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CENTERS FOR MEDICARE AND MEDICAID SERVICES
Medicare Evidence Development & Coverage
Advisory Committee

November 18, 2009

Centers for Medicare and Medicaid Services
7500 Security Boulevard
Baltimore, Maryland

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Panelists

Chairperson
Clifford Goodman, Ph.D.

Vice-Chair
Saty Satya-Murti, M.D., F.A.A.N.

Voting Members
Catherine Eng, M.D., F.A.C.P.
John Cox, D.O., F.A.C.P.
Philip B. Gorelick, M.D., M.P.H.
Josef E. Fischer, M.D.
Nora A. Janjan, M.D., M.P.S.A.
Norman S. Kato, M.D., M.P.S.A.
Stephen Pauker, M.D., M.A.C.P., F.A.C.C.
Gurkirpal Singh, M.D.
Craig Umscheid, M.D., M.S.C.E.

Patient Advocate
Susan Kendig, J.D., M.S.N.

Industry Representative
Kim K. Kuebler, M.N., A.P.R.N.-B.C.

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Guest Panel Members
Janice Cormier, M.D.
Naomi Lynn Hurwitz Gerber, M.D.
Lucinda A. Pfalzer, P.T., Ph.D.

Guest Speakers
Jane M. Armer, Ph.D., R.N., F.A.A.N.
Stanley G. Rockson, M.D.

CMS Liaison
Tamara Syrek Jensen, J.D.

Executive Secretary
Maria A. Ellis

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PANEL PROCEEDINGS

(The meeting was called to order at 8:08 a.m., Wednesday, November 18, 2009.)

MS. ELLIS: Good morning and welcome

committee chairperson, vice chairperson, members and guests. I am Maria Ellis, the executive secretary to the Medicare Evidence Development and Coverage Advisory Committee, MedCAC. The committee is here today to discuss the evidence, hear presentations and public comment, and make recommendations concerning the diagnosis and treatment of secondary lymphedema.

The following announcement addresses conflict of interest issues associated with this meeting and is made a part of the record. The conflict of interest statute prohibits special government employees from participating in matters that could affect their or their employer's financial interest. Each member will be asked to disclose any financial conflicts of interest during their introduction. We ask in the interest of fairness that all persons making statements or presentations also disclose any current or

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previous financial involvement in a company that manufactures equipment, garments or devices used to treat or diagnose lymphedema, a facility in which lymphedema is treated or diagnosed, or a company that develops guidance for the treatment or diagnosis of lymphedema for public policy-making. This includes direct financial investment, consulting fees and significant institutional support. If you haven't already received a disclosure statement, they are available on the table outside of this room.

We ask that all presenters please adhere to their time limits. We have numerous presenters to hear from today and a very tight agenda, and therefore cannot allow extra time. There is a timer at the podium that you should follow. The light will begin flashing when there are two minutes remaining and then turn red when your time is up. Please note that there is a chair for the next speaker, and please proceed to that chair when it is your turn. We ask that all speakers addressing the panel please speak directly into the mic, and state your name.

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For the record, voting members present for today's meeting are: Dr. Saty Satya-Murti, Dr. Catherine Eng, Dr. John Cox, Dr. Philip Gorelick, Dr. Josef Fischer, Dr. Nora Janjan, Dr. Norman Kato, Dr. Stephen Pauker, Dr. Gurkirpal Singh, Dr. Craig Umscheid, and

Dr. Susan Kendig. A quorum is present and no one has been recused because of conflicts of interest.

The entire panel, including nonvoting members, will participate in the voting. The voting scores will be available on our web site following the meeting. Two averages will be calculated, one for voting members and one for the entire panel.

I ask that all panel members please speak directly into the mics and you may have to move the mics since we may have to share.

If you require a taxicab, there is a signup sheet at the desk outside of the auditorium. Please submit your request during the lunch break.

Please remember to discard your trash in the trash cans located outside of this room.

And lastly, all CMS guests attending

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today's MedCAC meeting are only permitted in the following areas of the CMS site, the main lobby, the auditorium, the lower level lobby and the cafeteria. Any persons found in any area other than those mentioned will be asked to leave the conference and will not be allowed back on CMS property again.

I would like to turn the meeting over to Dr. Goodman.

DR. GOODMAN: Thank you very much, Maria. Maria, should we go down our list for declarations now, or after my remarks?

MS. ELLIS: It's up to you.

DR. GOODMAN: Let's go down the list.

Cliff Goodman, vice president of the Lewin Group. The Lewin Group is a health care policy consulting firm and is a subsidiary of Ingenix, a health care information firm. Ingenix in turn is a subsidiary of United Health Group.

DR. SATYA-MURTI: Saty Satya-Murti. I am a neurologist and health policy consultant. I used to be a contract medical director for a number of years. I have no conflicts of interest.

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DR. GOODMAN: I wanted to add that I have no conflicts of interest.

DR. ENG: Dr. Catherine Eng, geriatrician and internist, clinical professor, UCSF, and medical director of On Lok Senior Health Services. I have no conflicts of interests.

DR. COX: John Cox. I'm a practicing

medical oncologist in Dallas, Texas with Texas Oncology, a large group practice, and I have no conflicts of interest.
DR. GORELICK: Phil Gorelick, professor and head of neurology, University of Illinois at Chicago. I have no conflicts of interest.
DR. FISCHER: Josef Fischer, professor of surgery at Harvard Medical School and an active practicing surgeon and researcher. I have no conflicts of interest.
DR. KATO: Norman Kato, private practice in cardiothoracic surgery in Simi, California. I have no conflicts of interest.
DR. PAUKER: Steve Pauker, Tufts University division of clinical decision-making and health policy, and I have no conflicts of

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interest.
DR. SINGH: I'm Gurkirpal Singh, adjunct clinical professor of medicine at Stanford University epidemiology and outcomes research. I have no conflicts.
DR. UMSCHEID: My name is Craig Umscheid, I'm a hospitalist at the University of Pennsylvania, I'm a clinical epidemiologist, I codirect the Hamlin Center for Evidence-Based Practice. I have no conflicts of interest.
MS. KENDIG: I'm Susan Kendig, I'm a women's health nurse practitioner, associate teaching professor and coordinator of the women's health nurse practitioner option at the University of Missouri St. Louis. I'm also an attorney in private practice and I have no conflicts of interest.
MS. KUEBLER: Kim Kuebler, oncology nurse practitioner and medical pharmaceutical consultant representing industry. I have no conflicts of interest.
DR. CORMIER: Janice Cormier. I'm a surgical oncologist at the M.D. Anderson Cancer Center and a clinical investigator. I have no conflicts of interest and I'm a guest panel

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member.
DR. GERBER: I'm Lynn Gerber, I'm the director of the Center For the Study of Chronic Illness and Disability, George Mason University. I have no conflicts of interest.
DR. PFALZER: I'm Lucinda Pfalzer, professor of physical therapy at the University of Michigan Flint campus, and I'm a clinical researcher.
DR. GOODMAN: Thank you very much. Do

keep in mind, although we've got a packed agenda today on a very important topic, we need to ensure that we get to all of our speakers and those who will be providing public comments. Further, we expect that we're going to need all of our allotted time for panel discussion and deliberation and as such we will need to stay within our allotted times. In addition to your own cognizance of time, as we were reminded by Maria and CMS's special lighting system, I won't hesitate to let speakers know when you've got a minute or two remaining, and we'll stick to that. We'll also consider, and this is important, that if you're going to say

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something to us today, it's important enough that we hear it, including our devoted court reporter, to your right. If you aren't recognized by me and speak into a microphone, not only will we not hear what you've got to say, but our court reporter may not be able to enter what you said into the record. And so if it's important enough to say, it's important enough to capture in the record, which means we will need to recognize you and you will need to move to a microphone. That way we will get your important insights.

With that, why don't we leap into our ambitious agenda, which will be taken lead for us by Jean Stiller from CMS, so Jean will start. And as always, our speaker on deck should be at the ready.

MS. STILLER: Good morning and thank you. Chairman, panelists, members of the public, I would like to, on behalf of the Centers for Medicare and Medicaid Services, I would like to welcome you to today's meeting on the diagnosis and treatment of secondary lymphedema.

I would like to take this opportunity

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to introduce myself and the CMS analytical team responsible for today's meeting. My name is Jean Stiller and my role is lead analyst for the project. Dr. Susan Miller is acting director for the Division of Items and Devices and is also lead medical officer on this project. Maria Ellis is the MedCAC executive secretary, and Dr. Louis Jacques is the director of the Coverage and Analysis Group. I would also like to thank my many other colleagues at CMS who worked to help prepare today's presentation.

The goal of today's MedCAC meeting is to clarify the adequacy of the available evidence that supports the diagnosis and treatment of secondary lymphedema. Dr. Susan Miller will kick off today's event by presenting basic information relevant to our discussion today on the topic of secondary lymphedema.

Next we will hear a presentation by Dr. Mark Oremus and Kathryn Walker of the McMaster University Evidence-based Practice Centre. You will hear details about the research they conducted in response to the

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technology assessment commissioned by the Agency for Health Care Research and Quality. The technology assessment is one of the primary inputs used by the panelists to formulate recommendations on today's topics. Panel members were also provided with additional background materials determined relevant to the subject matter. The TA along with additional materials from today's MedCAC can be found at the web address on the slide.

Next we will review the MedCAC panel questions, and finally we will hear presentations from invited speakers and other interested parties. Questions posed to MedCAC panels consist of voting and discussion type questions. For those questions in which panelists are asked to express a degree of confidence, individual panel members will be asked to respond with a score from one to five. A score of five indicates the panel member is very confident in response to the question posed, whereas a score of one indicates a complete lack of confidence in response to that particular question.

Discussion type questions are not

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scored but allow for a free exchange of ideas in the area surrounding that particular topic. I will now read aloud each of the eight questions that the panel will later react to by either casting an individual score in the case of a voting type question, or discussing in detail for the case of the discussion questions. Out of the eight questions posed, seven questions will be scored; only one question, question number eight is used for discussion purposes.

Panel question one. How confident are you that there is sufficient evidence to determine if the listed diagnostic strategies

can reliably identify and stratify the severity of secondary lymphedema, including subclinical disease?
A, imaging techniques: Part one, lymphoscintigraphy, lymphangioscintigraphy; two, MRI/CT; three, ultrasound; four, Tc-hexakis MIBI scan.
Part B, quantitative techniques to determine limb volume and skin elasticity: Part one, tissue tonometry; part two, perometry; part three, circumferential

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measurements; part four, water displacement; part five, bioimpedance.
C, patient-reported symptomatology.
Part D, physical exam.
Part E, other.
Panel question number two. For only those items where the answer to number one is at least in the intermediate range, which is defined as a mean score greater than or equal to 2.5 on question one, how confident are you that each of the listed diagnostic strategies reliably identifies and stratifies the severity of secondary lymphedema, including subclinical disease?
Part A, imaging techniques: Part one, lymphoscintigraphy, lymphangioscintigraphy; part two, MRI/CT; part three, ultrasound; part four, Tc-hexakis MIBI scan.
Part B, quantitative techniques to determine limb volume or skin elasticity: Tissue tonometry; part two, perometry; part three, circumferential measurement; part four, water displacement; part five, bioimpedance.
C, patient-reported symptomatology.
D, physical exam.

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E, other.
Panel question number three. How confident are you that secondary lymphedema can be classified into prognostic stages of severity, in other words, staging that is useful to guide choice of therapy or predict response to therapy.
Panel question number four. In clinical studies of treatments for secondary lymphedema, how confident are you that there is sufficient evidence that an improvement in each of the following measures is strongly associated with an improved health outcome?
Part one, affected limb circumference.
Part two, affected limb volume. Part three, symptom assessment. Part four, affected limb

function, strength, endurance, range of motion, sensation, et cetera. Part five, ADL, activities of daily living abilities. Part six, frequency of skin breakdown or ulceration. Part seven, frequency of occurrence of local infection. Part eight, quality of life assessment. Part nine, other.
Panel question five. How confident are you that there is sufficient evidence to

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determine if each of the following treatment strategies produces clinically meaningful improved health outcomes for patients with secondary lymphedema?
Part one, pneumatic pressure devices; part two, exercise-based activities; part three, massage-based treatment; part four, compression bandaging, compression garments; part five, psychosocial support; and part six, other.
Panel question number six. Please answer question number six only for those treatments where the panel had at least an intermediate range of confidence, defined as a mean score greater than or equal to 2.5 on question five that there was sufficient evidence to address this issue. How confident are you that each of the following treatment methods produces clinically meaningful improved health outcomes for patients with secondary lymphedema?
Part one, pneumatic compression device; part two, exercise-based activities; part three, massage-based treatment; part four, compression bandaging, compression garments;

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part five, psychosocial support; part six, other.
Panel question number seven. How confident are you that the conclusions regarding the diagnostic strategies as a group which was referred to in question two, and the treatment methods as a group referred to in question number six are generalizable to Medicare beneficiaries with secondary lymphedema?
Panel question number eight. Please discuss any clinically important evidence gaps pertaining to the diagnosis and/or treatment of secondary lymphedema. What trial designs would support the closure of such existing evidence gaps?
I would now like to introduce Dr. Susan Miller, who's the acting director for the

Division of Items and Devices and the lead medical officer for this MedCAC. Susan is a board certified physician in physical medicine and rehabilitation with over 20 years of experience in academic and community settings.
DR. S. MILLER: Thank you, Jean. Good morning and welcome to our MedCAC.

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Lymphedema is a condition divided into two forms, primary and secondary. Primary lymphedema is relatively rare and is due to developmental abnormalities. Secondary lymphedema is a more common disorder, and in this condition the transport of lymph fluid is interrupted due to injuries to the lymph vessels, causing lymph fluid accumulation in the affected body parts. In the United States lymphedema is largely a consequence of surgery and radiation treatments used for therapies of cancer.
However, it is also estimated that a significant portion of the secondary lymphedema experienced in this country is associated with venous disorders, trauma, limb dependency, cardiac diseases, and other such conditions.
It has been estimated that lymphedema is experienced by as many as three to five million persons in this country. This number is an estimate, however, as there is really no universal accord as to how to measure this condition.
Specifically, there has been no consensus regarding the threshold of fluid

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accumulation in a limb which will define the disease process. Similarly, there has been no agreement how to quantify the condition either during the period of diagnosis or during its treatment phase.
I will quickly review for you in a very brief manner several methods which can be used to either diagnose or treat lymphedema.
As Jean mentioned, there are many imaging techniques.
Lymphoscintigraphy is one of them.
This is a study in which a radiologic substance is injected into a patient and is picked up by the local lymphatic system. Images are then taken over a defined period of time and the flow of the lymphatics is noted. There are traditional tracer agents which are used in this process but as noted, Tc-hexakis 99 MIBI is a new radioactive substance that is used for this process that is now being used in certain

centers. MRI scans, CT scans and ultrasound studies are used to look for characteristically abnormal patterns of lymph fluid collection in the affected tissues.

These imaging techniques, as I said,

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are used diagnostically, but they are not routinely used to quantify the amount of lymph fluid that has accumulated in the affected soft tissue. For that purpose there are other methods of assessment. They include a water displacement technique that provides a direct measure of limb volume. Here the affected limb is submerged into a cylinder filled with a known quantity of water. The amount of water displaced by the arm or the leg represents the volume of the limb.

Another technique, circumferential limb measurement, is accomplished with a flexible nonelastic tape measure placed around the limb at either bony landmarks and/or given intervals around the arm or leg. Then the limb is considered either a truncated cone or a cylinder in order to make a geometric calculation of the fluid that it contains.

Opto-electronic volumetry, also know as infrared perometry uses infrared light sources and sensors to create a two-dimensional shadow of the affected limb and then again, a series of measurements is taken to calculate the fluid accumulation in the limb.

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Using these and other techniques, a measure for the purpose of diagnosis or follow-up of lymphedema may be made either by comparing the affected limb to the presumably unaffected one, or by comparing a baseline measurement, for example from either a preoperative measurement of an arm of an individual who is about to undergo a mastectomy to a similar measurement taken at a later date.

Using these techniques and measures, lymphedema has been defined differently by different authors for different purposes. For diagnostic purposes, commonly, though not exclusively, it is required that at least a difference of 10 percent or 200 milliliters in volume or at least a two-centimeter difference in girth be present between the affected and the comparison measurement in order to define the condition of lymphedema.

Other means of diagnosing and quantifying the disease process are also noted in the literature. They include multifrequency

bioimpedance analysis. One can also assess lymphedema, as noted in the literature, through an evaluation of the softness or hardness of
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the skin in the affected extremity. This is performed by tissue tonometry.
In addition to these methods, there are clinicians who use physical exam as well as history-taking to make the diagnosis of lymphedema. For example, in the lymphedema community there are many who believe that the condition can be subclinical in nature, meaning that no signs of swelling are appreciated on physical exam even though patients report abnormal symptoms in the affected body parts. Therefore, by either taking a traditional verbal history or through the use of a structured interview tool, symptoms such as complaints as skin being tight, jewelry being tight, itching, burning and the like may be considered of sufficient diagnostic weight in order to initiate treatment.
And there are also clinicians, as I mentioned before, who make the diagnosis of lymphedema based on physical exam alone.
As there are numerous ways to assess for the diagnosis of lymphedema, there are also numerous ways to treat it. I will confine my remarks to those that do not involve
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pharmaceuticals and surgery.
Pneumatic compression devices are pumps that push air into a sleeve or garment around a lymphedematous limb or portion of the body. These devices may have a single bladder or a system of bladders which inflate and deflate in a manner which is expected to aid or direct the flow of lymph in the affected extremity to an area of the body in which a healthier lymph system is likely to exist.
The multiple bladder pump systems generally work in a sequential manner in that they inflate first distally and then proximally. Characteristics of inflation pressures, timing of inflation-deflation cycles, length and frequency of individual pumping sessions vary in the literature.
Massage therapy, known mostly as manual lymphatic drainage, involves the use of a light touch gentle massage technique that follows the pathways of the lymphatic vasculature, and is again delivered with the intention of directing fluid away from the affected areas and towards healthier lymphatic pathways. Treatment times

and frequency of sessions vary in the literature.

Volume reduction of the affected body parts is also treated by the use of compression bandaging or compression garments. Compression bandages are frequently used after some amount of lymph fluid has been removed from a limb. In this technique, which is also known as wrapping, two to three layers of short stretch bandages, and these are bandages that are much much less extensible than your traditional Ace bandage, these bandages are placed strategically around the limb. Again, frequently the application is accomplished so that distal pressures in the limb are expected to be higher than proximal pressures, and this is in order to create a pressure gradient which hopes to direct the limb fluid to healthier systems in the body.

