at this first question, discuss the strengths and weaknesses of the information available to assess this risk, I mean, there are levels of evidence in cancer treatment. We know what those are. It's Level I is a prospective randomized controlled trial, and Level IV or V is some expert

somewhere saying something. And then in between it's all the rest.

So all the evidence presented on the incidence and prevalence is Level II or III evidence, at best. So we don't have the best available evidence, but I almost, again, coming back to my original where I come from perspective, to me, it doesn't matter if it's 1 in 300 or 1 in 7,000. You know, it's too much. It's something that is in a process of treatment of a condition that we would not otherwise do if we knew the patient had cancer, and there are alternatives. There are alternatives to power morcellation in an intra-abdominal cavity without containment even if containment worked, and we're going to get to that question later.

So my response to the first question is the evidence is weak; but to me, we're coming at it from the wrong perspective. The perspective has to be when somebody comes to market with a new therapy to treat cancer, the onus is on them to prove it is equivalent to standard of care at the time. And we're being asked almost to do the reverse. So the standard of care for many decades and indeed, a century, in oncology circles was en bloc removal of the tumor without disruption, and that has served us well to come up with the fact that we know for Stage -- FIGO Stage I and II sarcoma, uterine leiomyosarcoma, you get a 60-70-80-90% cure rate.

And so if you're doing something different than that, the onus is on us to try to dig up the data to figure out -- to piecemeal why it's not working. It's on the device manufacturers to prove that it is equivalent to the

standard of care. And it's interesting to me that the device manufacturers withdrew the device because of some concerns, I think, over that.

So the evidence is Level II to III evidence, but to me, it doesn't matter. I think the perspective has to be, should we be morcellating in the open abdomen things that might be cancerous tumors? And as a surgical oncologist, the answer is no.

DR. DIAMOND: Okay.

Dr. Isaacson, anything to add?

DR. ISAACSON: Keith Isaacson.

I just want to go back to what Dr. Moore said. I disagree a little bit. I don't think we're going to have to give a range of 1 in 350 to 1 in 7,000. I see no reason why two reasonable groups -- because I don't think either one have an agenda, personally. I don't think the FDA has a separate agenda, and I don't think this other group does. Why they can't work together to come up with a more reasonable estimate because -- and in all respect to Dr. Shriver, if you're not a cancer surgeon, most of us try to educate the patient the best we can with the best information available, knowing that there are times that it's still lousy information, you still give them the best information available.

When there are options, if you believe in the shared decision-making process, where the patient should be involved and her family should be involved in making a decision for what's best for them based on their values and their preferences, and we do need to have more accurate data.

And I think it's possible. I think it is possible that we can somehow settle the difference between 1 in 7,000 and 1 in 300 if the two groups will work together. And that's what I would encourage over the next several weeks. Hopefully, that's all it would take to kind of reconcile those two hugely different numbers.

DR. DIAMOND: Dr. Afifi, anything else from what you said before?

DR. AFIFI: Nothing more from a statistical point of view, but I just want to congratulate Dr. Shriver for saying, in a much better way, what I wanted to say earlier.

DR. DIAMOND: Dr. Neuman.

DR. NEUMAN: I would like to agree with what has gone so far. There definitely is an issue in terms of the data itself. But, again, as Dr. Shriver commented, the real issue is what can we do to make the data better? And I don't know that going through an extensive study to determine whether it's 1 in 7,000 or 1 in 350 or 1 in 472 is going to help us as much with that. I certainly agree with what was said in terms of patient counseling, and I think it's important that we give our patients the best data that we have. But I'm wondering whether we would be better off trying to put our effort into trying to reduce the number, whatever it is.

DR. DIAMOND: All right.

Dr. Talamini, anything to add on this? Or, otherwise, we'll let

you be the lead-off on Question (b).

DR. TALAMINI: This is Talamini.