Pressure garments, also known as lymphedema sleeves or stockings, are available either as custom-made or prefabricated units. They also may be obtained in a design, again, in which distal compression is greater than that provided proximally.

Very frequently combination treatments are provided to those with lymphedema. Complete or complex decongestive physiotherapy, also known as complex physical therapy, is a program of manual lymph drainage, compression bandaging, exercise, and in addition, meticulous skin care, altogether designed to reduce the accumulation of lymphedema in the affected body parts and its complications.

Sometimes pneumatic compression devices are added to this therapy. CDT as it is called, is applied in two phases. The role of the first phase is to treat lymphedema accumulation. Such treatment usually involves one and sometimes two sessions a day for several weeks. After the performance of about three-quarters to an hour of manual lymph drainage, multilayer bandaging is applied. The patient then participates in range of motion and other gentle active exercise and the bandages remain in place for approximately 21 to 24 hours until the next treatment. Once Phase One is completed, patients transition to a maintenance program and wear bandages or garments as they are able, continue an exercise program and their skin routine, and receive

massage therapy and/or pneumatic pumping as needed.
Last but not least, so often forgotten in the treatment of lymphedema are the psychosocial consequences that may become apparent in this chronic condition. The methodology used to both recognize and treat these abnormalities is beyond the scope of my presentation today but should not be considered of lesser importance than any of the technology which we will speak about today.
DR. GOODMAN: Panel, before we proceed, our next step is going to be looking at the TA from the McMaster Evidence-based Practice Centre. Are there any focused concise questions at this time for either Ms. Stiller or Dr. Miller? Dr. Pauker.
DR. PAUKER: When you talked about defining lymphedema and you talked about a difference of 200 cc's, a volume change of 200 cc's, is that same volume change applied to both upper and lower volume?
DR. S. MILLER: Yes, to the best of my knowledge, the arm and the leg definitions are the same.

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DR. PAUKER: Thank you.
DR. GOODMAN: Other questions at this time? Okay. Dr. Miller, yes?
DR. S. MILLER: I will now invite Dr. Mark Oremus and Ms. Kathryn Walker of the McMaster University Evidence-based Practice Centre to present the technology assessment which discusses the evidence for the diagnosis and treatment methods that are used in secondary lymphedema.
DR. GOODMAN: Yes, and as they make their way to the podium, I want to welcome Dr. Janjan. Dr. Janjan, could you state your name, affiliations, and any disclosure with regard to the conference.
DR. JANJAN: Thank you, I'm sorry I didn't get a wake-up call this morning. I am Nora Janjan, I am an adjunct professor of radiation oncology and symptom research at M.D. Anderson and I have no conflicts.
DR. GOODMAN: Thank you. Dr. Walker.
MS. WALKER: It's Ms. Walker. I'm a physical therapist and work at the Evidence-based Practice Centre at McMaster University. So to begin today, I'm going to

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give you a very brief overview of lymphedema and the lymphatic system, as Dr. Miller has

already given us a fantastic overview. Lymphedema is a pathological condition of the lymphatic system, and the lymphatic system along with our arterial venous system makes up the circulatory system. Lymphatics transport lymph, which is a clear fluid that originates as interstitial fluid. The role of lymphatics are generally threefold, to transport lymph, to maintain homeostasis and to assist with immunity. The lymphatic system drains into the venous system.

When lymph edema arises there is swelling, called edema. Lymphedema often results from an accumulation of protein-rich food in the interstitial space. There can be subsequent inflammation, adipose tissue, hypertrophy and fibrosis. The swelling can also lead to decreased mobility and function, and disfigurement.

Lymphedema is a chronic condition and has significant morbidity physically and psychologically.

As Dr. Miller mentioned, there's

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primary lymphedema, which is a congenital condition, and secondary lymphedema, which is an acquired condition. Staging of lymphedema is often done by examination of the physical condition of the limb, though as the International Society of Lymphology has pointed out, a more inclusive staging system needs to be formulated. Historically there is Stage I to Stage III, and at present there are some clinicians who look at Stage 0, which is a subclinical condition.

As Dr. Miller has already pointed out, there are many causes of lymphedema. Filariasis, which is an infection caused by the nematode Wuscheria bancrofti, is the biggest cause globally, though in the United States the biggest cause is from malignancies and their related treatment. As you can see on this slide, we also have other less common causes of secondary lymphedema.

The incidence of secondary lymphedema is poorly documented. From the little literature that we do have, we know that the incidence of upper extremity lymphedema following the treatment for breast cancer has a

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large range, from 24 to 49 percent. The incidence of lower extremity lymphedema following cancer treatment is 5 to 80 percent. It has been shown in some studies that sentinel

node biopsy appears to reduce the incidence of lymphedema in cancer patients. The diagnosis of secondary lymphedema is typically accomplished through clinical history and physical examination, as Dr. Miller mentioned. Often a differential diagnosis is needed to rule out other causes of swelling, and sometimes we need to establish if primary or secondary lymphedema is present if it's not obvious. When imaging is required, lymphoscintigraphy, MRI, CT or ultrasound can be used, amongst others. The diagnosis of secondary lymphedema involves a physical examination as I mentioned and as Dr. Miller has already gone over in detail. We know we can measure it through limb volume assessment, through limb volume circumference measurement, volumetry or perometry. Also we can use tonometry to measure tissue resistance. Tissue dielectric constant has been talked about in the

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literature briefly, measuring an electrical parameter to judge the tissue water content, as well as bioimpedance, which as well measures tissue water content. The treatment of secondary lymphedema through nonpharmaceutical nonsurgical methods are numerous, and Dr. Miller has already gone over some of those and the proposed mechanisms. Quickly, there is compression techniques, which is done through low stretch bandaging or compression garments, and it's thought to restore the hydrostatic pressure in the limb and improve lymph flow. Intermittent pneumatic compression, IPC, uses pneumatic cuffs that are connected to a pump, and the theory is that they increase the muscle pump effect in the limb and helps move lymph forward. There can be uniform or sequential application of the IPC. Complex decongestive therapy, has multiple therapies combined, and there's two phases typically. Phase One is manual lymphatic drainage plus compression bandaging, skin care and moderate exercise wearing bandages. Phase Two is the self-management phase where you use

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compression bandages or compression garments, skin care and exercise. There's also manual lymphatic drainage, which we must point out is not traditional massage, because traditional massage is too deep for lymphedema, at least

it's hypothesized, and it could crush the delicate lymphatics inside it, so we use a lighter technique called manual lymphatic drainage, which Dr. Miller spoke about.

Exercise is often employed. Once again, the theory is that it enhances the muscle pump effect and also, it helps maintain a proper weight which, we know obesity can contribute to increased lymphedema.

There's also some talk about laser, ultrasound and aquatherapy as potential treatment, though the literature is somewhat sparse there.

Now, to go over our actual TA, we were asked to do a systematic review on diagnosis and on treatment of lymphedema, so it split out into two sort of separate ones within the big TA. Our databases that we searched are listed there and there were five of them, searched up

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to March 20th of 2009. As you can see, mesh term, search term lymphedema was exploded and all subheadings are searched. Titles to all citations in the database were searched using the key word lymphedema. Reference lists of published review articles and inclusion articles were searched.

So, the inclusion-exclusion criteria was different, obviously, for diagnosis and for treatment. For diagnosis, the articles were included if they had English language, they examined the sensitivity or specificity, or the psychometric properties, reliability, validity, responsiveness of the diagnostic test, and if they had a pediatric or adult population that was diagnosed with secondary lymphedema or suspected of secondary lymphedema.

The treatment systematic review had the inclusion criteria of English language, and it had to be a randomized controlled trial or observational studies with a comparison group. They had to be pediatric or adult patients diagnosed with secondary lymphedema as a result of any illness except filariasis. All forms of treatment for secondary lymphedema except

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surgery or drug therapy. General exclusion criteria were studies where the combined results of primary and secondary lymphedema, it's not possible to tease out the effect.

Screening, trained raters applied the inclusion-exclusion criteria to the citations obtained in the literature search. There were three levels of screening, title and abstract,

two of those, and then a complete manuscript screen. There were two screeners per article. Studies that passed full text screen proceeded to full data extraction, and information extracted from the diagnosis and treatment articles are listed on the screen, such as sample size, inclusion-exclusion criteria. For quality assessment, we employed a tool called QUADAS for the diagnostic studies. It has 14 items phrased as questions that examine potential sources of bias, and you answer yes, no or unclear. The general domains are listed on the slide. For the quality assessment of the randomized controlled trials and the treatment studies we used the Jadad scale. The Jadad scale is yes-no questions covering six domains

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as you can see on the screen, randomization, double blinding, tracking of withdrawals and adverse effects, use of statistics, inclusion and exclusion criteria. For the observational treatment studies we used the Newcastle-Ottawa scale, which evaluates three broad domains as seen on the screen. Overall quality of the extracted articles was rated as good, fair or poor, in accordance with the Agency for Health Care Research and Quality methods. We answered the key questions using a qualitative descriptive approach. We were not able to do a meta-analysis because there is too much clinical and methodological heterogeneity. And this is just an example, an illustration of how our search proceeded. We did our literature search which yielded 3,186 titles and abstracts. After our first title and abstract screen we narrowed it down to 434 articles. We did a second title and abstract screen which yielded 145 full text articles after which, when we did full text screening we excluded 86, and that left us with 28 treatment

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articles and 31 diagnosis articles. I will pass it on to Dr. Mark Oremus now for the rest of our presentation.

DR. OREMUS: Good morning everyone, thank you for allowing me to present the remainder of the technology assessment. We were asked to look at several key questions related to diagnostic and treatment studies for lymphedema, and over the next few minutes I'm going to summarize what we found

with respect to each of these questions. The one overriding theme to keep in mind as I go through the slides is that for many of the questions there was little or no evidence in the literature, or where there was evidence it was very fragmented evidence, there were studies on one or two treatments, studies on several treatments, but never the same treatment. So when you put it all together, it was very very difficult if not almost impossible to draw conclusions that could be generalized. So we will keep that in mind as we progress through this presentation. So before I get into the key questions, I would just like to talk a little

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bit about our quality assessment. As you can see, both the diagnosis and treatment studies were generally fair in terms of their quality. There were a few that were very good, there were a few that were poor, but generally we found the quality fair. I will start with the diagnostic testing studies, and the first key question we were asked to examine had to do with inclusion criteria, what were the types of criteria used to include patients into these diagnostic testing studies? So as you can see, the preponderant majority of these studies included persons with breast cancer. The next most preponderant criterion was the age, and as you can see here on the slide, age criteria for inclusion in these studies were very liberal, there tended to be floor or ceiling ages and anybody above or below these floors or ceilings were included. In about ten of the studies the mean or median ages were greater than 50 years of age, which makes sense because most of these people were cancer patients and cancer tends to be diagnosed in midlife or later. We were asked to assess whether or not

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a gold standard exists to grade or measure the severity of lymphedema. We did not find based on our retrieved articles any gold standard. In fact, only three of the studies retrieved in the diagnostic section included any sort of a grading scheme. As you can see here, the first of three grading schemes had categorized on circumference differences between the affected and the unaffected arm, but this scale was developed by two of the individuals in the study and those individuals didn't provide any details about whether they validated their

measurement scales prior to use in the study. Another grading scale, the second of three, was this ordinal scale, five points, ranging from healthy to very sick, and the authors who used this scoring scale didn't provide any scoring rules for determining where you classify somebody on this scale. They indicated that their scale was similar to existing recommendations but they didn't provide any further details other than to say there was some similarity. In another study there was an imaging scale used and as you can see, the score range

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for this imaging scale was from zero, normal, to eight, very severe. But again, the authors who used this scale didn't provide any scoring rules or any details on the development of the scale. So really, there is nothing in the literature that we could find that indicated that such a gold standard might exist. We were asked to look at the comparator tests used in the diagnostic studies. The primary comparators were changes in limb volume or circumference, and one or both were used in the majority of the studies of diagnostic tests. In two studies the comparator was a clinical exam and one of the comparators was an author-developed questionnaire that was used to compare to a diagnostic test. So, the de facto gold standard is changes in limb volume or circumference. Next we were asked to examine studies that reported on the sensitivity and specificity of diagnostic tests for lymphedema, so we found seven studies that addressed this issue. Five of them were focused on lymph

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volume or circumference, four looked at self-report, and one included isonitrate scan and clinical examination. The sensitivities and specificities with one exception were generally very good, going up to as high as 100 percent. But it was not possible to rank order any of the tests in terms of performance because there were too few studies to generalize, so we're starting to see some of the themes that I mentioned at the start of my half of the presentation, too few studies to really generalize. The studies involved persons with three different types of conditions, underlying conditions underlying

the lymphedema, and a mix of different tests were used. So we can't really conclude anything general about sensitivity or specificity.

We were asked to look at reliability as well and we found eight studies on this issue, six of them involving our familiar friends limb circumference and limb volume, and there were also a couple of studies looking at tissue resistance, there was a study of bioimpedance, and a study of truncal skin fold.

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And as you can see from the intraclass correlation coefficient, they were generally very good. The bioimpedance study used something called covariance to assess reliability, and low covariance indicates good reliability. So from what we've seen, the reliability of these tests was generally very very good.

21 studies looked at validity. 16 of them were looking at limb volume or circumference. There was one study comparing tape measure versus perometer. Another study looked at ultrasound to measure skin thickness versus circumference. Then there was one study that had several measures such as bioimpedance versus perometer and tape measure, and also the lymphedema and breast cancer questionnaire. Another study looked at bioimpedance versus perometer, and there was another study comparing bioimpedance and tape measure. Correlation coefficients, again, generally fair to excellent. Lowest correlations were between bioimpedance and perometer, and bioimpedance versus the breast cancer questionnaire. In one of the studies

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the authors used an undefined measure of bias to measure validity but we were unable to determine exactly what they were getting at with this measure of bias.

Responsiveness to change was only examined in two of the studies, and as you can see in the first of the two, they were able to determine the smallest differences that were detectable by use of these three tests. And in another study comparing limb volume and water displacement, they found a standard error of the mean to be less than 150 milliliters. So, really nothing in our study set related to responsiveness.

So, we were asked to look at the frequency and length of time for which

lymphedema should be assessed using diagnostic tests and in nine studies there was only a single assessment of lymphedema done using a diagnostic test. 22 studies used two or more assessments. Three studies were conducted with multiple assessments but the authors didn't indicate why they were looking at multiple assessments, and in several of these studies the specific purpose of conducting multiple

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assessments was not to assess a protocol for the diagnostic test but really to assess reliability and validity. So at this point in time we can say that no one has really looked at whether the frequency or length should vary by test method or if they did, we didn't find any evidence that we can provide generally about this issue because of, again, the heterogeneity in our studies.

So, we were asked also to examine whether any of the diagnostic tests used in the studies might have ended up influencing the choice of lymphedema treatment or patient outcome, and only three of the diagnostic studies specifically mentioned a treatment that the patients were receiving. However, these studies were not conducted to examine whether the choice of test influenced treatment or outcome. In these studies the ongoing evaluation of these treatments provided the authors with an opportunity to investigate diagnostic tests, but they never set out to link tests and the treatments. None of our studies mentioned specific patient outcomes, so we could not answer this question due to a lack

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of evidence.

I'm now going to switch over to the treatment half of our report and again, we were asked to look at inclusion and exclusion criteria in these studies evaluating the treatment of lymphedema, and we found 28 different criteria across the 28 different treatment studies. The most preponderant inclusion criterion was secondary lymphedema due to breast cancer, and generally secondary lymphedema was defined by excess volume or swelling. Of course, there were various definitions of what constituted excess swelling. Few of the studies had age criteria and there tended to be various different elapsed periods of time between cancer treatment and study end treatment.