I hesitate to say this, but I'll mention it anyway. Dr. Shriver, I certainly agree with you, being a general surgeon, and I'm doing plenty of surgical oncology. The example, though, that perhaps at the other end of the spectrum to think about -- and it's not a complete analogy -- is when we take out a gallbladder that turns out to be an adenocarcinoma. So we would never intend to take that gallbladder out and spread cancer into the peritoneal cavity, but it occasionally and rarely happens. If we thought it was going to be a cancer, we wouldn't do it. And I don't think this situation is exactly like that, but I think that's at the other end of the spectrum because I think too many gynecologists, these are unsuspected malignancies even though they're normally dealing with masses in the form of fibroids. That's just a little bit of perspective.

But for Question (b), based on currently available information, please discuss the magnitude of the risk, I think this is pretty simple. Numerically, the magnitude of the risk is pretty small; individually, the magnitude of the risk is huge, because if you're upstaging a cancer into the peritoneal cavity, as we've discussed, for any given individual, that's a tragic outcome.

DR. DIAMOND: Okay.

Dr. Shriver.

DR. SHRIVER: I just want to respond to the gallbladder question, since this is on the record. So you're correct. Sometimes occasionally you take out a gallbladder and it has adenocarcinoma cancer, but there's better imaging, we know, in patients who have gallbladder polyps or a mass that's in the gallbladder. They should actually not undergo a minimally invasive cholecystectomy. And so the imaging is much more specific in terms of being identified to those patients beforehand.

DR. DIAMOND: Dr. Brown.

DR. BROWN: So I'd like to answer Question (b).

So, based on the currently available information, please discuss the magnitude of risk, so I've been practicing for almost 25 years, and I was taught by people like Dr. Cohen and others that informed consent is extremely important. And I think that we do have vast experience that -- oncologic surgeons and oncologists have been operating on women with fibroids for many, many years and should have and continue to give them informed consent.

And so I think if we even use the largest risk estimate, it's less than 1%, and that is what I generally tell my patients, what I instruct my residents, when I'm talking to them, if they're going to operate on a woman with fibroids, whether you're doing a hysterectomy, a myomectomy, or whatever, you need to remember that there is, in general, about less than a 1% risk that that fibroid will actually not be a fibroid. And that's a point I also

want to make here because I think we're confusing -- fibroids and leiomyosarcomas are completely separate entities.

So our denominator is not women with masses or lumps; it's women with fibroids. And so the risk of having an unsuspected malignancy is probably 1% or less and that is -- I feel very strongly patients should be informed of that. But the data that we really need in terms of the magnitude of the risk isn't that. It's not what's the incidence of leiomyosarcoma; it's not what's the incidence of unsuspected leiomyosarcoma. The magnitude of risk is, of those women who have a leiomyosarcoma that are operated on and either have a hysterectomy that is unsuspected at the time of the primary surgery, whether it's by abdominal hysterectomy, vaginal hysterectomy, whether they have a myomectomy, or whether they have abdominally or laparoscopically or vaginally, whether they have a morcellation of their whole uterus or of the fibroid, we need to be able to say what is the chance that that procedure is going to upstage their leiomyosarcoma.

We did not hear information -- we heard -- well, Dr. Cohen actually presented it, but we didn't talk about it, that the five-year overall survival for Stage I, surgically Stage 1 leiomyosarcoma, is 55%. That drops to 28%, 30%, et cetera, as you advance a stage. So upstaging is a very significant adverse prognostic factor, and that's why we need to know what is the risk of doing a myomectomy, of morcellating what you think is a fibroid and actually is a leiomyosarcoma in terms of causing the upstaging. And I would say that



we do not have any data from any studies that addresses this really at all.

There's one study by Dr. George et al. that just came out that tries to look at this, but what I think that we really need to do or what the FDA needs to do or someone really needs to do, since we can't do a study, it's never going to be done, we must get more information from the women and their families who this has happened to. We must get the details so that we can analyze what exactly was going on, what was -- you know, was there already dissemination, was there already pulmonary -- we don't know any of that. And so until we know that, we cannot answer (b). And I don't think a registry is going to help.