Most of the 28 criteria were spread

across a limited number of studies, so each criterion generally appeared in three or less studies. The criteria did not coalesce around any specific treatment modality and there was no evidence to suggest that the criteria may have differed according to treatment modality. We were asked to look at whether or

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not there were criteria to initiate or stop treatment for lymphedema in these studies. So except for a diagnosis of lymphedema, which was an inclusion criteria, there were no other criteria delineated by study authors to indicate whether or not treatment for lymphedema should be initiated. Five of the studies had stopping rules. Two studies stopped if there was an incident of adverse effects that went beyond a certain proportion of patients. In one study it was stopped if there was no proven benefits for treatment after a certain amount of time. In another study the completion of the therapeutic regimen indicated that it was time to stop the study, so there was no follow-up beyond the end of therapy. And in one study if the circumferential difference between the treated and unaffected arms increased beyond a certain point, then that study was stopped. Again, though, there were really too few studies to determine whether or not the stopping rules may have varied according to treatment modality. We were also interested in looking at

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the time of treatment initiation following the onset of lymphedema. Seven studies contained reports of the approximate time of recruitment of patients into the study following the onset of lymphedema. However, none of the studies talked about when treatment should be initiated. We assume that treatment was probably initiated soon after the patients were recruited but this was not specified by the authors of these studies. Another question had to do with whether or not the study authors indicated the type of professional who was responsible for delivering therapy. In 15 of our 28 treatment studies there was no mention of the type of professional needed to deliver therapy. The other 13 studies did contain some information. Five of these 13 studies actually contained mention of more than one professional. In ten studies the named professional

was a physiotherapist, and in six of these ten studies the physiotherapist was described as having been trained in specific techniques for the treatment of secondary lymphedema. In another two studies there was no description of
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the professional qualifications of the individual but that person was indicated as having been trained in the Vodder technique to deliver therapy for secondary lymphedema. Two studies used dietitians to deliver therapy. In two studies it was specifically mentioned that a nurse was included and these nurses were described as trained in edema or lymphedema management. And in four other studies, as we can see here in the screen, the type of professional was listed as I've shown. And in two studies treatment was specifically described as self-administered by the patients.
We were asked to look at some questions related to IPC specifically and the extent to which IPC may be responsible for reducing lymphedema, and we found a lack of clear evidence to indicate whether one type of IPC device was more effective than others and that was, again, because there were too few studies from which to make meaningful comparisons, and there was a lot of heterogeneity in these studies.
So we found seven different IPCs investigated against six different comparators.
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In two of the studies there was an unclear description of the type of IPC device used.
IPC was also delivered in conjunction with other treatments in five studies, so it was difficult to tease out the effect of IPC alone in these studies.
We were also asked to look at whether the effectiveness of IPC depended on different patient characteristics, but none of our treatment studies broke down any of the results by patient characteristics so we were unable to answer this question.
We looked at whether IPC treatment protocols may have been modified due to comorbidities or the effect of treatment on outcome, and none of the extracted studies contained reports of the need to modify treatment protocols on account of comorbidities. Most problematic comorbidities were addressed via exclusion criteria, so patients who may have a problematic comorbidity were simply excluded from the studies to begin

with.
Did the timing of IPC or the sequence
of use of IPC device affect outcomes? Again,
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there was no evidence to answer this question.
Five of the ten IPC studies did not contain
reports on timing and in the other five studies
there was a wide range of individuals included
depending on the finding. The treatment
regimens varied in the five studies with
information as to this key question, as you can
see here. So again, just because of the small
number of studies and all of the heterogeneity,
it was impossible to answer this key question.
Going back to treatments in general,
moving away from IPC treatment specifically, we
were asked what protocols for single modality
treatments may have produced the best outcomes
for lymphedema therapy. In only eight of the
228 studies were single modality treatments
examined. Most studies examined lymphedema
treatment as combination therapy. Six of these
eight studies, though, had unrealistic
comparators such as a booklet on healthy eating
versus some other treatment for lymphedema. In
one case there was no treatment, or instruction
to continue with the usual therapies, or usual
activities as a treatment. And the remaining
two studies simply didn't have any evidence
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whatsoever to answer the question. So overall,
we really didn't find enough evidence to be
able to address this question.
Looking at the effectiveness now of
combination treatments with some emphasis on
the use of compression to maintain gains from
other treatments, we were unable to assess the
effectiveness of these combination treatments,
again because of the heterogeneity of the
studies. There was just too much difference
across studies to draw general conclusions.
One study focusing on compression
looked at the use of compression to maintain
volume reduction. As you can see here the
compression garment was used in two treatment
arms, all of which involved combination
therapy, and really the purpose of this study
was to evaluate the addition of IPC to a
treatment regimen, and the IPC group had a
further reduction of lymphedema. However, we
can't tease out the specific impact of the
compression garments in this study.
What about comparator treatments used
in the lymphedema studies? Well, many of the

studies actually did not specifically identify
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which of the treatments they considered to be the experimental treatment and which treatment was considered to be the comparator. So we assumed in these cases that the more conservative therapy was actually the comparator and these conservative therapies included usual care, or sham treatment or no treatment. Active treatment comparators tended to be elastic sleeve, decongestive therapy, self-massage, bandaging, or simple lymphatic drainage. These active treatment comparators appeared consistent with what's done in usual care but there was no obvious gold standard comparator that really showed itself in these studies.
Outcomes used in the studies. A majority of the studies measured changes in limb volume to the affected area, six studies looked only at limb circumference, and there were other outcomes such as pain, heaviness, tension or quality of life. Range of joint motion was another popular outcome, and you can see several other outcomes, including grip strength, measures of muscle mass and things like that, using bioimpedance, skin fold
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thickness and tonometry.
What about the effects of treatment in actually reducing the lymphedema. Many of the studies did report that the various treatments used did reduce lymphedema volumes but it was extremely difficult to assess the relative benefits of different treatments because in these studies there were multiple different comparators and treatment measurements, there were multiple different types of measures of limb volume and circumference, and even if the measure was the same, maybe the definition of what constituted clinically significant change was different across studies.
Many of the studies reported within group pre and post treatment differences, but the authors did not provide between group comparisons, and when they did, sometimes they only reported between group P values, they did not provide any numerical differences in the studies. So again, the evidence was very diffuse.
What about looking at factors to predict treatment outcomes? Seven of the 28 studies of treatment looked at this issue and
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what they found was the pretreatment lymphedema status of the individual patients was the most common factor that was examined to predict outcome, and in one study better treatment responses were found in mild versus moderate treatment for lymphedema patients but in another study the authors found the opposite. One study reported that pretreatment volumes were predictive of response but they didn't give any data, this was just a comment they had written into their discussion. And an IPC study reported no influence of lymphedema severity on outcomes. Two studies reported no difference in outcome for the diagnosis of lymphedema within the previous year versus having a diagnosis at farther than one year. Another study found that compliance with the use of elastic compression sleeves actually had a better prediction of treatment response. Several other factors that were not found to be predictive in one or more studies included a history of prior radiation or chemotherapy treatment, type of previous surgery, history of infection, age, body mass index, gender, or the presence of active

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disease. Length of follow-up and length of treatment benefits, what were these generally reported to be in the studies? We found seven of 28 studies reported outcomes at six months or beyond, and in other studies we found that maintenance therapy was generally showing a durable benefit. Studies with compression garments, complex decongestive therapy, tended to show benefits for as long as six to 12 months. Adverse effects in the treatment studies were generally rare, as you can see here. They were also in many cases clinically mild. There was breast cancer recurrence in approximately two percent of the patients but this was not likely due to the administration of the lymphedema treatment. No studies reported on patient characteristics or etiologies of lymphedema that might increase or reduce the risk of adverse effects. So overall now, some concluding comments. Most of the diagnostic testing and treatment studies were conducted in breast

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cancer patients, so it's possible that some of these results may not be easily transferable to

other patient populations and further study would be recommended to see if these results might be transferable into other types of groups who might have secondary lymphedema. The psychometric properties were strong for measures of limb volume and circumference, but again, these properties could differ in different groups of patients other than persons with breast cancer. Limb and volume circumference appeared to be the de facto gold standard test of lymphedema, but the cutoff points used to indicate someone who is diseased versus not diseased, or to indicate severity of disease varied. As well, there were a multiplicity of methods used to assess limb volume and circumference, and this made it difficult to not only compare sensitivity and specificity across studies, but also to compare things like reliability and validity across studies. We found no evidence to suggest an adequate diagnostic testing protocol. There was no information in the studies on optimal

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testing frequency, no information on the time frame over which patients should be tested, nor whether any test method has a particular influence on outcome. We found no evidence concerning the optimal criteria to dictate when treatment should be initiated or stopped. There was no evidence regarding the superiority of one type of lymphedema treatment versus another. We found no evidence regarding treatment benefits in any specific subgroup of patients. Adverse effects were reported in only a very small number of studies and in these studies they were generally rare and mild, so probably not likely to be much of a clinical issue. After looking at the evidence and looking at the discussion sections of the articles we included, we found that in this literature there appears to be little or no agreement regarding frequency and duration of treatment, what treatment combinations should be tested in studies in this area, what if any

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maintenance therapy or maintenance therapeutic regimen should be used, nor was there any agreement on how long specifically patients should be followed up to assess whether or not

treatment actually makes a difference.
So, that concludes the presentation, and I imagine there will be some questions.
DR. GOODMAN: Yes. Thank you, Dr. Oremus and Ms. Walker as well, for an excellent presentation from the Evidence-Based Practice Centre at McMaster.
We can take a few questions now before proceeding to our next presenter. I will remind all of us that immediately after lunch there is a full hour set aside for more detailed questions to these and the subsequent presenters. But before we do move on, does anyone have any questions at this point?
DR. CORMIER: Dr. Oremus, thank you. Obviously, this was an incredible body of work to create a systematic review of this size with such a body of literature.
I'm a little bit concerned with the denominator in the top of your titles, that the denominator from which you selected these key

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60 articles was only 3,186. And when I went back to look at your search strategy, it looked like the search strategy was limited to the word lymphedema, either spelled in the English spelling or the American spelling in the title, and I'm wondering if there was any attempt, or you have any idea how many articles there may have been if we had expanded that to include key words and abstract words, or subjects.
Because certainly in examining the body of literature related to lymphedema, lymph swelling, or morbidity following surgical treatment, there would be a number of articles that I would be afraid that you may have missed, and 3,000 seems like a very small denominator by an order of about tenfold that I would expect to see in this field for the last 20 years.
DR. OREMUS: Yes. The search strategy was the search strategy that we had developed in conjunction with AHRQ, and also the investigative team had developed. It was a search strategy that we had intended to be broad but at the same time we also wanted it to be narrowly focused to identify articles

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specific to diagnosis and treatment. So while if you do expand the literature search to include things like swelling or edema, you may capture more articles, but I suspect you would capture a lot more noise as well. And given the flavor of the literature, even if by chance

something was missed, because the literature that we had extracted is so diffuse, I doubt that our conclusions would really have been any different from what they are now.
DR. GOODMAN: I would just add that the mesh term lymphedema was exploded, which gets you more, and I would add that the mesh indexers, the professionals who look at the literature and affix mesh terms to the records and to the citations also add their interpretation. They may not necessarily have to see the word lymphedema to label an article within this material as lymphedema, so that would probably help somewhat.
Dr. Fischer is next.
DR. FISCHER: Thank you. In your analysis of the studies, did you come across -- you did mention infection, and infection is obviously something which dramatically

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increases the severity. Were there any studies in which there was an effort at risk reduction as some people do with prophylactic antibiotics for the first year after node dissection, did you come across anything like that?
DR. OREMUS: I didn't specifically locate it or note it.
MS. WALKER: I was just trying to hear from over there. You're asking about prophylactic use of antibiotics?
DR. FISCHER: Yes. For a year I think is what most people use it, in an effort at risk reduction, and is it making lymphedema worse, or maybe not?
MS. WALKER: We didn't, probably primarily because our exclusion criteria excluded drug use or surgical interventions either after the fact, and a lot of prevention studies were also excluded because of that. Even in a nonpharmacological, nonsurgical treatment, if anything was prevention it wasn't really captured because of the nature of the questions that were asked, so they may exist but we didn't look at them.
DR. GOODMAN: Okay. Let's take one

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more question, is that Dr. Pfalzer?
DR. PFALZER: I do want to come back to this issue of the search terms because morbidity is certainly an issue, and I just wanted to cite one example. Bernice's article on sentinel lymph node biopsy did include lymphedema as one of the morbidity markers, and yet it's one of the, I would say key articles

that got published in this area that looks at lymphedema after sentinel node biopsy. So I think that your exclusion, or lack of use of the term morbidity really did affect this search.

DR. OREMUS: I would have to look at the specific article and see it in front of me to determine why it was excluded, but one of the major criterion that was applied was lack of a comparison group, so if there was no comparison within the study it definitely would have been excluded, but I would have to see the article to specify.

DR. PFALZER: I would be glad to provide it to you.

DR. GOODMAN: Good, I would like to see it too.

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Our first invited speaker, I believe is Dr. Rockson. As Dr. Rockson is making his way to the podium, I'd just remind us insofar as the body of literature that we're looking at today covers a 19-year period, that's 1990 through March of this year, and the entire body of literature is not quite 60 articles, 28 treatment and 31 diagnosis, so 59 articles over a 19-year period is our main body of evidence.

Welcome, Dr. Rockson. You're on, sir.

DR. ROCKSON: Thank you very much for the opportunity to present this morning. I think it will become clear that many of the presentations will repeat much of the material, because the points to be made are based upon the same set of inferential comments that one can make about this disease, about its diagnosis and management.

Before I begin, I would like to make just a couple of overarching comments about the content of my presentation. I would like to emphasize that from my perspective as a lymphedema practitioner and investigator this is of course a highly prevalent condition as we've already heard, one that has significant

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morbidity and implications for the patients, a very profound symptom complex, and obviously the work that we're doing here is very important.

The other point that I would like to make is while we're very emphatic about the definition including something about edema, which in turn translates into volume and assessments of volume, I do want to make the point that the biology of this condition is

such that its tendency towards inexorable progression also leads to a progression in which the edema component becomes subsidiary to many of the other structural changes that occur in the limb that in fact have to do with the patient's symptomatology, dysfunction and disability.

DR. GOODMAN: Dr. Rockson, I'm sorry just to interrupt for a moment. For our panel, Dr. Rockson's slides are at the very back of this weighty hernia-inducing volume that you have, so the very last set of Power Point slides in this particular volume, if you want to follow along. Please continue. Thank you.

DR. ROCKSON: So the point I would

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like to make is that anything that we decide is relevant to diagnostic inferences or therapeutic applicability that will change this inexorable sequence I think is well worth our consideration.

And finally, just a comment about the material that we just heard presented. I concur that the literature that is able to be analyzed in this field is regrettably small and very inconsistent in its overall scientific design, but the point to be made here I believe is that this is an area that paradoxically with the high prevalence of the condition has been relatively ignored among other things in funding sources, to do the relevant studies. Consequently, most studies are small, and to be able to draw aggregate inferences from the literature that exists is going to be a difficult proposition. Clearly we need larger and well designed prospective studies that are going to be well funded in order to provide the answers we would like.

Having said all of those things, I would like to just say a word about the problem from my perspective. Again, lymphedema is a

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very specific form of edema in which because of the nature of the interstitial fluid that collects and the biology surrounding the impairment in lymphatic flow, there are inexorable consequences to the structure of the affected tissues in the relevant part of the body, and this will in turn lead to the patient's clinical presentation.

Clinically, this is an important diagnosis for affected individuals. It's already been alluded that there is a risk of infection. There is clearly loss of function

and restriction of movement, and although I won't spend a lot of time on this this morning, and as Dr. Miller alluded in her comments, the psychosocial implications are profound, and these have actually been quite well quantitated in psychosocial observational studies. The other point that I would like to make, and I'm sorry if this doesn't project terribly well, is that lymphedema and its complex biology reflects the very vicious cycle nature of the underlying biology. If someone starts at 12 o'clock with some impairment in lymph flow, this is going to lead to a series

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of reactions that eventually become biochemical in nature, which in turn tend to propagate and advance the process. I think this conceptually argues for effective and early diagnostic strategies and obviously the institution of therapeutics that will help to break these cycles.

I know we're asked to consider primarily acquired or secondary lymphedema today. I do also want to make the point that the dividing line between these two broad groups is not as clear as the terms might indicate, this is not really a binary universe. In fact there is a tremendous spectrum, as we're learning in more recent observations, between the primary and secondary forms of lymphedema. Some are quite clearcut. If a child exits from the womb with lymphedema, that is clearly primary; if somebody contracts filariasis, that is clearly secondary. But in between those two extremes there are a variety of other conditions.

I also want to point out that the therapeutics in particular of primary lymphedema will not differ at all from those of

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secondary lymphedema, which is to say the condition, no matter what its pathogenesis, will respond to the interventions that are designed to limit edema accumulation.

As you've already heard, breast cancer is really the paradigm for the problem that we address in the United States because it has been at least until recent times the most common form of acquired lymphedema. One might argue that in recent years this is being eclipsed to a degree by the lymphedema associated with obesity, but at the moment this represents at least historically the most prevalent form.

There has been much excitement over the introduction of sparing techniques like sentinel node for the treatment of breast cancer patients, and while this is indeed a signal advance and it has always been hoped that lymphedema would largely disappear because of this, I do want to make the point that even limited surgical interventions like the sentinel node technique do carry a risk of lymphedema. So if you see an aggregate, this hazards analysis from a variety of studies

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looking at sentinel node compared to full axillary dissection, the latter carries a risk that is about two-and-a-half times that of what is seen with sentinel node techniques. So to translate that into real numbers, if we say that the average risk of the axillary technique is 25 percent, the risk of sentinel node is still going to be six to eight percent, so it's still a sizable number that needs to be dealt with.

No matter how patients get lymphedema, I think we can say, and this continues to be true, that lymphedema is a condition that is misdiagnosed, it's often treated too late, and very often unfortunately is not treated at all. It has certainly economic implications for patients. This is some very compelling data to show the increment of cost to an individual who has been treated with breast cancer and has lymphedema compared to those individuals who are treated for the breast cancer alone. Cancer is a costly disease, but it becomes substantially even more costly when lymphedema represents a complication. This is one of several studies that I

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will allude to in which the investigators of the study are actually sitting in the room, so I'm grateful to all of my collaborators in this broad field, and I will try to show a little bit of my own data as well.

Just to show you how things segregate in the lower extremity since we've heard so much about breast cancer, and this slide does insist upon the binary distinction between primary and secondary causes, but again, I want to urge that we not consider this to be an absolute. But here you see a list of the likely culprits that might occur in the lower extremity leading to the presence of chronic lymphedema.

I want to show you the spectrum of

disease that we typically encountered in the various stages of upper extremity and lower extremity. Here you have what would be called Grade I, meaning that there is some spontaneous resolvability to the edema with elevation or with recumbency, and you see involvement both in the arm and the leg. This would be Grade II, nonreversible changes in the left leg and in the right arm. And finally, Grade III,

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where this is sometimes called elephantiasis. When the condition exists over a long period of time, not only do we encounter inexorable changes in the soft tissues and in the cutaneous structures themselves, but there is also a tendency for the skin to become distinctly diseased with a cellular overgrowth, cysts developing on the skin and so forth. Infection has been mentioned a couple of times already. Here is a particularly profound example of cellulitis or soft tissue infection as a complication of chronic lymphedema of the limb. We don't entirely understand pathogenesis here but it is likely that not only is the enhanced interstitial fluid with its proteinaceous content a good growth medium for bacteria, but in addition it's very well recognized that there is an impairment in immune traffic that is related to the impairment in lymph flow, and these two factors probably lead to the establishment of bacterial involvement in the skin and soft tissues.

The problem with soft tissue infection in lymphedema is not only is it recurrent and

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not only can it be quite profound, but at the other end of the spectrum its manifestations can be quite subtle because of the impaired immune traffic, so it may be difficult to diagnose and very difficult to eradicate using standard antimicrobial regimens. Of course this is what we want to avoid in lymphedema. There is an inexorable tendency for this disease to progress. We certainly don't want to see it progress to this very end stage and deplorable degree. So just to review what is commonly accepted in the literature as a useful grading schema for lymphedema, this is what the International Society of Lymphology has proposed, and I won't read the words to you, but there are three basic grades. Some reversibility, spontaneously irreversible, and

then lymphostatic elephantiasis. And do recognize that at least the ISL and other investigators do believe that there is an inexorable tendency for this disease to progress through grades if it's not appropriately dealt with.
So here would be a characteristic, of
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course, of Grade I or Grade II, where one has the ability to actually move fluid with the examining finger, so this is called pitting edema. There is some confusion in medical education with the assumption that perhaps a pitting edema is present, it's not lymphedema, and a pitting edema -- I'm sorry -- if a pitting edema is present, it's not lymphedema; if a pitting edema is not present, it is lymphedema. That's incorrect, it really reflects the stage of the disease.
But eventually in lymphedema, in contradiction to many other forms of edema, we will get to a point where even the very firm and sustained pressure of the examining finger, there is little if any ability to displace fluid because, as I said, with time there is this inexorable tendency for the tissue biology to change where the edema or fluid component is replaced by cellular overgrowth and cellular architectural remodeling.
Here's an example of that by magnetic resonance imaging. This is an image of the cross-section of an upper extremity. You see the humerus here at about one or two o'clock,
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and what you see around the edges of this limb is this very thick grapefruit rind looking structure which normally would not be visible in a normal extremity. And this is in fact the skin that has been thickened to 20 to 30 times its normal dimensions by the presence of chronic lymphedema relatively pathognomonic.
This is what it looks like under the microscope. These are human skin specimens, these are specimens from the mouse model of acquired lymphedema in which I do my bench research, and in both instances you can see this 20 to 30 to 50-fold increase in the cellular thickness of the epidermal layer, tremendous increase in cellularity of the subdermis as well, with a tremendous inflammatory cell infiltrate.
This is a sirus red stain for collagen on a fluorescent image in which one can see the inexorable deposition of collagen

in the skin and the subcutaneous tissues, again, one of the hallmarks of the biology of this disease. One of the unfortunate aspects of this is that with time the remaining lymphatic collectors themselves become

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fibrosed, and at this point there is no chance to recover any lymphatic drainage function through these structures because they no longer have a lumen to carry fluid content.

I do want to mention just briefly the other grading scheme for lymphedema. This is not based upon the degree of reversibility and tissue change, but rather the size, and there's been some allusion to measurement of size. It turns out that while this is a good measure of the degree of edema accumulation, it is probably a less reliable measure of either the responsiveness to therapeutic interventions or to necessarily the predicted natural history of the problem.

What can be said, however, is that when one detects a case of lymphedema in its mild form, there is a very strong likelihood that without any substantive intervention, there will be a likelihood for progression from that mild stage to a more extensive stage, so I think this argues inferentially and strongly for taking an aggressive approach at finding mild cases of disease and intervening in an aggressive fashion.

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This would be, then, the flip side of that observation, which is to show that if one follows patients over time, there is going to be a tendency in a somewhat exponential and eventually linear fashion for the patients affected to increase.

I would like to say a word about diagnosis. This is considered to be one suitable and pragmatic diagnostic schema. In the evaluation of an edema patient with positive family history we begin thinking about some of the primary causes about which I will not say more this morning. With a negative family history, a differential diagnosis is chiefly surrounding lymphedema, venous lymphedema, and lipedema, which is a condition that can masquerade as lymphedema.

The physical examination is often extraordinarily helpful and one can proceed with a very discrete physical finding of lymphedema to directly recommend treatment. If the physical examination is marginal, one does

have these other imaging techniques and one can consider venography or other indirect measure of looking at venous function in order to
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determine whether that plays a role in the differential diagnosis.
The pathognomonic sign at least in the lower extremity of the presence of lymphedema is a so-called positive Stemmer sign, described by Dr. Stemmer, a German physician, in the 1970s as the inelastic nature of the skin at the base of the digits. The inability to tent the skin is a positive Stemmer sign, which is felt to be pathognomonic of lymphedema, and this allows me to make one other editorial commentary on the analysis of the literature. Much of the work that has been done in the diagnosis and particularly the therapeutics of lymphedema has been imported into the United States from a long history of such investigations in Europe. Much of that work was not published in English and it has simply been imported wholesale into this country based upon the substantive findings of European investigators, which may explain why there is some lack of description in our English-based literature on the data that supports these various modalities.
You've heard some mention about
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lymphoscintigraphic examination. This is a dynamic image of the impairment of macromolecular clearance from an involved limb, so if we inject a Tc-hexakis labeled macromolecule into the interdigital space in the dorsum of the hand, and you see the depot injections here. On the normal side there is rapid accumulation of the radionuclide which travels directly from the skin to the draining lymph node in the axilla. On the affected side there is delayed or absent appearance of the radionuclide in the draining lymph nodes. And in addition, one can see this pathognomonic finding of dermal backflow, which represents a certain amount of this macromolecular material that has ascended part way in the lymphatic vasculature, encountered lymphatic hypertension proximally and extravasated back into the tissues. So this is, again, a diagnostic examination.
Here is one of the conundrums about the imaging characteristics. This is an individual who has not progressed clinically over a five-year period of time insofar as the

dimensions of the limb, but if one looks at
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serial lymphoscintigraphy during that five-year period of time, there has been a loss of integrity of uptake in the nodal bearing areas of one affected leg, there is the appearance of dermal backflow, there is the appearance of lymphoceles and other extravasations indicating progression in the dysfunction of the lymphatic vasculature despite the fact that the objectifiable measured changes on physical examination have not changed.

A further conundrum here is the material published by Dr. Alain Pecking in France, again, in French, not in English, showing that in fact there is a very marked tendency for lymphoscintigraphy to be able to pick up lymphatic dysfunction in the absence of any clinical expression, which is to say the at-risk population has lymphatic dysfunction that can be imaged, and perhaps is worthy of intervention, despite the fact that no edema has yet occurred.

So one can see the functional correlative of that in this representative Kaplan-Meier analysis of the cumulative incidence of lymphedema in a breast cancer
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population, in this case 1,300 individuals, published in Cancer in 2001. All of these individuals became anatomically and presumably functionally abnormal at times zero, but you can see that while there is initially a somewhat exponential accrual of cases, it is not immediate, and case accrual occurs throughout the five-year period of observation, and if one were to draw this relationship out to 20 years, there would still be a subtle but real accrual rate over time. So this tendency for lymphedema to exist as a latent form of dysfunction poses a real challenge to both diagnostics and therapeutics.

There is, however, a growing body of evidence, and I apologize there are too many words on this slide, but perhaps you can read it in the handout that has been given to you, but there is an early literature to suggest, again, a small number of patients that if one detects these patients early and undertakes an intervention, the severity of the condition can often be eliminated and in some cases reversed in a very short period of observation, which argues strongly for developing sensitive
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diagnostic techniques. One such technique that I think has tremendous promise is what can be called bioimpedance spectroscopy. If one acknowledges that the limb is a given length in which an electrical message can be transmitted, then the impedance to that transmission will be determined by the amount of fluid content in the length of that hypothetical tube. And if one varies the frequency of application of the electrical signal, one can derive a variety of information from that limb so that at lower frequencies one is looking at extracellular fluid, and at higher frequencies both extracellular and intracellular. This is the basis of bioimpedance analysis which historically has been done by looking at ratios of impedance between an index limb and a contralateral presumptively normal limb. The early literature surrounding this suggests that if one can find even a fairly broad range of normal for the population, let's say three standard deviations around the mean, the deviation of this ratio outside the normal range predicts reliably with a positive

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predictive accuracy of perhaps 98 percent or 99 percent, the development of lymphedema within a six to nine-month time frame. This is what the technology would look like, one form of this bioimpedance spectroscopy unit, with the electrodes that are attached to the skin. So simply done, noninvasive, FDA approved, and a device that I think merits a lot of our further investigation. So, there's a growing body of literature to surround the use of this and its use in early clinical assessment. And more recently, Lee Worth, who's been one of the developers of this technology, has shown the very tight correlation between bioimpedance values and another technique that was mentioned earlier today, perometry. I'd like to say just a word about management and again, I will harken back to the ISL grading schema. Our belief is, although this is not well substantiated yet by the existing literature, I alluded to the one paper in Cancer that suggests that early intervention may blunt development of disease, but it is our

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belief that this is the relationship that governs the inexorable progression of

lymphedema severity through those grades over time with the hope that the earlier one can identify such an individual, one can help the individual to fall off this curve and arrest the forward progression and perhaps reduce the severity of the disease.

You've already heard about the components of lymphedema management so I won't go into that in much detail, but again, you've heard about the so-called MLD, which works by opening the lymphatic capillaries in the skin. The degree of stretch that is placed on the skin is crucial because one does not want so much stretch as to increase in capillary arterial inflow, which will of course increase the lymphatic flow and mitigate the effect of opening the lymphatic capillaries. Once fluid enters the lymphatic capillaries, the auto-contractile nature of the vasculature above carries the fluid more proximally. The multilayer bandaging is not meant to be a compression technique but rather to create a compartment in which musculature

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contraction and the arteriovenous contraction actually augments lymphatic flow, and this has been demonstrated by semiquantitative and quantitative lymphoscintigraphic imaging, again, in the European literature. And the exercise, of course then will work synergistically with the placement of bandages themselves.

In the maintenance phase, the bandaging largely can be eliminated in favor of the compression garment that you've already heard mentioned. It's important that this be properly fitted and that the patient be compliant with its use. The purpose of the garment is not to make the limb smaller, the purpose of the garment is to prevent its growing larger, so that once the patient achieves a nadir of limb volume, this can ideally be maintained by a properly fitted and properly replaced garment. Sometimes nocturnal compression is used but this is not mandatory.

And just to indicate, there is a very fine interplay between the elements that constitute the acute management under the hands of a trained physiotherapist and the management

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that the patient undertakes in self-care. The effectiveness of this can be shown somewhat graphically but also numerically. Here is one of my patients who prior to the initiation of

therapy could not wear a pair of shoes, could not go into a store and buy a pair of pants that could be properly fitted to his legs. And after a period of eight weeks of therapy, while his leg was not completely restored to normal volume, it's clear that he could now wear trousers and shoes.

Here is some aggregate data published in 2007 to look at, again, not each element of this intervention, but looking at the intervention as an aggregate complex, which includes both the physical techniques, the bandaging and the garments to create a single endpoint, which is reduction of edema volume. And here you can see that despite relatively wide confidence intervals, there is in fact a statistically relevant reduction that is significant in edema volume that is both acute and sustainable, although there is some recidivism in the self-management phase. Of equal importance, I would say, is

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the ability to control symptoms. We do know that these patients significantly report pain as a correlate to the presence of edema. And here you can see using a validated quantitative sore of degree of pain and patient by patient, and each line represented a significant, with one outlier, a significant effect on reduction of pain with use of the modalities that I just mentioned. Again, here's some more quantitative information suggesting that not only does edema reduce, but there is a reduction in the reported incidence of pain and the reported use of medications to control the pain.

Just a couple of words about adjunctive therapy. There is a strong body of animal literature to suggest that intermittent compression in fact has an augmenting effect on lymph volume. What appears to be critical is the deflation time between inflations that allow the capillary collectors, sorry, the lymphatic collectors to fill and propagate the fluid forward. This is a study that we published in our center in 2002 looking, again, at adjunctive use of intermittent pneumatic

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compression in the acute phase of management to standard MLD and multilayer bandaging, and you can see this substantial additional reduction in volume that we saw with the addition of intermittent pneumatic compression.

With the newer generations of devices,

one is able to look at characteristics including the actual application of pressure sequentially in the garment and the wave of pressure that will then be applied to the patient, and one can compare the different forms of this intervention.

Here is a device that we worked with significantly in recent research called flexi-pumps that operate under lower prevailing pressures and gives a pressure curve that shows this deflation time quite clearly that is necessary for the propagation of lymph flow in comparison to another device that may not work by quite the same principles.

DR. GOODMAN: Dr. Rockson, about three minutes.

DR. ROCKSON: Okay. Here is a study showing the efficacy, again in the maintenance phase, by the addition of this device over the

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standard self-management with massage and the garment, and again, one can see the numerical increment in effect.

I'm going to skip over these slides in the interest of time. I'm going to skip over laser.

I just want to say a word about surgery, which is really to some degree beyond the scope of the current considerations, but there has been some discussion, again, about lymphatic venous anastomosis, but suffice it to say when looked at objectively, it does not appear to have a very dramatic effect on edema volume and is difficult to really substantiate that it is going to have a large role.

This is a surgery that does seem to have a role in the Grade III patients. When the pitting edema component is no longer present, most of the edema is imbued by the presence of an increase in adipose deposition in the limb which can be removed surgically through a relatively noninvasive surgical technique, and this is a sustained result seen 12 years after the initial intervention and removal of this material, another example of a

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successful intervention, and here's one of the leg.

I want to conclude by really creating a segue into the next talk, which is tools that we need for the future. I would like to talk about one tool that I'm involved in that is the present going into the future. I've been working with the Lymphatic Research Foundation

over the last four or five years to create a comprehensive lymphatic patient registry and linked by a repository. This project has been undertaken in collaboration with my institution and also with the Feinstein Institute. Our aims are to create a sustainable disease-specific national registry for patients with lymphedema and all other lymphatic diseases, and link it to a bio-repository for future translational and basic investigational work. The Feinstein bio-repository has the ability to provide this portion of it, and they currently house about a million aliquots derived from 35,000 patients.

This registry is now live, it is entered by the patients through an interface on the Internet, because we do understand that

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these patients are geographically dispersed, they often are disenfranchised from the health care system so we don't want to rely on health care professionals as the locus of entry. We feel that we can reach the patient population in universal proportions and we hope that if a body like this is convened in the next two to five years, that we will have the requisite clinical data and also biological data to be able to more compellingly answer some of the questions that you're trying to address.

Thank you very much for your attention.

(Applause.)

DR. GOODMAN: Thank you, Dr. Rockson. Dr. Rockson, do I understand that you're going to have to depart the building by, what, 10:15 or 10:30?

DR. ROCKSON: Right after the break.

DR. GOODMAN: We would normally maybe have just a question or two for you now and then get to more later, but since we can't do the latter, if the panel has some clear and well thought out questions that you can present to Dr. Rockson, if any now, we will take them,

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and then we'll have to make a slight adjustment in the balance of the day, and will probably break before the next presentation. Yes, Dr. Pauker, and please speak directly into the microphone.

DR. PAUKER: The diagnostic tests compared the affected to the unaffected limb, but how often is it bilateral, and if it is, then what do you do?

DR. ROCKSON: So, the diagnostic

techniques suffer to a large degree from this problem of bilateral disease. Certainly lymphoscintigraphy to a degree will become more difficult when the disease is bilateral if one wants to compare, for example, transit time to the draining lymph nodes. Bioimpedance spectroscopy as originally defined also looked at ratios of affected to unaffected side. In the latter case there are new algorithms being developed in which one can actually compare extracellular to intracellular predicted fluid content, which will circumvent some of that. So I think that we're just poised at the point where the bioimpedance approach will be able to be used in bilateral disease. Bilateral

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problems are encountered much more commonly in the lower extremities but we actually do see it in both.

DR. GOODMAN: Dr. Satya-Murti.

DR. SATYA-MURTI: Very quickly. One of your patient's scintigraphy actually did not progress after a while, and you also showed another Kaplan-Meier curve where they flattened out. So I'm just wondering, how many of the subclinical test-based diagnosed lymphedema patients have been sequentially followed without preselection to see how many of them stabilize and do not become clinically obtrusive? We need to know the natural history in large numbers, do we not?

DR. ROCKSON: We do indeed, and that's one of the reasons for the creation of the registry, for example, because really no natural history data has been acquired in sufficient numbers. What I think we can say is that if one presumes that postsurgical patients, for example, are anatomically abnormal and presumably dysfunctional physiologically from the time of intervention, there's going to be some requisite discordance

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between what one sees clinically from the imaging data.

One of the reasons I'm particularly excited by the bioimpedance technique is that in the data that's been acquired in asking just the kinds of questions you're asking, even when defining the population norms fairly broadly, when an individual exits that confidence range there is a high predictability, nearly universal, to the progression to clinically detectable disease. So I think that approach of trying to look for subtle changes not in

lymph clearance but in the flip side of that, which is accumulation of interstitial fluid volume at a subclinical degree, that might seriously be helpful. However, your point's well taken. What we need more than anything else are broad observations of the populations at risk to determine what the natural history is.

DR. GOODMAN: Thank you. Dr. Kato and then Dr. Fischer.

DR. KATO: I will yield to Dr. Fischer first.

DR. GOODMAN: Go ahead, Dr. Kato.

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DR. KATO: I'm having kind of a difficult time understanding subclinical disease. Is subclinical disease the people at risk or is subclinical disease people who have, since we're talking about patients who have had some kind of intervention, that have had the intervention just before it becomes manifest with symptoms and signs that we classically describe as lymphedema?

DR. ROCKSON: So, I think you could define a variety of subclinical populations. One might be a purely clinical level, a group of patients who are defined at risk because they have had some indexed surgical intervention, for example, so we already recognize them to be at risk, who report symptomatology in which there are no objective measures of an increase in lymph volume, for example. That would be one category. A second category defined largely by Alain Pecking would be a group of individuals in which scintigraphic functional imaging is abnormal despite the fact that there is no detectable disease. That would be a subclinical form of lymphatic dysfunction.

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And the third would be any modality in which one can, for example with bioimpedance spectroscopy, detect the presence of increased, the biological impact of increased interstitial fluid content despite the fact that the limb measurements are normal.

DR. KATO: So under that, under those conditions then, would you in order to try to prevent, let's say prevent lymphedema from occurring, you would recommend a study, whether it's, and you can tell me which one you would do, in order to identify those high risk individuals so that surgery or an indexed operation could be minimized, or something

could be done to try to avoid that, or is that data available?
DR. ROCKSON: There is just a little bit of data available. I showed some material from one of these studies performed at the Naval Hospital in Bethesda in which an early intervention was undertaken using perometry as the index measure for a small and subtle increase in limb volume, and then a very peremptory intervention to try to, and a very simple intervention at that, to try to limit
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the progression of edema. And that was a successful intervention, albeit in a very small category of patients.
What I would propose as a very useful intervention would be to take some universally applicable repetitive and simple measure, for example like bioimpedance in a high risk subgroup, for those following axillary lymph node dissection, and then to identify at the time of an observation that bioimpedance ratios are deteriorating in the wrong direction, to then stratify patients into various arms of, not to use a pun, of intervention, including nothing, to determine whether doing nothing versus doing something and what those somethings might be will change the outcome over time.
DR. GOODMAN: Thank you. Dr. Fischer.
DR. FISCHER: Thank you. That was a very complete and nice presentation. You did mention lymphovenous anastomosis, and there has been a great deal more interest in Europe and a remarkable lack of interest in the United States in the surgical approaches.
DR. ROCKSON: Yes.
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DR. FISCHER: I am aware of one paper which I have, it's not a good paper, it was a good journal, of a French experience with groups of lymph nodes transplanted and microsurgical anastomosis. Are you aware of any other -- I mean, I would have rejected the paper if I had reviewed it, I would have rejected the paper, but are you aware of any other similar kinds of experiences? Because, not so much for the actual outcomes, but it has rather interesting future scientific types of experiments that it suggests.
DR. ROCKSON: Here's what I know. I've had conversations with some scientists in Europe who are interested in this lymph node fragment implantation on a scientific basis.