I think the way to do it is to use the fact that there is now more awareness of this and to ask for more information from all the individuals that this has been -- and their physicians, including detailed operative notes, pathology reports, everything that the FDA and the device makers or whoever can look at to try to answer (b). Because you have no way to answer (b) without that information.

DR. DIAMOND: Dr. Snyder.

DR. SNYDER: And then, you know, just to add to what you've already identified, and it's been identified elsewhere, we would need the magnitude of that risk for endometrial adenocarcinoma upstaging. I mean, we know that yes, there's an early warning sign, there's an endometrial biopsy, but we know that those aren't perfect, either, and likewise for pap

smear.

DR. DIAMOND: Okay, let's see. We'll go back the other way this time.

Dr. Neuman, anything you'd like to add with regard to (b)?

DR. NEUMAN: No.

DR. DIAMOND: Okay.

Dr. Afifi.

DR. AFIFI: Just a general remark, that we humans, in general, are not very good at interpreting risk estimates. There is a lot of research that shows that when presented with a certain figure, 1 in 100, let's say that's the right number, let's say, then most people would think, no, no, that's not going to happen to me. And how much that should be taken into account is something that I think more behavioral scientists need to be consulted, as well.

DR. DIAMOND: Okay.

Dr. Isaacson.

DR. ISAACSON: As far as discussing the magnitude of risk, I think I already said everything.

DR. DIAMOND: Okay.

DR. ISAACSON: Thank you.

DR. DIAMOND: Dr. Shriver, anything to add?

DR. SHRIVER: Yes. The magnitude of the risk of upstaging from

a Stage I endometrial or leiomyosarcoma to a Stage III or IV is obviously devastating. I think, again, I come back to if you start at the beginning and a device or a therapeutic was coming to market versus the standard -- and I think colon cancer is an example of this in terms of the surgical approach. About 10 or 15 years ago colon cancer, for a hundred years, was taken out through open surgery. Then the question was here's minimally invasive surgery, can we approach it with minimally invasive techniques? And so there were concerns over some anecdotal and other reports, report site recurrence and so forth.

So I think what happened there was the right thing was done. It was demanded that a randomized controlled trial be performed; patients were consented properly into a randomized controlled trial of minimally invasive versus open colectomy. It was multi-center, so forth. And so that's the way you can provide consent for small aspects of risk that once you're under 1% or 0.1%, I mean, patients again are going to reasonably think, well, the odds are good, but this won't happen to me, but if it happens to you, the magnitude is very significant.

So, again, I come back to if this were working the other way and they were coming to us with morcellation intra-abdominally in an unprotected environment of a potential tumor, we would demand equivalency studies to standard approach. But we're being asked to treat it the reverse way, and so that puts us in a difficult position. But the issue is

that the magnitude, for 1(b), it's very significant for those who are upstaged.

DR. DIAMOND: Thank you.

Dr. Wentzensen.

DR. WENTZENSEN: The only comment, maybe, is that it would be very hard to evaluate this in a trial. I mean, I think those numbers --

DR. SHRIVER: That's exactly right.

DR. WENTZENSEN: But it's impossible. I mean, that's --

DR. SHRIVER: Which is why it should be a Class III device.

DR. DIAMOND: Dr. Snyder, anything else? If not, Dr. Iglesia.

DR. IGLESIA: Okay. So my only thing is that it's less than 1%, whether it be 0.2, 0.01%, the issue is I think that we're very close to getting enough data to say, okay, don't use this in people who have very high-risk looking fibroids based on their MRIs, the heterogeneity, density, et cetera. Don't use this in postmenopausal women who are bleeding and you haven't done adequate evaluation.

We really need to get some clear guidance out there for all of us who are in clinical practice, because you know the magnitude of the risk is great for those who this happens to. We need to do a better job. And I think, you know, the data is close, and there probably are some people where morcellation should be contraindicated.

DR. DIAMOND: Dr. Moore.

DR. MOORE: Lisa Moore.