And when you do this in an animal model, what happens is that initially all of the lymph node, the cellular content of the lymph node becomes necrotic and disappears, but the stroma of the lymph node survives. And if you follow these nodes over time, they do repopulate both with islands of D-cells and the T-cell areas, and one can see the persistence of the high endothelial venules. One can presume that if

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all of that occurs, the node could actually orchestrate some vascular ingrowth into it so that over time at the very least, one would have some preservation of immune traffic function in the affected limb, if not the actual homeostasis of fluid.
But at a clinical level, the group in France had their one report. There are some groups in Japan that have reported about this as well. Nothing in the United States yet on a clinical level.
DR. FISCHER: And I think the importance of that lymphovenous anastomosis, if you take a group of nodes, which is really sort of not particularly necessary and not in danger of causing lymphedema in the other extremity, and you anastomose the lymph channels, and there lymphoscintigraphy reveals some function in not all the nodes, but a significant number.
DR. ROCKSON: Right. Of course the limb-to-limb anastomosis, you as a surgeon know that that would be a challenge in itself.
DR. FISCHER: But we could do that, given the volume of people who are practicing.
DR. ROCKSON: Sure.

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DR. GOODMAN: One more question from Dr. Eng, and then we're going to move on. Dr. Eng, a precise question.
DR. ENG: Dr. Rockson, I'm referring to the graph, freedom from progression from mild lymphedema, and at the start it's Stage I, and what the graph shows, at least as I interpreted it, is that 60 percent of patients progress in this study, but what stage do they progress to?
DR. ROCKSON: They progress to variable stages and it will depend on the length of time that they're observed in the absence of treatment. So Stage I, Grade I will progress to Grade II next.
DR. ENG: There's a corollary on the ISL grading schema. Can you give me, of the universe of patients with secondary lymphedema,

what proportion is Grade I, Grade II and Grade III? So that for me at least, I would like to know what the proportionate burden of disease is.

DR. ROCKSON: Okay. This data as you heard is quite sparse, so I'm going to extrapolate from my own clinical experience. I

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see about 50 new patients a year and I would say if I integrate my experience with that, I would say about 30 percent are Grade I, perhaps 50 percent are Grade II, and 20 percent are Grade III.

DR. GOODMAN: Thank you very much, Dr. Rockson. We wish you could stay later, but you may have follow-up questions by e-mail or otherwise if necessary.

Unless anyone on the panel objects, I propose that we take a 10, not 15-minute break right now. So we can take a prompt 10-minute break, and then we will proceed to hear Dr. Armer's presentation, and then we will try to make up some other time later in the day. I'm conscious about saving time for other, for public comments, so let's take ten now. Thank you.

(Recess.)

DR. GOODMAN: Our next speaker is Dr. Jane Armer. She's the director, among other things, of the American Lymphedema Framework Project. Dr. Armer, welcome, and thank you for modifying, going with our modified agenda, and please do proceed.

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DR. ARMER: Thank you. It's a privilege to be here to share my views with the panel and this audience, and particularly to follow Dr. Rockson, who's a colleague that I respect greatly. I was at a meeting this weekend with several keynotes on personalized medicine and pharmacogenetics and the second of the keynote speakers said, there was a quote, everything has been said but not everything has been said by everyone. And I think we're going to have some of that thinking today as we hear our points of view presented in slightly different viewpoints, different words, but a commonality of what we're going to hear today. I shared here with you my affiliations, my academic home as well as the organizations that I'm a member of. I was invited to be a part of this group because of the research we're doing in post breast cancer lymphedema, and I'm also an advocate, a

survivor, and a person who has secondary lymphedema. I want to point out what's not on this slide, and that's that I have no financial disclosures to make. Myself, my appointment at the university and my research are not

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supported by other third-party sources other than the National Institutes of Health. This is the charge that I was given in presenting to you this morning, to discuss the means by which evidence-based medicine can best be pursued in order to determine the appropriate diagnostic and treatment methods for lymphedema to inform public policy. I want to say that I think today is the time that we can make a difference. A multitude of factors makes 2009 the opportune time for change in the field of secondary lymphedema. For one thing, we have a recognition of the need for consensus in our field in measurement and diagnostic criteria. We have available today approved assessment tools and protocols for measurement and surveillance. We have an increased emphasis in our health care delivery system on evidence-based practice. And we have the emergence of adjunct therapies that we need to take into account in the best care of our patients. We also have an enhanced collaboration among our disciplines and among the organizations in the field of lymphedema. Perhaps the last two points are most

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important. We have improvements in cancer detection and treatment that are leading us to have more survivors, more years of survivorship and more people at lifetime risk of developing secondary lymphedema. We also are faced with economic challenges. There's a need for us to evaluate health resources and coverage for extending access to care for those that are in need of this care. In terms of how common the problem of lymphedema is, we know that studies have a wide range of reports, from three to 87 percent of breast cancer survivors may develop lymphedema, depending perhaps on whether they develop infection after their treatment, which is where the 87 percent comes in. And the three percent, perhaps those with lowest risk such as sentinel node biopsy, and those that are followed only a short time after their treatment, rather than a longer period of time. The medical textbooks report 15 to 20 percent occurrence of breast cancer lymphedema.

The discrepancies in our literature are due to the difficulties we have in measurement, in diagnosis and in terms of

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follow-up. We have consensus panels formed for measurement of outcomes in the U.S., the United Kingdom and Australia, and internationally to address some of these issues.

There are two common misconceptions in our field that I want to address immediately as we begin this discussion. One is that in our contemporary surgical intervention for cancer, particularly for breast cancer, lymphedema no longer exists; that is a common misconception.

The second misconception is that lymphedema risk is limited to immediately after treatment; that's a second misconception that we need to deal with.

First of all, in the published studies following sentinel lymph node biopsy, in these 15 studies we see a range of zero to 23 percent occurrence of lymphedema, with an average of six percent, in more than 4,000 cases that were followed after sentinel lymph node biopsy. So if a patient needed only sentinel lymph node biopsy, if their lymph nodes were clinically and pathologically negative, even in that case, more than a thousand new cases of lymphedema would occur per year, and we know that these

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are the lower risk cases for lymphedema.

Clinically, patients do need to progress to axillary dissection to manage their cancer in many cases and those people have higher risks of developing lymphedema after their treatment. Our studies, in looking at incidence, prevalence and severity, are estimated in the literature by a variety of criteria, by retrospective and prospective designs, varying lengths of follow-up, and often we've got a baseline measurement. The data I'll show you in just a moment is based on circumferences, symptom report, volume change by perometry, and a prospective design with a seven-year follow-up and a baseline measurement between the time of diagnosis for breast cancer and the start of the treatment for breast cancer.

In this study from our research program at Missouri, we did four identifying criteria commonly used in the literature, and you can see that the incidence of lymphedema based on each of the criteria increases every six months, perhaps the highest percentage is

reported by 12 months, but that's just over
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half by each of the criteria. We see that by 30 months, 41 to 91 percent meeting these various criteria will meet that standard. This takes into account, then, that second misconception that lymphedema occurs near the time of treatment. It does continue to occur, and as Dr. Rockson pointed out, over the lifetime of the person the risk is there.
Beyond our study at Missouri, in these 13 studies that are assessing volume either by volumeter or by perometry, we see a range of 11 to 68 percent occurrence of lymphedema in breast cancer patients, with an average of 19 percent over 2,000 patients aggregated. When we look at circumference as the criteria, we see a range of zero to 70 percent with an average of 21 percent occurrence over nearly 4,000 patients across these 12 studies.
As we look at lymphedema following breast cancer specifically, we know that there's more than 2.5 million breast cancer survivors in our country who are at lifetime risk for developing lymphedema. It has been documented that up to 70 percent, depending on the criteria used, may develop lymphedema after
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breast cancer treatment, and some onset is as late as 30 years after treatment. If we use the conservative estimate of 20 percent of breast cancer patients developing lymphedema during their lifetime, that means half a million women developing lymphedema during their lifetime in this country alone. Early recognition and treatment of lymphedema provides optimal outcomes and may alleviate or minimize physical and emotional burdens of this condition.
Most of the literature deals with breast cancer lymphedema. Here out of 99 studies reviewed, 44 deal with breast cancer lymphedema. We have here the sample size of each of the studies based on breast cancer, melanoma, genitourinary, and gynecological malignancies. We have the range of lymphedema within this set of studies, the mean incidence of lymphedema within this set of studies, and here is the cancer prevalence, the number of cancer cases per year in the United States in each of these groups of cancers.
Now if we take the average incidence of lymphedema across these numbers, in these
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columns you will you see the potential lymphedema development in these cancers, and if we aggregate those, that's 1.4 million Americans due to cancer treatment developing lymphedema. That's an enormous segment of our society.

The societal impact of secondary lymphedema based on even the lowest estimates, we know that hundreds of thousands of women develop lymphedema following breast cancer. The lymphedema occurrence for melanoma, sarcoma, head and neck cancer, gynecological and genitourinary cancers may be even higher than the occurrence for breast cancer. There are more than 1.5 million newly diagnosed cancer survivors every year in our country and more than 11.4 million cancer survivors living at risk for lymphedema. Secondary lymphedema related to cancer treatment, trauma and damage to the lymphatic system potentially affects over a million individuals and families in our country.

This is a complicated model that shows the multifactorial nature of secondary lymphedema. Particularly this model was built

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for breast cancer lymphedema, but it shows the predisposing factors in that upper box which includes factors like genomic variation, family predisposition, premorbid conditions, treatment factors related to the cancer treatment, BMI, body mass index, and other possible trauma to the limb or the body part to be affected. We see on the left side the protective mechanisms of problem solving and social support. We see in the lower circle the coping mechanisms and symptom management that would come into play as symptoms emerge related to lymphedema. Limb volume change and symptoms, the anthropometric measures and the self-reported measures have largely been the ways that we have come to understand the true occurrence and the impact of lymphedema.

In the outcomes box here we have psychosocial adjustment, overall quality of life, functional health status, and now an economic category there looking at the economic impact of lymphedema.

In terms of prediction and risk management for secondary lymphedema, health-related quality of life measures such as

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the impact of disease-specific problems and generic measures of functioning and well-being

are the best predictors of future health, of inpatient and outpatient expenditures, of response to treatment, job loss or disability, work productivity, and mortality. In the continuum of disease-specific and generic health measures, we have measures such as limb volume change as a clinical marker, we have symptom self-report by our patients as measured by the lymphedema and breast cancer questionnaire, we have the impact of disease-specific problems in lymphedema such as measured by the functional living index for cancer, the FLIC, and we have generic functional well-being assessments such as provided by the SF-36. Using these measures and preliminary data from our data set at Missouri, we're able to show that even minimal limb volume change impacts quality of life. Here we have our data segregated into four groups by five percent increments in limb volume change, with the first group being that of less than five percent change after breast cancer treatment.

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The purple bars are the symptom self-report by the patients undergoing the limb volume changes. As you would expect, symptom reporting increases with increased limb volume change. The blue bars are the SF-36 or the functional scales, and that's interesting in that there's a trend for function to decrease as volume increases, but it's not statistically significant at this point in the analysis. The green bars are the FLIC or the quality of life assessment, and there is a significant increase across the four segments of limb volume change such that it's statistically significant even for mild and moderate change in limb volume. So in the five to 10 percent and then 10 to 15 percent, there's a significant impact on quality of life, which is important for us to remember in working with our patients. We also have a recent study by Tina Shih at M.D. Anderson that looks at the cost of breast cancer-related lymphedema. Shih used a large insurance data set and looked at two-year cost differences for breast cancer survivors with lymphedema and without lymphedema. The difference in cost and health expenditures

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between these two groups was more than $22,000 for the two-year period. The cost related to cancer treatment was about $8,500, the cost not related to cancer treatment was $13,500, so it

shows the economic impact on our society and on our families and patients with breast cancer lymphedema.

In terms of reducing lymphedema occurrence and impact, early detection and intervention hold the greatest promise of reducing this widespread condition, and there I cite a publication by Dr. Rockson that he mentioned earlier today.

The identification of epidemiological and clinical factors associated with risk, incidence and progression will provide the necessary foundation for preventive intervention.

Personal and historical characteristics such as have been discussed somewhat today, age, weight and section, radiation therapy, axillary dissection, are generally believed to affect a woman's risk of lymphedema after breast cancer in particular, and research has found that patient compliance

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is one of the most important factors in treating lymphedema. Interventions to increase self-care for risk reduction and management is essential for optimal outcomes.

I will spend very little time on the ISL stages of lymphedema because that was addressed by both Dr. Miller and Dr. Rockson, but I want to point out that the zero category of subclinical or pre-lymphedema, I would quote Dr. Foldi from Germany in saying that perhaps those people who have undergone trauma to the lymphatic system from surgery or radiation may be actually latent stages of lymphedema waiting for emergence over their lifetime, implying that if we live long enough after such trauma to the lymphatic system, lymphedema may well emerge as a known entity.

I also will just briefly address this very fine study recently completed in 2008 by Stout and her team at Bethesda at the National Naval Center. Theirs was one of the pioneering studies in risk reduction intervention, the surveillance model. As Dr. Rockson has pointed out, in this study of three percent limb volume change, that subclinical category of

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lymphedema, patients were fitted with a 20 to 30 millimeters compression garment, and I would mention that this was a measurement by perometry. At the end of 12 months postoperatively the patients who were in the garment had returned to a near normal baseline

limb volume.
The team here proposed a three percent volume change from baseline as a diagnostic criterion for subclinical lymphedema that would require us to put into place conservative management and prospective surveillance to identify lymphedema before it becomes mild, moderate or severe. And quoting then from the 2008 article, when used in the context of a surveillance program, and these five particular measurements are mentioned, these measurements may prove efficacious in diagnosing subclinical lymphedema.
Dr. Leigh Ward at Queensland University in Australia suggests that we can learn from the chemistry field in terms of assessments of lymphedema and that we could come together on a standardization of measures and accept a certain technical and analytic

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data interpretation protocol. He gives as an example the consensus statement on the worldwide standardization of the hemoglobin A1c measurement for diabetes, which has brought together the countries of the world in the assessment and the management of diabetes. We could do such a thing with lymphedema if we come to agreement about measurement and consensus. And this does involve a surveillance model, that we're not waiting for an extreme emergence of the disease, but early detection.
Dr. Ward also points out that we should remember that none of the methods for anthropometric assessment replace clinical judgment. Here's a quote by Stanton. Careful examination of the arms of patients with breast cancer is vital. Comparison of arm volumes or circumferences alone will not detect early breast cancer lymphedema and will result in an underestimate of its prevalence in studies of complications of axillary surgery. And I might suggest, this may be a factor in the discrepancies in our literature because we normally are using a diagnostic criterion

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that's based on anthropometric measure without a skilled clinician examination of those patients being followed.
This slide portrays five of the systematic literature reviews that have been done in our field between 2003 and 2008. We have the McMaster study that has been shared with us today. There is a systematic

literature review underway by the American Lymphedema Framework Project that we hope to have available in early 2010. So, these studies are going to not have the most -- these five studies are not going to have the most current literature that has evolved even since 2007, which was the closing review date for the ONS PEP Card.

I would point out that these first two studies are Cochrane reviews in the United Kingdom. The International Lymphedema Framework was by expert consensus as a best practice model for the management of lymphedema. The systematic review of common conservative treatment for lymphedema secondary to breast cancer is from Australia. And the most recent of this set that I'm going to spend

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a little bit more time on this morning is the Oncology Nursing Society Putting Evidence into Practice PEP Card.

That's the most recent of these evidence-based reviews, and I want to go over just quickly what those recommendations by level of evidence are. We reviewed the literature from 1997 through 2007 specifically and applied the rigorous criteria that were used across the ONS PEP Cards, not only for lymphedema but for other symptoms that are a part of the oncology practice. The purpose of the PEP Cards are to provide a clinical guideline for practitioners based on the best evidence in the literature.

For this lymphedema PEP Card, three expert teams of clinicians paired with researchers were brought together to review current clinical practice guidelines, systematic reviews, and 218 research studies. Detailed evidence tables were created, reviewed and weighted. These are available on the ONS web site, and there's a chapter in a book of PEP Cards that have our final details here.

The PEP Card design looks at red,

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yellow and green as a stoplight vision. The red is stop, the evidence indicates that these interventions are ineffective or may cause harm. The yellow is a caution, there is not yet sufficient evidence to say whether these interventions are effective or not as a standalone therapy. And here the italics and the bolding that you see are my emphasis; otherwise, these quotes are directly from the PEP Card as I go through levels of evidence.

The green means go, evidence here supports the consideration of these interventions in practice.
The first level of evidence under the green category is recommended for practice, with effectiveness demonstrated by strong evidence from rigorously designed studies, meta-analysis or systematic reviews. The criteria to be met in the recommended for practice are more than two multisite well conducted randomized controlled trials with more than a hundred subjects, or a panel of experts' recommendation derived from the literature search with quality ratings as part of that literature review.

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The second green category is that of likely to be effective, with effective benefits exceeding harm. Effectiveness is demonstrated by evidence from a single rigorously conducted controlled trial, well designed trial with small samples, or guidelines developed from evidence and supported by expert opinion. Here one randomized controlled trial with more than a hundred patients or more than one study site would meet the criteria. Guidelines developed by consensus or expert opinion without a quality rating would fit into this category.
Now under recommended for practice is complete decongestive therapy, with evidence of the highest level from our literature supporting CDT for the treatment of lymphedema.
I'm not going to go into the components in detail because Dr. Miller presented that very nicely. I would just summarize it to say that CDT is a two-phase therapy with five key components that are listed here. The asterisks besides the key components are there because these key components were also tested separately as standalone and will be discussed later if there is an asterisk there.

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As far as CDT, the intent of therapy may last 10 to 20 days depending on the individual, and may last four to six weeks depending on the timing or whether it's once or twice a day. There's intensive CDT for lymphedema that is moderate or severe, and modified CDT which may exclude one or two components of the five, is indicated for mild to moderate lymphedema. A key point too is that CDT is administered by a specialty trained therapist. We know from the outcomes in the literature that early intervention with CDT is

less costly and less burdensome, and has better outcomes.
The second recommended for practice as a standalone, but a component of CDT, is compression bandaging. Compression bandaging aims to reduce the swelling and prepare the limb for gradient compression garments. Specialized expertise, again, is required for the initiation and the monitoring of compression bandaging, and it's a part of both the intensive and the maintenance phase of caring for the patient with secondary lymphedema.

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Third in the recommended for practice is the treatment of infection, which has been a topic of interest this morning. This is based on expert opinion and consensus. We know the people with lymphedema are at increased risk for infection. We have criteria for hospitalization. We have a protocol for oral antibiotics at the first onset, first observation of infection, and that might lead technically to IV antibiotics if there's no response to the oral. We know that infection is recurrent in up to 20 percent of the patients, and I will deal with prophylactic use of antibiotics in just a moment.
Under the likely to be effective green category is maintaining optimal body weight. Now these are in likely to be effective because the studies are less sufficient than to be recommended for practice. We know that there's evidence of effectiveness, but not as great a level of evidence. It's very difficult for us to isolate patient factors from treatment factors in our assessment of risk and onset of lymphedema, but evidence to date supports that a BMI score of greater than 30 is a risk factor

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for lymphedema. So that evidence in the literature about BMI associated with lymphedema emergence, it is thought that maintaining optimal body weight is likely to be effective.
The second likely to be effective intervention is manual lymph drainage, which again, is an integral part of the five components of CDT. It also has been evaluated as a standalone. Systematic reviews and individual studies supports the use of MLD for lymphedema treatment as a likely to be effective category, and again, MLD practitioners require training at the specialist level.

The third under likely to be effective intervention is that of skin care, again, it's a component of CDT. When looked at alone, it's felt by expert opinion that it is an integral intervention in lymphedema management and is likely to be effective, so we have here this standard, impeccable skin care is a cornerstone of lymphedema therapy.

Now the next category, which are the yellow on the PEP Card, are benefits balanced with harms. Here clinicians and patients

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should weigh beneficial and harmful effects according to individual circumstances and priorities. Here randomized controlled trials, meta-analyses or systematic reviews may have documented adverse events in certain populations, so the practitioner has to make a decision about benefits and harms for this particular case and for this particular population.

The second category in the yellow category is effectiveness not fully established as a standalone therapy. Data currently are insufficient or of inadequate quality. The intervention may not have sufficient data for standalone therapy. And again, the italics and the bolding are my emphasis here. Well conducted case control studies or poorly controlled randomized controlled trials, there may be conflicting evidence or statistically insignificant results. Further study is needed as a standalone.

And I would make the point here, I may make it again later too, our field is very dynamic. The literature reviewed for this PEP Card was through 2007, with publication in

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2008. There have been new studies that have emerged since March, before March of 2009 and since March of 2009 that need to always be considered in our weighing of the evidence. And it's dynamic in that an intervention could move up or down depending on new research, it isn't always in one direction. We have to have larger samples, more rigorously controlled designs, and then we will have the best support for our interventions.

DR. GOODMAN: Dr. Armer, just about a minute or two, please.

DR. ARMER: Okay. Benefits balanced with harm include exercise, which with larger samples is starting to move toward likely to be effective, but right now it's in the benefit

balanced with harm. Prophylactic antibiotics with recurrent infection is in this category. Effectiveness not fully established as standalone therapy. Here we have compression garments and self-manual lymph drainage as components of full CDT but are not fully researched as standalones. We have hyperbaric oxygen, low level laser, pneumatic compression

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pump, surgical intervention and specialized dressings for lymphatic ulcers that are all promising adjunct therapies and are in process, many of them, in more rigorously designed trials right now. Effectiveness unlikely does not have any interventions in our field at this time. In this categorization, not recommended for practice, are drug therapy such as diuretics and benzopyrenes where there could possibly be harm. I'm going to go through some of these summary slides until I come to my main summary slide. In terms of recommended for practice and likely to be effective, those green categories, the recommendation for research in this area is that we need further research on dosing, on frequency, on indications and contraindications, on bundled interventions, on these crucial interventions with adjunct interventions, to see what our best outcomes are. In the yellow, benefits balanced with harm and effectiveness is not fully established as standalone therapy, we need further research

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with rigorous design such as randomized controlled trials, larger samples, adjunct, standalone and bundled interventions followed over time. Not recommended for practice, we need further exploration discovering animal models, and at the molecular level we need tissue registries and advancements in genomic research. In conclusion, evidence at the highest level supports CDT and its five components for the treatment of secondary lymphedema. There's increasing evidence that the use of individual components of CDT under the guidance of a specialty trained therapist for mild to moderate lymphedema, and recently in -- mild, moderate and severe lymphedema -- and recently in subclinical lymphedema, and promising

studies are underway evaluating adjunct therapies under selective circumstances. In the final summary, we need more well designed studies with precise measurements, larger well defined study cohorts, followed over a longer period of time, with standalone and bundled interventions

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incorporating our standard of care versus optimal care guidelines. Together these will lead to more definitive evidence-based recommendations for optimal management of secondary lymphedema.

DR. GOODMAN: Thank you very, very much, Dr. Armer.

(Applause.)

DR. GOODMAN: Dr. Armer, if you wouldn't mind, we're going to have at you after lunch and we will have more time to spend with you then.

DR. ARMER: My pleasure.

DR. GOODMAN: That's great, and we'll actually ask you after lunch to sit up front so we can pose those questions to you then, as opposed to now. Thank you very much. We now have our lineup of scheduled public comments and we have 13 scheduled public commenters, and they will go in the following order to the podium. And I would ask the obvious, A, do stay within the five minutes, and we would appreciate less than five minutes where you can get to your most important points. B, to be ready on deck for when it is

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your turn. The order that I have, I'll give you the first five that I see, and they are Robert Weiss, Kathleen Francis, Linda Miller, Walton Taylor and Steven Schonholz, those are the first five. And again, please do stay within your five minutes. Please also remember that we really care most today about where there is evidence for our MedCAC questions. We care about the evidence, less about the pathophysiology. We heard a little bit about epidemiology today, that's fine, but the panel is going to have to address where is the evidence, how strong is it and what does it say about diagnostic and therapeutic interventions. Robert Weiss, you're first, sir.

MR. WEISS: Thank you. I would like to commend you all to the written handouts that I gave out which do have notes on the bottom of the various view graphs, and these notes

contain specific citations that I think may be very important.
My name is Robert Weiss. I'm an independent patient advocate. My wife is a 17-year breast cancer survivor who has had
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lymphedema from day one. I am intimate with the daily care of lymphedema. I help patients all over the country in helping them cope with this condition, I do research, et cetera, et cetera. I do not receive any remuneration from any companies. My activities are funded by the Social Security Administration with monthly checks.
(Laughter.)
I'm going to skip over the summary charts because I'm going to deal with each chart separately. We all heard about the modalities of the primary treatment of lymphedema, these are the primary modalities as defined by Foldi and developed over the last 70 years in Europe and Australia, there are adjunctive modalities that are just coming to bear that have even less evidence, but they're used to supplement the primary modalities.
Of the methods used to measure lymphedema, there are about a dozen completely different methods. There are a number of reviews of these methods that are referred to here. The message that I want to get across here is that although there are no methods that
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are absolute standards for measurement of lymphedema, all of these methods have application in specific cases for measuring the progress of the treatment. And so the method chosen by the surgeon or each physician to measure the effectiveness of the treatment that the patient receives, most of these have definite applications in addition to their clinical applications.
Actually going back to the measurement issue, there's one other point that I want to make. The traditional methods of measurement deal with limbs, arms and legs, mainly arms, but there is an epidemic of breast and torso lymphedema, abdominal lymphedema, these are not measurable by those traditional methods. There are new methods of bioimpedance and tissue characteristics and measurement of water in the tissue that are coming to bear as very viable methods of measuring lymphedema in other places of the body.
It's estimated by Ronka that up to 80

percent of breast cancer survivors have skin thickening, which are preliminary signs of lymphedema. The actual clinical lymphedema,

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she measures by skin thickness as being 23 percent. So there is a problem with breast lymphedema as well as arm lymphedema. There are many mechanisms that apply to the effects of compression and these are not limited to the increase of tissue pressure that increases venous uptake, but they are directly related to lymphatic uptake and lymphatic transport, and these don't get very much attention.

DR. GOODMAN: One minute.

MR. WEISS: There are a number of reviews. I want to mainly see if you can get a copy of the California review. It's a very excellent review that was done in conjunction with a piece of legislation in California. Randomized studies, almost every one of them comes up with a positive significant result for any modality with some population, used either singly or in combination. Systematic studies show, for instance, that all of the physical therapy interventions are favorable. There are about 20 trials in progress. This didn't come out very good. There are cohort studies that I list here, about 2,200

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patients, and roughly a 48 percent change in using combination. This is a chart that echos what you've heard before. There is a vicious cycle where lymphedema causes cellulitis, and cellulitis causes lymphedema, you've got to break that cycle, and this is something that's not been researched in terms of coverage.

DR. GOODMAN: Mr. Weiss, thank you very much, we will move on. Thank you very much for your contribution. Dr. Francis is next.

DR. FRANCIS: Good morning. I'm Kathleen Francis, I'm in private practice. I see lymphedema patients exclusively at this point. I'm the chair of the medical advisory committee of the National Lymphedema Network. I'm the medical director of Klose Training, a therapist certification training school, and I'm the medical director of the St. Barnabas Lymphedema Treatment Center. This is going to test my speed talking skills. This slide, I just want you to know that there has been a paucity, as we've seen,

of clinical research over the last 20 years,
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but there's been an enormous advance in clinical treatment of lymphedema ove the past 20 years in this country from essentially zero to successful treatment to treat this enormously disfiguring and disabling condition. Successful treatment is available for patients now and was not available 20 years ago. Causes of secondary lymphedema are legion. You will notice that these findings of the diagnosis and treatment are generalizable to the Medicare population because most of the causes of lymphedema are most prevalent in the Medicare population. Pathophysiology of lymphedema, as we've seen, is relentlessly progressive, and we see enormously disfiguring and disabling lymphedema in people that are not diagnosed in a timely manner and are not treated in a timely manner, and this is what we're seeking to address. Diagnosis of lymphedema at this point is mainly based on clinical assessment, preferably by a clinician who has experience in lymphedema evaluation and management. We are seeking more and more research on diagnostic
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modalities that will enable us to have a test for lymphedema, but at this point it's largely clinical. However, lymphoscintigraphy has been shown to be an excellent way of determining lymphatic function and it is used in patients for whom the diagnosis is equivocal or perplexing, or we have further questions that can be answered by lymphoscintigraphy. MRI and CT scan, ultrasound, et cetera, are generally used at this point in time to exclude other causes of lymphedema, and they have been shown to be quite effective in this way. By the way, you have a handout that I provided you with, and it has citations under the slides in the notations section. I'm not going to talk about measurement methods. Stages of lymphedema simply remind us that this is a relentlessly progressive condition, and all of us clinicians who have been involved in the treatment of lymphedema have seen the enormous effect of the delay in diagnosis and treatment of lymphedema, and ongoing attempts to provide better staging systems are ongoing, you will see that in your
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citations.
In terms of complete decongestive therapy, we've seen several presenters who've shown us the evidence regarding complete decongestive therapy. Even the technology assessment, which questions the high level of the evidence, the studies have shown effect, have shown effectiveness in the clinical world in treating lymphedema and relieving patient suffering. So we have numerous studies, although they may not be of the highest quality, that show effectiveness. We are relieving our patients' symptoms and we are preventing complications, and this is just one example of the enormous improvement that can be achieved, and this was CDT alone.
Manual lymph drainage increases lymphatic pumping, helps direct lymph to unobstructed territories, reduces fibrosis, which is a serious problem.
Compression bandaging and garments, as we've seen, have been evaluated, and the literature will show us that it helps to reduce ultrafiltration, helps with foam material to reduce fibrosis, improves sufficiency of the

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muscle pump in enhancing lymphatic and venous return, and in those ways helps to reduce volume of the extremity.
Remedial exercises, there's also literature to suggest that that improves venous return, improves lymphangial motoricity, improves lymphatic return.
Breathing exercises may create a suction effect, as some of our newer research is showing, in the thoracic ducts, which may help with drainage of peripheral lymphatics, and also of course improve range of motion and strength.
Home maintenance is absolutely essential. If patients do not continue to use compression during the day, and in many many cases overnight as well with specialized nighttime compressions or compression bandages, the lymphatics, the limb refills and the lymphedema again begins to progress.
Regular exercise, self-care, weight management, because obesity is an enormously prevalent cause of lymphedema in today's society, especially in the United States.
In terms of pneumatic compression

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pumps, they are an excellent adjunctive therapy after CDT in the home maintenance phase. They

can take the place of manual lymphatic drainage, self-drainage, which many patients find difficult to learn. The more advanced programmable devices are what we as clinicians recommend, as opposed to single chamber or non-programmable devices, and some of the newer technology in pump devices allows decongestion of the proximal root of the limb and the trunk to alleviate problems like fibrotic rings and proximal congestion.

Thank you very much.

DR. GOODMAN: Thank you very much, Dr. Francis. Next, Linda Miller.

DR. L. MILLER: Good morning and thank you for the opportunity to present today. My name is Linda Miller, I'm a physical therapist with a clinical doctorate in physical therapy, also a certified lymphedema therapist. I will avoid going into too much detail about pathophysiology of lymphedema but I do want to focus on something that has not been talked about a lot, which is the venous component of the lymphedema. We've talked a

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lot about the lymphatic component. This is a schematic of the interstitium, and really I just wanted to point out to you how the arteriovenous complex is intimately related with the lymphatic, initial lymphatic system, and in order to maintain balance, arterial inflow needs to equal venous and lymphatic return, and assuming all systems are intact, that in case does happen.

When you look at the literature, there are basically two sources of lymphedema formation. We've talked primarily today about the lymph drainage failure component, but there is in fact a plethora of data that talks about the actual decrease in venous return. In some of the literature it's been demonstrated that up to 80 percent, or 70 percent of women with breast cancer lymphedema have a venous insufficiency in that limb as well. So I think the need for multimodal treatments is, because we need to actually address the lymphatic and the venous component of the edema as well.

Here is an example of a patient with significant varicosity on her lymphedematous limb, a breast cancer patient. Another

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patient, venous, obviously some venous abnormalities, so the question is whether the lymphedema causes the venous problem or the venous problem causes the lymphedema, unknown,

and for us clinicians it may not make a difference. We also know that the venous and lymphatic capillaries are related, so that chronic dysfunction of one can lead to chronic dysfunction of the other. Clearly we can, it's really difficult to determine whether or not this is primarily lymphatic in origin.
So we need to remember that the venous and lymphatic capillaries are intimately related. Our treatment techniques as clinicians have to address both systems, not just the lymph system and not just the venous system.
As has been mentioned several times, we know that when we treat it comprehensively, many times with the components of CDT, we get the best results. But recent research by Rockson and Dr. Szuba has actually shown us that if we add a pump to treatment we actually can get better results, not just in maintenance, but also in the treatment phase

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when we clinicians are working with patients. This is a picture and is for demonstration only. This patient was treated for this picture only just with the pump, so we see that pumps by themselves can cause volume reduction. But how do they decrease volume reduction? Research suggests that current literature, or that pumps do not move the protein. That's one of the reasons why it's so important that we as clinicians do other techniques to actually move the protein and make the tissue changes that are needed.
If pumps don't move protein and lymphedema is a high protein condition, where do they fit in? Well, we need to remember that edema volume is a combination of the fluid and the protein piece, those things both need to be treated together in order to maximize reduction.
We know that to treat the fibrosis and the tissue component of the edema we need to do things like manual lymph drainage, compression and exercise. Lots of literature supporting that.
The fluid component of the edema is

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maximally reduced through the use of intermittent compression. Again, a fair bit of literature for that as well.
One very important premise that I would like to leave you with today is that manual lymph therapy and intermittent

compression reduce edema by attacking different systems, one is the lymph system, the other is the venous system. Supplementing one for the other is not medically indicated.

DR. GOODMAN: Less than one minute, please.

DR. L. MILLER: Again, manual lymph drainage and intermittent compression each significantly decrease limb volume, but because it's not just a volume issue, we know that we need to do the other techniques like manual lymph drainage and compression. As Dr. Szuba's study showed us, if you add a pump to treatment of lymphedema using standard congestive therapy we actually can increase mean volume reduction, maintenance, and it also increases mean volume reduction.

A recent study I just published also demonstrates that pumps decrease limb volume

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and that that decrease is commensurate with pressures, so in this particular setting, the higher the pressure, the more limb reduction.

DR. GOODMAN: Miss Miller, thank you very much.

DR. L. MILLER: Thank you.

DR. GOODMAN: Next we have Dr. Walton Taylor.

DR. TAYLOR: I am Walton Taylor, a breast surgeon from Dallas, Texas. I'm going to talk about bioimpedance spectroscopy. I'm one of a growing number of breast surgeons who have brought into our practice an early detection of lymphedema, trying to detect patients with stage zero lymphedema that was discussed in the NIH, or in Cancer of 2008. I see roughly 120 breast cancers a year and only see three or four cases of lymphedema per year. Until the idea of bioimpedance spectroscopy came out, we did not use tape measures or even look for measurement of lymphedema because the tests were too cumbersome and unreliable. The only time we did it was if we enrolled patients in Z-10 or Z-11 and it was a required clinical protocol.

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We see, as I mentioned, eight to ten breast cancer patients per month, and LDEX is the promotional name for bioimpedance spectroscopy that we use. It gives us a number that we can see, a measure like a vital sign, much like you measure a pulse, we can measure their LDEX number and get a number for the actual fluid volume in the at-risk extremity.

We are seeing the same results in our practice that the NIH saw in their trial published in Cancer.

We brought this into our practice after a review of the NIH data and also looking at the data showing the perometry and bioimpedance spectroscopy seemed to correlate very nicely. We've been doing it for 14 months, have identified four patients, one male, three female, and intervened in all of them with just a sleeve. NIH data suggested that if we take those patients and put them in an off-the-shelf sleeve with a hand piece, treat them with that for one month just wearing it during the daytime. In their study all of them reverted back to their preop baseline measurements, and we've seen that in our

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practice.