I think that we don't have enough data to assess the magnitude of the risk, but it doesn't really matter because I think what's an acceptable number of patients that you would allow this to happen to, and the answer is zero. But the other side of that coin is that there are a certain number of patients who are going to want this option for their surgical procedure who are at low risk. We don't have currently any way of identifying which patients those are. And I was listening to Dr. Brown, and I would think that when the laparoscopy was performed and they had the scope inside the abdomen, they would have looked at the peritoneal cavity, and they would have noted seeding, possibly. Possibly not. And so I think that there is not enough data to assess the magnitude of risk, but I think that any amount of risk is too great to take.

DR. DIAMOND: Dr. Hillard.

(No audible response.)

DR. DIAMOND: Dr. Brown, you already -- nothing else?

Dr. Mattrey.

DR. MATTREY: Yeah, I think Dr. Shriver presented to us a criteria that seemed to be logical on preoperative MRI, that if the fibroid is black and does not look weird, it is going to be a fibroid, not a sarcoma. But at least it dichotomizes the patients to establish risk. But if it has any inkling of being unusual on the MR up front, then you weigh the other factors in to better determine risk. But there is no data to assess magnitude of risk right

now other than you say in those patients that we saw the pictures on, the probability is very, very low that they're going to have a sarcoma.

DR. DIAMOND: Dr. Gallagher.

(No audible response.)

DR. DIAMOND: Dr. Simon.

DR. SIMON: You know, the only thing I would add is it's not so much the magnitude of the risk, it's really what's the magnitude of the risk of dissemination, and to me, that's the informed consent question. You know, if you talk to a patient and you would say, well, the magnitude of risk of you having a fibroid is anywhere from -- I mean, a leiomyosarcoma from 1 to 300 to 1 to 7,000, but really what you should be telling the patient, frankly, the magnitude of the risk, if it turns out you do have a leiomyosarcoma, the magnitude of the risk is really substantial because you're going to be upstaging your cancer and you're going to be in an entirely different category of disease, and you're going to be very, very unhappy if that's the case.

And so I think the question should really be changed to say what's the magnitude of the risk of upstaging, because that actually is a much more relevant question to ask because suddenly, this patient is in a very different disease category at the end of this procedure and that's, to me -- and that's a great magnitude in the use of morcellation.

DR. DIAMOND: Ms. Aronson.

MS. ARONSON: Yes, I agree with what Dr. Simon is saying and

focusing on that magnitude of risk, we're only seeing the last part of this question. And the sentence just that is previous to this is about morcellation, and I would add that morcellation does increase the magnitude of risk.

DR. DIAMOND: Okay.

Ms. Mattivi.

MS. MATTIVI: I think we can argue for many long hours about the magnitude, about quantifying the magnitude of the risk, and in the meantime the impact of that magnitude, as many have pointed out, is great to the individual. I think the other part of this question is how hard is it to decrease that magnitude of risk.

DR. DIAMOND: Okay.

Mr. Gardner.

MR. GARDNER: So I'm probably the last person to speak today, and I apologize because I might just add some confusion to this. I agree wholeheartedly that the question here really is what's the magnitude of risk of upstaging the cancer, but I feel like we're asking that question in a silo, when I think the rest of the question is, okay, what is the magnitude of risk of alternatives?

For instance, if the risk of unsuspected sarcoma is 1 in 500 and half of those would be upstaged, then we're looking at the risk of 1 in 1,000, and I know the worst outcome of that is death, but what's the mortality risk of abdominal hysterectomy, for instance? Is it less than that, worse than

that? It would be tragic if we move people from a procedure now that has a slight risk, albeit a real risk, to something of greater risk.

DR. DIAMOND: Okay.

If there are no other --

DR. YUSTEIN: Dr. Diamond?

DR. DIAMOND: Yes.

DR. YUSTEIN: Dr. Corrado wanted to add --

DR. DIAMOND: Sure. Dr. Corrado.

DR. FISHER: And then I have a question after that.