And the nice thing about bioimpedance spectroscopy is I don't have 12 measurements, I don't have a variety of referrals, I have a measurement I can do in my office that I can do in a matter of minutes and can give me a single number that I can follow from visit to visit to visit.

My last case of lymphedema occurred over 14 months ago, before I brought this into my practice and started looking for this. She has Stage II lymphedema, I have now put her on permanent disability because she can no longer work. You know, as a surgeon, lymphedema is a complication of the disease and the care we provide, the radiation they get, the axillary dissection they get, the sentinel node they get. It's our job to try to sit there and minimize the complications of the care we provide, but providing good care. Sentinel node has been a great progress there but as we just heard, 16 percent of those patients still develop lymphedema.

How do we do it? We bring our patients in, we show them that it's not covered

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by Medicare at the moment or insurance at the moment, we do the measurement, we explain to them about lymphedema, and we review the stages of lymphedema with them. If we get it, if we find a bump, that they've fallen out of the normal range and made a substantial change, we send them from there straight to the drugstore, they make their choice, they buy a sleeve. I call them every two to three days to make sure they're wearing it, they don't have to wear it

during the daytime, and we follow them to make sure they're having the appropriate response. As I mentioned, all of our patients that we did evaluate had an appropriate response. So just in summary, I think bioimpedance is very accurate for detection of subclinical lymphedema. We see the same results that NIH has seen in their practice, and with our prospective management plan we allow patients to develop something that we only have to treat. If we can catch it early, we can prevent a lot of the other expenses that are out there. The $18,000 a year for the first two years with a pump can be reduced to a hundred dollars for a sleeve and a hand piece

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in a subset of patients. That's all I've got. Thank you.

DR. GOODMAN: Thank you very much, Dr. Taylor, very helpful.

(Applause.)

DR. GOODMAN: Next is Dr. Steven Schonholz, he will be followed by Oscar Alvarez, Maureen McBeth, Sheila Ridner, Steven Dean and Caroline Fife. Dr. Schonholz.

DR. SCHONHOLZ: Thank you very much. What I would like to do is go over my experience in managing lymphedema. Over the past two years we've diagnosed around 210 cancer patients that, during that time we've had an incidence of around 11 percent lymphedema, and we've been using bioimpedance for over two years on all of our patients. Now what about the challenges that we wind up facing? Well, what about tape measures? Well, it's inaccurate, it doesn't really wind up working. Do physicians really wind up going every four centimeters, picking out the lengths, and then using a volume equation to make a differential between the two

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arms? No, they don't. Can I put water displacement in my office, something that's not FDA-approved? No, I can't. Do I wind up using the perometer, which costs a lot of money, special training, can I do that? No, I can't do that either. Did I find out that using bioimpedance was very quick, was very easy, reproducible and FDA-approved? Yes, it was, and that's why I decided to incorporate it. Then we also have the fact that there

are different readings, so how do you define lymphedema? Well, is it greater than 200 centimeters, is it 200 mls of fluid, is it 150 mls, is it 50 mls? What about a five to ten percent change? There's not a standard way to check, and the bioimpedance gives you a score that you can check and follow with a particular person.

We followed the NIH model that validated our experience, that we screen every person preoperatively, every person. Because the idea was, you don't know if this person is going to get sentinel node or axillary

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dissection and we want to know the person's baseline. What we then ended up doing was following that person postoperatively, did another measurement at three months, and then every six months after that.

It's a progressive disorder so we're able to take these measurements very quickly and easily. I do not have to do this, I can have the nurse do it, I can have a PA do it. My medical assistant is the one that winds up doing it, and it's very easy to read, and I'm able to decide what type of therapy the person needs right afterwards, which is typically just a sleeve. However, I do have all my patients see a lymphedema therapist because I want to see the evaluation by the lymphedema therapist and how it relates to the bioimpedance.

Now there are quality of life issues, there are a lot of people out there that wind up wearing the sleeve, have to wear it all the time, and boy, would they like to take it off during a wedding or a hot day. What I wound up doing because I was getting such good results with the bioimpedance, I took people that had been wearing sleeves for years, I got a

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baseline study on them. If they were at normal findings, no subclinical lymphedema, I followed these people very closely, and I was able to figure out how long it took before subclinical lymphedema occurred on these people, and put them back in the sleeve for four weeks to get them back down to a normal range.

So what I'm doing, it's a lifestyle issue. These people do not all have to remain in a sleeve every single day. There's a time frame in which they will get an accumulation of fluid that will occur, and I can figure out what that is.

I have two patients, one that was a

concert pianist and gave piano lessons. Very anxious about lymphedema. She looked me up on line, found out we can detect subclinical lymphedema stage zero before it's clinically evident, because she knew she wouldn't be able to work if this occurred. She traveled from Boston, an hour, and we've been following her ever since.

I have another lady that had had the sleeve on for five years, tried the same thing, she's now out after a year, it's almost 14

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months, with no recurrence of any lymphedema, no sleeve. I don't know how she was detected the first time, maybe it was a transient lymphedema, but she is doing wonderfully.

The applications from the technology is also good for research.

The other thing that I've incorporated into the practice with breast cancer is that in every patient we wind up getting data after they've completed the radiation therapy, after the actual chemotherapy, before actual chemotherapy. Perhaps we can identify high risk individuals by what we wind up seeing for subclinical lymphedema rather than waiting for them to present with a swollen arm. Thank you very much.

DR. GOODMAN: Thank you, Dr. Schonholz.

(Applause.)

DR. GOODMAN: Next, Dr. Oscar Alvarez.

DR. ALVAREZ: Good morning. I would like to share with you our experience with intermittent pneumatic compression the last two-and-a-half years in conducting randomized controlled trials. I'm the director of the

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wound care program at Calvary Hospital. Calvary Hospital is known for the management of symptoms. We manage lymphedema at its very end stages and we're specialized in complex wound care.

In summary, I wanted to just give an answer, I'm going to skip through a lot of these slides because it was originally prepared for a longer talk, but I want to show you clinical proof that IPC improves lymph flow, and also as you can see from this graph that IPC stimulates the development of lymph channels, and this is new information not yet published.

These are the answers to the MedCAC questions. We do feel there's plenty of

evidence to suggest that, with good confidence, that IPC can produce clinically meaningful results, and that those are based on RCT results as well as literature surveys. The same with question six. We feel we have high confidence based on our experience at Calvary over all these years and a literature review. And question seven as well, we feel we

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have high confidence. I want to talk to you about a prospective randomized clinical trial recently completed, except for the analysis of the quality of life section. This is prospective, randomized at one center, open label control standard care meaning compression, so it's adjunct, IPC is adjunct to standard care. We're running a 32-week duration trial where the primary endpoint was wound healing. A secondary endpoint involved edema control and quality of life. Inclusion-exclusion are kind of normal for this population. We kind of want patients who have good arterial flow that have a chance of healing. This is an intent to treat. Wound pain, leg edema were measured and the measurements are shown, and we did a time to heal with a Kaplan-Meier chart. These patients have extensive lymphedema, and these are BOWs, big old wounds. These are the hardest wounds to treat. These patients would gladly live with their lymphedema if their wounds were healed. The study involved IPC plus

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compression or compression alone. IPC with a four-chamber unit and either a half or three-quarter sleeve, one hour twice a day. It was diary kept, preset and locked at 50 to 60 therapy sessions, with decubitus decision daily diaries. IPC devices were checked every four weeks, and the subject and family were taught to insert the product. The wounds were measured planimetrically and here, the incidence of wound healing was statistically significant in the group that received both IPC and compression compared to the group that received compression alone, and that was at eight months. The pain is also improved in these patients dramatically, specifically in the first three or four weeks, and that was

statistically significant better in the patients that received both IPC and compression. The rate of healing was nearly doubled when IPC was added to the compression regimen. Leg edema was decreased, but only by 19 percent or so after a 20-week period, so

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edema does not change quickly in these patients, these patients have deep fibrotic disease, where the edema is difficult to compress properly. Since 2006 we've been working with Dr. Waldemar Olszewski, who has been doing some work looking at the movement of lymph with IPC, and clearly he's shown that IPC moves lymph both in healthy and in lymphedema-affected individuals at the calf and at the thigh. Furthermore, lymphoscintigraphic studies before and after IPC therapy show that after six and nine months, new lymph channels can be seen, as well as decreased lymphatic flow. With IPC in conjunction with compression, new lymph channels are noted after 16 weeks.

DR. GOODMAN: One minute, Doctor.

DR. ALVAREZ: This is the close-up of that. You can see te new lymphatic channels forming with combined IPC therapy after 18 months of therapy. In conclusion, these are the conclusions, that we think the amount of lymph flow is directly proportional to the pressure

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provided by the IPC therapy, the more pressure, the more flow. Acknowledgements. My colleagues at Calvary. Funding for this study was the New York State Department of Health and Human Services, the RTS Family Foundation, and BioCompression provided the pumps at no cost. Thank you very much.

DR. GOODMAN: Thank you, Dr. Alvarez.

(Applause.)

DR. GOODMAN: Next is Maureen McBeth.

MS. MCBETH: Good morning. My name is Maureen McBeth, and I'm a physical therapist and cancer rehab specialist at Mercy Medical Center here in Baltimore, Maryland, and I'm here on behalf of our facility, which also uses preoperative baseline measurements. I was able to convince my breast surgeons to purchase the research device for bioimpedance spectroscopy. We've already heard enough about what

bioimpedance is and the different methods, but I would like to make sure that we understand there is a difference between the devices out there and we need to be using bioimpedance spectroscopy. Single frequency BIA, most of

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you may have one of those scales in your bathroom that you step on, it runs a current sort of indirectly through your body and tells you unfortunately that you need to exercise more. Bioimpedance spectroscopy on the other hand, and those would not be appropriate for measuring lymphedema, we need to look at the lymph segments, and BIS can do that by the electrode placement, and with my research device I can actually look at all four limbs and I also get their body composition analysis in terms of their body fat, which is very important for my breast cancer population. So I would like to skip through, again, we've seen enough of that science that my other colleagues so eloquently presented. This is what the software would look like, but this is what I would like to get to. We had a great question from the panel, what is subclinical lymphedema, so I have a demonstration. You can see these very small volumes that we're potentially talking about. What does it feel like to my patients? I came up with this 83 milliliters, this is the Stout, et al., study that you've all heard

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about with subclinical lymphedema. This is my 12 grams of paper towels, and I'm going to submit this evidence to you in a moment after I pour this into the dish, hopefully these paper towels soak it all up. And this is the subclinical lymphedema that my patients can feel, this is the subjective complaint they come into my office with, but unfortunately their surgeons, not my surgeons, but many other hospitals say well, I can't see anything, you must not have lymphedema. So I respectfully submit this and thank you for your time.

DR. GOODMAN: Thank you very much, Ms. McBeth.

(Applause.)

DR. GOODMAN: It should be noted that that was a pre-post N equals one study design.

(Laughter.)

DR. GOODMAN: Next is Dr. Sheila Ridner.

DR. RIDNER: Hi, thank you. I'm

Sheila Ridner, from Vanderbilt University in Nashville, Tennessee. I wish to disclose that one of my currently three funded studies is

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funded by Tactile Systems. However, the testimony that I am presenting today is based on research that I directly conducted at Vanderbilt and is geared towards the specific questions the panel has asked us to respond to. Question number one, I present testimony regarding volumetric measurements of patient-reported symptomatology. As you've heard, bioelectrical impedance has lots of clinical applications. I've used bioelectrical impedance in my research since 2002 in over 400 people. I've compared this technology in healthy normal breast cancer survivors with lymphedema and breast cancer survivors without lymphedema. I believe that sufficient evidence exists to support the use of, in my case, single frequency bioelectrical impedance to identify and stratify arm lymphedema. I've also used multifrequency impedance in other studies and found that it correlated highly with single frequency. However, all volumetric measurements used in limbs to measure breast cancer do not provide me accurate measurement for truncal lymphedema, a new, I think rapidly emerging problem in

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breast cancer survivors, particularly those who get radiation. So we have a lot of work to do in terms of measurement, work with non-limb lymphedema, which is one of the major points I wish to convey to the panel. Lymphedema doesn't just happen in your arms and legs. I have looked at symptoms since 2002 in various studies. I have found in breast cancer survivors with lymphedema, there is a symptom cluster that includes loss of confidence in their body to perform as it should, decreased physical activity, fatigue and psychological distress. They also have altered sensations in their limbs that are distinctly different from surgical arms in breast cancer survivors who have not developed lymphedema. Based on some of my early work, we're in the process of designing three different assessment tools to use to assess lymphedema symptom intensity and distress. We are gearing these tools specifically towards the arms, head and neck lymphedema, which we see in large volume, approximately 25 percent of our

patients at Vanderbilt with head and neck
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cancer develop lymphedema. We're also developing an instrument to assess truncal swelling.
We have found in the course of our development studies that there are some universal symptoms regardless of the origin of the area of lymphedema. Heaviness, tightness, tingling and self-reported swelling appear to be universal symptoms. I agree with the previous speaker, we need to listen to our patients when they tell us they just don't feel right, because they know what's going on in their body better than any of us in this room ever will know.
Testimony was also presented regarding pneumatic compression devices and psychological support research. I've conducted one study looking at pneumatic compression in both cancer-related and non-cancer-related lymphedema as a home-based intervention. We did pretest measurements using the SF-12 and then we did post-intervention measurements. In all areas on the SF-12 following home use of the pneumatic compression device we saw significant important clinical improvement. We
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also saw reduced expenses for manual lymphatic drainage, bandaging and simple MLD.
Self-care is a critical component of lymphedema and I hope that we consider reimbursement issues for self-care as the panel makes its decision.
Psychosocial support, I just last month completed a three-year study looking at expressive writing in breast cancer survivors in order to address the psychological issues that they've had. We have done preliminary analysis for the narratives in our experimental group, which is the emotion based group. You will see here nine themes that emerged in these writings, marginalization being the number one theme, marginalization as patients, marginalization as humans, they perceive themselves as no longer being important to society.
DR. GOODMAN: Less than one minute, please.
DR. RIDNER: Thank you. Based upon their own words, many breast cancer survivors do have clear psychosocial issues that we are not addressing today, and I would only plead
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that these issues also require addressing. Lymphedema is not just swelling, it is a complex of symptoms, all of which may require a multidisciplinary team approach to management. I thank you for your time and urge you to just consider that lymphedema research is just now coming to fruition. Please give us some time to do it. Thank you.

DR. GOODMAN: Thank you very much, Dr. Ridner. Next is Dr. Steven Dean.

DR. DEAN: Hi. I'm Steven Dean, I'm a vascular med specialist from The Ohio State University and I am representing the Society of Vascular Medicine.

A couple of salient points concerning the Society for Vascular Medicine is in your handouts and an overview, again, is in your handouts.

The Society of Vascular Medicine regarding the questions, for question number five we have at least intermediate confidence, for question number six -- and this is regarding the use of pneumatic compression devices. For question number six we have intermediate to high confidence that they're

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effective, and this is based on our discussion of the evidence and our members' years of experience with promising clinical practice. For question number seven we have intermediate to high confidence that pneumatic compression devices produce clinically meaningful improved health outcomes and are generalizable for the Medicare beneficiaries.

Now let's examine the clinical evidence for meaningful improved health outcomes for patients with secondary lymphedema. Pumps have been used as a successful adjunct to home care programs for secondary lymphedema patients including Medicare beneficiaries for over 20 years, and significant outcomes include positive limb reduction, reduction of lymphatic edema, and achieving and maintaining tissue reduction, and including the attendant positive outcomes listed below.

Clinically meaningful outcomes have been published and are listed in your handout as follows, and I feel it's important that we mention some of the novel innovations in pneumatic compression device technology. Some

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pneumatic compression devices now offer special sequencing, including light pressure to the

trunk and torso as well as treatment to the limbs, which is thought to mimic manual lymphatic drainage and complex decongestive therapy.

High level or level one evidence development has not kept pace with the treatment paradigm, but widespread clinical acceptance and success with advanced PCDs does testify to their important role in home treatment programs for secondary lymphedema patients, and I encourage you to keep in mind that clinicians base treatment on a combination of existing clinical evidence, underlying physiology, and expert opinion in clinical practice experience.

I'd also encourage that Medicare recognize patients with secondary lymphedema due to nontraditional noncancer causes such as obesity. Obesity may actually ultimately turn out to be the most prominent cause of secondary lower extremity lymphedema. Take Dr. Caroline Fife's data, just published in 2008, looking at 17 U.S. wound care centers involving roughly

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15,000 patients. 74 percent of morbidly obese patients had lower extremity lymphedema, a phenomenal number.

Data from our institutions. 21 patients with lower extremity lymphedema, elephantiasis nostras verrucosa or Stage III lymphedema, the worst lymphedema, a main BMI of a remarkable 55.8. A couple of illustrative photographs of the particularly virulent combination of morbid obesity and Stage III lymphedema. I might also point out that a diagnostic test is not required to make the diagnosis of lymphedema in these patients.

Now, although a highly, highly effective technique in the clinic setting, I would just encourage the panel to realize there are limitations of complex decongestive therapy and bandaging in the morbidly obese patients with lymphedema in the home setting. Self-truncal massage is typically not possible. Self-application of bandaging is typically not possible. These patients often have a hard time simply putting on their shoes. Caregiver application of bandaging is often similarly not possible as well; their caregivers are elderly,

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they cannot adroitly apply such bandages.

But we feel that lymphatic pumps with expanders are a viable treatment option in this particular population, that is in the home

treatment setting, not in a clinical setting. Finally, limbs such as these, possibly relatively easy to treat in a home setting, but again from a comparison standpoint when you have a patient like this, and I see these on a regular basis, that's where we feel that pumps are a better treatment option in a home setting. Do I have level one evidence to suggest that? Of course not, but I would think when you compare the photographs, it would be self-evident.

And also keep in mind what I referenced earlier, alternative causes of lymphedema such as chronic venous insufficiency, which is a frequent causal or associated component of obesity-associated lower extremity lymphedema. In data from our institution, 71 percent of patients with Stage III lymphedema had associated chronic venous insufficiency.

DR. GOODMAN: Less than one minute.

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DR. DEAN: And finally, in conclusion again, the SVM, Society of Vascular Medicine reiterates support for the evidence regarding pneumatic compression devices as stated earlier: Question five, intermediate confidence; questions six and seven, intermediate to high confidence. But we recognize that current scientific and published evidence may not wholly inform or reflect current practice's standards used in recommending PCDs to Medicare patients with secondary lymphedema.