DR. DIAMOND: Okay.

DR. FISHER: Dr. Talamini is going to try to beat me to it.

DR. TALAMINI: I just wanted to endorse Dr. Brown's concept that if we look intensively at the patients who have been affected by this and understand how they got there, that may really help inform creating an effective paradigm or protocol to avoid it in the future.

DR. DIAMOND: Dr. Corrado.

DR. CAREY-CORRADO: Yes. I wanted to draw the Panel's attention to Section 2.2 of our Executive Summary. It's the section on uterine sarcoma. And we do briefly summarize some SEER cancer statistics. Specifically, annual percentage change for incidence in mortality for cancer of the corpus and uterus not otherwise specified. So, unfortunately, the data are not available by histology.



However, mortality from cancer of the corpus and uterus not otherwise specified had a significant annual percent increase among white women age less than 50 from 1988 to 2010, and African-American women less than 50 from 1995 to 2010, and African-American women 50-plus from 1997 to 2010. Once again, the data are not available by histology.

DR. DIAMOND: Dr. Fisher.

DR. FISHER: Thank you.

To paraphrase Dr. Simon, Dr. Talamini, I think when we look at (b), the incidence may be small, but the severity may be great if you're the person that has it, and I think everybody is pretty much in agreement.

Where I need the help of the Panel is for (a). I've heard everything from the analysis is weak, so I'd like to kind of get a little bit more definition on what weak means, you know, was it the analysis itself, not enough data, how could I strengthen it? Because I also hear that maybe we can get together in a couple weeks and do a corroborative effort, which we're all about. Okay, we'll do it. But I don't want to go through that effort if we don't have the data and it's not going to mean anything, and after a couple months we're going to say, hey, it's weak, because I also hear from the other side of the table that maybe we don't have the data that we need.

So I'd kind of like to know -- I'll even give Dr. Afifi the last writ on this, and if we decide that we're going to move forward, what does FDA need to do? And maybe it's a reanalysis. Do we work with somebody? Is

there additional data that we should take into consideration, or is it really going to mean anything if we do rework these numbers?

DR. DIAMOND: Dr. Afifi.

DR. AFIFI: I think that finding a better estimate of prevalence is probably not as important as putting it more in the context of assessing the upstaging risk because I think that is the fundamental question. I would advise that you spend your time more on trying to estimate the risk of upstaging rather than the number that you already looked at.

I have a logistical question. Can we leave our papers in here when we leave?

DR. DIAMOND: You're jumping ahead because we have people with their hands up. But no, you'll want to take your papers with you.

DR. AFIFI: Okay.

DR. DIAMOND: Dr. Isaacson.

DR. ISAACSON: Yeah. Again, I go back to -- I disagree with Dr. Afifi and some of the others. I think it is crucial that we try to get better data on the true prevalence and incidence because we have to counsel the patient with the best data we can, and from that you can then say what's the risk of upstaging, which I think that's going to be less controversial. But what is so important for us when we're talking to the patient is try to have a better understanding between these data and the FDA data, between the Pritts data and the FDA data, see which one is right.

So I do think, I strongly encourage you to work together in the next few weeks to try to see if you can resolve that. And I think about Dr. Talamini's example of the gallbladder. We're faced with this all the time where we're giving patients the best information we have. We have ovarian cysts constantly that are, say, endometriomas, where we know there could be as high as a 1-to-3 risk of a clear cell carcinoma associated with it. And we have to tell the patient this is the risk, but you're a fertility patient, and you have to say clearly, if I upstage you and turn you from a Stage I to a Stage II because I spilled it, that is going to have significant consequences.

So this is not an isolated disease in which we're giving the patients the options, giving them the best information possible and having them involved in the choice that's going to be made based upon, again, their values, their preferences, and having the best data available. So having the good data, there's nothing in my mind that's more important than that.

DR. DIAMOND: I think Dr. Brown had her hand up first.

DR. BROWN: So, again, you know, the federal government only has so much resources, and I would say that I would advise to put the resources towards looking at this. I don't know if it's the right analogy, and we talked about the Class III. I think now, you know, we're hearing things, so I'm just suggesting that you delve deeper into what you're hearing; ask for the details on all of the cases that are already in the MDR, the other ones that are happening; ask, solicit people to report about incidences of any type of

malignancy after use of uterine morcellation and get the details, because I think it was a really good point.

Not only will it give you a way to estimate for the woman who's trying to consider whether I should have a minimally invasive procedure and whether it's myomectomy or morcellation for my fibroid, but more importantly, just like with QA, we analyze when things go wrong so we can find a way to prevent it. And I think you're more likely than studying all these theoretical things about the bags and whatever, delve into the actual cases where this happened because you may be able to find a way to prevent it from happening.

DR. DIAMOND: Dr. Talamini.

DR. TALAMINI: Just in terms of the data, as well, I think the OSHPD California database, the SPARCS New York database, even though they don't have histology and pathology, the patients can be followed longitudinally with individual identifiers so that if later they carry an ICD-9 code of leiomyosarcoma, that can be found. So it may not be the FDA's place, but I think there are methodologies to get better numbers, potentially, even with data that's out there right now.

DR. DIAMOND: Dr. Afifi.

DR. AFIFI: Just one more thought about the reconciliation that was suggested by Dr. Isaacson. There have been meta-analyses in which judgment was made. I was involved, for example, in some that included this

method. A judgment is made as to the quality of the paper, and that could be done by a conference with Dr. Jones and Dr. Pritts or maybe some of her colleagues, and you could then select from the much larger group of papers used by Dr. Pritts, those that are considered to be of high enough quality and comparable to the ones that Dr. Jones included, and that could then result in a larger group and just reanalysis of that, using the GLIMMIX random effects method that they used.

DR. FISHER: Thank you.

DR. DIAMOND: Dr. Yustein.

DR. YUSTEIN: So I was wondering if some folks on the Panel can expand on this, maybe Dr. Brown. You know, I'm hearing that FDA should kind of dive into the individual cases a little bit more. You know, I think people on the Panel recognize we don't have a national medical system like European countries. We don't have access to that data. Maybe I've been jaded by the MDRs a little too much, but I don't think MDRs are the way to get that information even if we were to go back to individual patients.

There is significant underreporting, so I'm not sure we have that right mechanism. So what are the alternatives for collecting this additional information on each case that occurs? Is that something that the professional societies should be doing? Is that something others should be doing? I don't think -- we don't have a national medical system here where -- like England and Australia, where a lot of the stuff is kept and the

government has access to those records. And MDRs is not the way to go. I'm just telling you that.

So I'd be very interested in hearing where are you thinking that we're going to get this information, and are we the right people or are the professional societies the right people? I mean, the physicians at the table, you guys are the ones that find out on the front lines whether or not your patient had a leiomyosarcoma after the surgery; we're not. And so what is the responsibility of the physician community to help us out there?

DR. DIAMOND: Dr. Brown.

DR. BROWN: So I'm just a little confused. So we're talking about a device that's been approved by the FDA. Does not the FDA -- and you've gotten some new information from various sources that there might be a problem with the device. There is no mechanism for the FDA to maybe work with the companies to send a letter out to everyone that has been sold one of these devices or to send some type of general announcement out? That doesn't exist, that mechanism doesn't exist?

DR. YUSTEIN: But who is the end person that has that information? The company doesn't have the information on the patient. The doctors are the ones that have the information on the patients, the hospitals are the ones that have the information on the patients.

DR. BROWN: Right. So FDA -- I mean, I'm sorry. But you issued a statement in May and April that all the doctors and everybody and patients

and everyone heard about, and I think that helped probably stimulate a lot of people to maybe even connect the dots or report it, so is it not possible, in that context, to ask for the physicians, the women themselves to send in their information, that there's no mechanism for doing that?

DR. YUSTEIN: Sure. And I think in our Safety Communication, if you read the whole thing, it actually encourages people to report. However, the key word there is "encouraging." We can't mandate that every physician report every event and every patient report. And I think, you know, just from the numbers I presented today, we had 21 MDRs. You've heard people in the audience saying 100, 130 cases, so it's a fraction of what's going on out there. So even when we encourage people to report, we're not getting the real picture of what's going on.

DR. DIAMOND: Dr. Gallagher.

DR. GALLAGHER: I'm wondering, time-wise it may not work, but my thought is this particular thing is a sarcoma, it would be perhaps something to work with the NCI on developing a study. That could be done if that would involve multiple centers and whatever to look at these kinds of cases, to do a retrospective review, perhaps, of cases of this particular type of sarcoma and walk them back by looking at medical records or whatever to obtain some of the information.

DR. DIAMOND: Ms. Mattivi.

MS. MATTIVI: So what I'm struggling with at this point in the

evening, besides being massively hungry, is I understand and I emphasize and I also want more data, and I want more data that I can wrap my arms around and that I can understand. And in the meantime, in the quest for that data, I hate to see women being continued to be put at risk as they undergo these kinds of procedures.

I think, as Dr. Shriver has pointed out, if there are alternatives that obviously don't increase the risk to the patient and could substantially decrease the risk to the patient, those are also things that I'm really hoping that this committee discusses tomorrow as we go forward with the conversations. Again, understanding the need and the want for the data to support those decisions, but that there also might be other strategies that can be taken in the meantime in that quest for data.

DR. DIAMOND: All right, let's see.

I guess the comment I wanted to make was that there is also a problem with the papers in the literature in that the papers that reported incidence in the literature are those centers which have had a patient with that condition in which -- then gives them the opportunity to look and see out of that numerator that they have at that institution, what is the denominator of the patients that that came from. And so the question becomes what is the denominator of other institutions which did not have something in the numerator which led them to initiation of a manuscript for scientific -- to enter to the scientific literature.



Let's see. I think, unless there are other comments, I'm going to try to sum up the diverse comments that we've had for Dr. Fisher and Dr. Yustein.

So with regard to Question 1, I think it was a general consensus that the data that we -- there were lots of concerns with the data that we had and the strength of that data. One individual described it as Level II or III; others described it as weak, and another described it as not sure what the effects even were.

There were different numbers presented by FDA and by Dr. Pritts, and there probably would be a value, it was thought, to have a number that we could share with patients as to what the risk is.

Having said that, for the patient that has an unrecognized or occult leiomyosarcoma that is operated upon, it is obviously a potential for a very devastating disorder with very significant consequences on their life.

It was thought there is a need for additional data, and one thing in particular is that if an individual does have a leiomyosarcoma and it is removed en bloc at the time of myomectomy as opposed to morcellation, whether that be a time of an open procedure or a laparoscopic procedure, it doesn't sound like we have any data at all as to what the consequences of that are on outcome, although if there is a subsequent upstaging of the disorder, again, that would have a very significant impact on outcomes.

Does anyone on the Panel want to add to that as a general

summary?

(No response.)

DR. DIAMOND: If not, then Dr. Fisher, Dr. Yustein, is there anything else you'd like us to address with regard to Question 1?

DR. FISHER: No, sir. Thank you very much for the input.

DR. DIAMOND: All right. And I think, then, we will call it a night.

But we have three announcements before we go, which are -- as Dr. Afifi asked before, don't leave any belongings, take things with you.

LCDR ANDERSON: Okay, don't leave any belongings. Press, do not contact STEs until the meeting is officially over. And we're going to ask for the members of the public to leave and then the panelists.

Thank you.

(Whereupon, at 6:23 p.m., the meeting was continued, to resume the following day, July 11, 2014.)

C E R T I F I C A T E

This is to certify that the attached proceedings in the matter of:

OBSTETRICS AND GYNECOLOGY DEVICES PANEL

July 10, 2014

Silver Spring, Maryland

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