We urge MedCAC to recommend to CMS to take the following: Protect lymphedema care by maintaining the coverage benefit for PCDs, including advanced technology for appropriate patients. And please recognize obesity and other noncancer diagnoses in its definition of secondary lymphedema in Medicare coverage policy. Thank you.

DR. GOODMAN: Thank you, Dr. Dean.

(Applause.)

DR. GOODMAN: Thank you. Next is Dr. Carolyn Fife.

DR. FIFE: Podiums are difficult for

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the vertically challenged. I'm Dr. Caroline Fife from the University of Texas Health Science Center in Houston. My travel expenses were covered by the Alliance of Wound Care stakeholders, a multidisciplinary consortium of physicians, clinics and manufacturers, and I

have had a research project funded by Tactile Systems through the Institute of Molecular Medicine, and I'm going to tell you about that very briefly.

In response to your MedCAC questions, we feel that pneumatic compression devices do provide clinically meaningful improved health outcomes for patients with secondary lymphedema. I should add that for ten years I have been the director of the lymphedema treatment center affiliated with the University of Texas Health Science Center, where we've treated many patients. Because many of the previous presenters have already discussed data that's pertinent to this with regard to the level of evidence for PCDs, I'll focus on a couple of salient points I'd like to bring up. And that is that the randomized controlled trials have largely focused on

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post-mastectomy cancer, breast cancer of the upper extremity, or lymphedema of the upper extremity, which is a poor paradigm for evaluating the effectiveness of PCDs. Breast cancer is an easy way to do randomized controlled trials because there's often an unaffected side. There's almost never an unaffected side in lower extremity lymphedema for secondary lymphedema. As you see in this patient, even though there's a less affected leg, it is still affected.

The patients most likely to need pneumatic compression, with the exception of chest wall in breast cancer, the patients most likely to need PCDs are those with lower extremity lymphedema, which is why you've seen so many photographs like that this morning. These patients respond dramatically to pneumatic compression, but post-mastectomy lymphedema is a poor paradigm for studying them because it is very difficult to design a randomized controlled trial in such a multifactorial situation.

There are also new designs in pump technology for which current research has not

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kept pace with the standard of clinical practice, which causes me to make the comment about the difference between efficacy and effectiveness. Efficacy is determined by RCTs under idealized conditions, but effectiveness is the ability to produce an effect in the real world, and that is in fact what we're discussing here, how to produce clinical

effectiveness with these very difficult challenging situations, which I think you can understand would not be typically enrolled in a randomized controlled trial.

PCD technology can emulate more sophisticated techniques now in terms of the way the lymphatics work. We are also hindered by the fact that we have not had adequate imaging, not because we need to diagnose these patients, because as you saw, that's a clinical diagnosis that's very easy to make, but because it has been difficult to identify an imaging technique that is quantifiable, which allows us to compare one modality with another, we believe that that barrier has now been broken.

We now have a novel imaging technique using indocyanine green currently under research at

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the Institute of Molecular Medicine funded by $16 million of NIH funding and DOD funding which allows us to visualize in real time and quantify lymphatic flow. You can't appreciate it with these still images, but imagine they are in real time like an angiogram, only of the lymphatics. So we're now able to use this technology to compare one pump with another, to look at manual lymphatic drainage technology, and to determine the optimal way in which to administer these technologies.

This is what we've been waiting for.

At last we will be able to understand the biology, and what is perhaps most important about this is that indocyanine green provides evidence that post-mastectomy lymphedema is actually a form of primary lymphedema, that is, some patients with post-mastectomy lymphedema were genetically predisposed to develop it.

This causes us to question the most basic preconceived notions of our disease, and that being so, the way forward is really continued research which is currently underway. We hope that we will now be able to do head to head comparisons of programmable pumps versus

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non-programmable pumps, look at the impact of chest and trunk appliances, and the other types of research that need to be done.

So in answer to your questions, we have at least intermediate confidence but we have high level confidence based on existing research for questions six and seven, and I would like to recommend that you update your coverage policies to reflect current standards of care for patients with secondary lymphedema.

DR. GOODMAN: Thank you very much, Dr. Fife.
(Applause.)
DR. GOODMAN: Thank you. Next is Dr. Paula Stewart, who will be followed by Dr. Whitworth and Susan Morgan.
DR. STEWART: Good morning. I'm Paula Stewart, I am a founding member and vice president of LANA. I also served on the NLN for over ten years, and I'm a stakeholder in the American Lymphedema Framework Project. And I'm a clinician that has served thousands of lymphedema patients over the last 18 years. You have a very thick handout in front of you that included a lot of information for

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those of you who are less familiar with lymphedema. I've included in that handout a definition of lymphedema, a schematic of the lymph system. I've also included the function of the lymphatics and some of the epidemiology. In terms of diagnosis, as mentioned earlier by many practitioners, we use mostly clinical evidence, medical history and a physical. For complicated cases we will use lymphoscintigraphy, bioimpedance for the upper extremity, and MRI or CT in cases that include cancer. The newest iteration of ISL staging published in 2009 includes Stage 0 and late Stage II. These are pictorial representations of Stage I, Stage II before and after CDT. We see a late Stage II here, and Stage III before and after CDT.
In the treatment of lymphedema, pneumatic compression pumps are adjunctive to CDT. Single chambers should never be used; they can cause reflux into the leg. Multiple chamber sequential compression devices have the complication of a proximal ring of fibrosis with genital edema in the lower extremities. In newer models, truncal pieces are useful for

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decongesting buttocks, breasts and trunks, which can be challenging to bandage. There are contraindications to compression devices which are listed above. In conclusion, intermittent pneumatic compression is ineffective as a sole treatment for lymphedema, it is adjunctive. Single chambered devices should never be used. Exercise alone is ineffective in treating lymphedema but it is an integral part of CDT, both Phase One and Two. An association between BMI and lymphedema has been drawn many times this morning and exercise is important in

controlling BMI. In conclusion, exercise is effective in enhancing the well-being of those with lymphedema and should be included. Manual lymph drainage includes both manual lymphatic drainage and simple lymphatic drainage. These alone are not effective in treating lymphedema but are an integral part of CDT. If incorrectly administered, manual lymph drainage can be damaging, and specialized therapists are necessary. The benefits are listed below. MLD has little research but clinically is considered a key component of CDT. I have pictorial representations of

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manual lymph drainage and bandaging techniques. Compression is the key to the treatment of lymphedema. We use multilayer bandaging in the first phase of CDT and compression garments in Phase Two. Bandages are inelastic in order to provide a high working pressure, a low resting pressure, and are applied in a gradient. They are infinitely adjustable, which is useful in the treatment of lymphedema. Bandaging indications are listed below, and there are contraindications and cautions with bandaging. This is an example of bandaging the hand. We see here MLD and bandaging of the lower extremity. Compression garments are the primary method of applying compression in Phase Two or the maintenance phase of CDT. We see here a thigh high compression garment. Which compression garment will be used and the degree of compression will depend on many factors, which are listed. Compression garments come in two varieties, the flat knit which is for ready to wear, or circular knit, which are typically for custom garments.

DR. GOODMAN: Less than one minute.

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DR. STEWART: Our conclusions are that garments are essential to the treatment and management of lymphedema. Psychosocial support is undisputedly important in the treatment of lymphedema. Complete decongestive therapy has been discussed, there are parts one and two, the goals are listed, and we see that CDT must be provided with a toolbox of options available to treat the patient with lymphedema. Less severe lymphedema requires less intervention, more severe requires more intervention. Costs of not treating lymphedema are enormous. This is a woman who required an

amputation because of infection from her lymphedema. Infection affects about 15 percent, 10 to 15 percent of patients with lymphedema, and by treating lymphedema we can reduce the costs associated with cellulitis. I have extrapolated the savings using 2003 numbers to be $1.8 billion nationwide.

DR. GOODMAN: Dr. Stewart, thank you very much for your time. Very helpful.

(Applause.)

DR. GOODMAN: Dr. Pat Whitworth is

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next, please. And again, the panel is very appreciative of you staying within the time limit, we do appreciate that.

DR. WHITWORTH: Hi. I'm Pat Whitworth. I'm the director of the Nashville Breast Center, I vice chair the breast committee for the American College of Surgeons oncology group, and I'm past chair of the board for the American Society of Breast Surgeons, past chair of the research committee.

The American College of Surgeons oncology group has published a couple of papers you've seen data from already. One of these was a randomized trial of 891 node positive patients who were randomized to either have a completion axillary node dissection or observation alone, so they could either have had a sentinel node only or they had an axillary dissection. We were disappointed when we discovered, contrary to what we expected, that sentinel node biopsy was associated with a significant degree of lymphedema, in this case six to eight percent at six to 12 months. Completion axillary dissection at six to 12 months was 11 percent.

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We conducted another larger trial, over 5,300 patients, where we saw essentially the same thing, seven percent lymphedema described as greater than two centimeters increase of size of the involved limb at six months.

So I'm a researcher but I'm also in practice. I'd like to wait for randomized controlled trial data on everything I do, but my patients would suffer tremendously if I did that. We treat about 220 new breast cancer patients a year, that's myself, two nurse practitioners and our physical therapist, who's also a certified lymphedema therapist. We have about 20 percent Medicare patients, 80 percent private insurance patients. We treat all

economic groups.
Based on compelling evidence and based on the big need that you've already seen today, I began to incorporate bioimpedance screening of our treated patients for early lymphedema with hope of preventing lymphedema. You have heard a lot about treating lymphedema, that's very important, that was a step forward from what we used to do, which was to say, ah,

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ma'am, just be thankful you're alive. Then we got a little friendlier and a little better doctors, and we could treat lymphedema with decongestive treatment, but what we would really like to do is not treat lymphedema, we would like to prevent it.
So this was an opportunity here, not with randomized controlled trial data but with very compelling data from the NIH study, a study showing equivalence between impedance and perometry, and we began to use this in our patients.
If evidence-based medicine is where science meets real life clinical practice, then this is what happens. One day your office manager comes in and says how are you going to support this, can we do this, can we afford to offer this service to our patients? So we said well, we'll find a claim, a CPT code that's a miscellaneous code that's appropriate for this, and we'll use it. What happens if you use a miscellaneous CPT code? You get a cycle of denials, appeals, denials, appeals, but we decided to try this to really make an effort, maybe things will move forward, maybe they'll

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cover this. What we found was that our ability to analyze our accounts receivable went away, we just got this very large group of charges that weren't paid.
So we stopped doing that and we offered this on a fee per service basis. What we saw was that offered on a fee per service basis with an advance beneficiary notice that Medicare or the insurance company was likely not going to pay for this, patients were very willing to pay for this service at a reasonable cost. But unfortunately, that's the patients who could afford that treatment. That leads us to a concern about patients who can't afford that treatment and that's why I'm making these comments today.
We know that sentinel node biopsy in spite of the promise has not eliminated

lymphedema, and about 20 percent of patients go on to axillary dissection anyway. There's an FDA-cleared device with a compelling data set that can very simply discover lymphedema before it becomes a big clinical problem, and we believe that if Medicare coverage occurs, that will lead other third-party payers, we won't

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end up with this two-tier system where people who can afford it the least end up with this very costly illness. Thank you.

DR. GOODMAN: Thank you very much, Dr. Whitworth.

(Applause.)

DR. GOODMAN: Our last scheduled speaker is Susan Morgan.

MS. MORGAN: Good morning. My name is Susan Morgan. I provided a handout to the panel, I do not have a Power Point presentation, but I am a clinician with 22 years experience treating lymphedema. I'm a retired nurse and certified manual lymph drainage therapist. I've been involved in treating both primary and secondary lymphedema patients since 1987, and I am the chairman of the Lymphedema and Wound Care Consultants of America and the executive director of the Lymphedema and Wound Care Institute in Houston. Between 1987 and 1992, our company treated 4,860 lymphedema patients exclusively with compression pumps, and we recommended a compression sleeve at night for maintenance. At that time we found that 87 percent of our

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patients had excellent results while they were in treatment, but due to an inability to don compression garments or afford one, only 46 percent were able to maintain edema reduction after 90 days, and 21 percent of those patients would again have an onset requiring additional visits or hospitalizations. During that time we decided to align ourselves with leading physicians, researchers and hospital facilities, and were instrumental in developing our first hospital-based facility with Dr. Caroline Fife at Hermann Hospital. There we incorporated their first CDT program, which included bandaging in the pump therapy area where patients could be evaluated for pump efficacy, and these patients were trained to use pumps and do self-bandaging. Again, due to the inability to either afford or apply a compression derma bandage, we found that over 55 percent of these patients

could not maintain edema reduction, and less than 41 percent of our patients were unable to remain compliant to a daily pump protocol after 90 days. They were very disgruntled because going to a hospital clinic was difficult

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because of the Houston traffic, there was a cost involved for parking, and they were just, you know, really disappointed with that.

In 1996 we developed our satellite program with independent clinics which were essentially located throughout the Houston metropolitan area. Recognizing the restrictions of many of our lower extremity patients, we designed our centers to be easily accessible, grade level, handicapped accessible with free parking, to encourage visit compliance and address the financial restrictions of those with limited incomes. We currently operate five facilities in Houston, and our staff includes physicians experienced in diagnostics and the treatment of lymphedema, wound care, cardiac care, vascular specialists, nutritionists, and also a psychologist. We believe this multidisciplinary approach is an integral part of providing a truly comprehensive decongestive therapy program, in addition to the other components of CDT as we know it.

Each of our patients is pumped in our facility for a minimum of 30 minutes and

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measured before and after pumping to determine patient tolerance, appropriate pressures, and to demonstrate their understanding of the equipment, treatment time and duration. Only after this can a patient be discharged with a pump for home use, and we follow up with that patient at 30, 60 and 90-day intervals. We have had an excellent long-term result from these protocols and currently have an 83 percent compliance rate among our lower extremity patients who historically are a noncompliant patient population, and a 92 percent compliance rate with upper extremity patients who conversely tend to be ultra-compliant. Less than four percent of our patients have required additional courses of therapy and less than one percent had to be hospitalized for recurrent infections.

We also know that since that time we have treated 11,108 secondary lymphedema patients with CDT. Of those patients, 9,334 have obtained pressure pumps for home use.

1,774 patients did not meet the clinical coverage criteria; however, we have documented that 9,172 of those patients have documented

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positive outcomes using both CDT and pumps and have had extraordinarily good long-term results in maintaining their edema reduction.

DR. GOODMAN: Less than one minute.

MS. MORGAN: 1,936 patients have required additional courses of therapy, unfortunately, due to the inability to self-bandage and don compression.

We sent the MedCAC questionnaire out to 281 physicians that are in our database in Houston. We received 226, stating that these -- 226 physicians sent back the questions.

They answered for question five, six and seven that they were confident that, there was an intermediate to high confidence level in the current diagnostic testing and treatment available. We hope that these numbers show that patients receiving a comprehensive and multidisciplinary approach to treatment get better long-term results.

Our goal is to try to save Medicare money. We know that Medicare and other payers are spending millions of dollars annually on lymphedema and we're trying to eliminate and prevent ongoing episodes of infection,

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osteomyelitis and recurring infections.

Therefore, we respectfully request that Medicare continue coverage for compression pumps and consider reimbursement for other forms of compression bandaging and compression garments as an integral part of comprehensive decongestive therapy.

DR. GOODMAN: Thank you, Ms. Morgan, thank you very much.

(Applause.)

DR. GOODMAN: Thanks to all of our 13 scheduled speakers. The panel very much appreciates your insight. Every single speaker provided comments there were valuable for our deliberations.

Next we're going to move to our nonscheduled speakers, and rather than ask you to come to the podium, we will ask you to come to the front of the room and speak to the standing microphone. I believe I see seven nonscheduled speakers, and I apologize in advance if I don't do right by your name, either because of my mispronunciation or because I can't handle your handwriting.

The first person will be Nicole Stout,
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followed by Steve Cantor, then Deborah Gross, and I understand these are two-minute presentations, so there is even more of a constrained time format, and we appreciate your forbearance with us. First up is Nicole Stout.
MS. STOUT: My name is Nicole Stout, and I plead guilty to being the lead author on the study that supports subclinical diagnosis that you're having a problem getting your head around.
But today I'm speaking to you as a clinician. I am a member of the board of directors of the American Physical Therapy Association, and we represent over 70,000 physical therapy professionals in the United States. You heard this morning about how integral the physical therapist is, and central to assessing, managing and treating lymphedema. The problem that therapists contend with is that right now the current Medicare reimbursement structure, it doesn't just limit therapists in managing and treating lymphedema, it's downright prohibitive to therapists. You've seen this morning espoused the need for preoperative assessment. That is not
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currently paid for under reimbursement structuring through CMS. Prospective surveillance is not reimbursed. Compression garments that are effective at mitigating this condition are not reimbursed. So we're failing our patients with the current Medicare policy. The techniques that you've heard espoused this morning are sensitive, repeatable, reliable, and if they're used in the context of protective surveillance, we will decrease and possibly prevent the onset of lymphedema. The physical therapy professional is central to that, and having those visits reimbursed appropriately through CMS is integral in prevention. We can't let policy continue to fail our therapy contingency. Thank you.
DR. GOODMAN: Thank you, Ms. Stout.
(Applause.)
DR. GOODMAN: Next is Steve Cantor, from Medical Solutions, I believe.
MR. CANTOR: Good morning. My name is Steve Cantor and I am a national DME provider of pneumatic compression devices, and over the last 15 years of being in business, we have
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supplied over 15,000 in-home medical devices, pneumatic compression devices for the Medicare industry. We have collected hundreds of testimonies from patients who have sent in testimonies to us telling us how the pump has helped them in their daily lives and how much it has helped effectively treat and manage their secondary lymphedema. I can state after looking at all of these testimonies and talking to all the doctors that we've actually worked with, with high confidence that this modality, this pneumatic compression device even when used alone, because a lot of these patients live in rural areas, they cannot reach clinics, they cannot do self-bandaging, have been very effective in managing secondary lymphedema in the Medicare population.

As we all know, there's 80 million baby boomers that are about to enter the Medicare system, and in this Medicare system it is now more important than ever that we the providers, clinicians, physicians and CMS make these needed treatments, not only pneumatic compression devices but all the treatments that we've discussed here, available and payable

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earlier in the disease management process. If we wait, more costly complications will occur, draining our Medicare resources and seriously affecting the lives of our older populations, and I think we should be taking care of this older population as we all will be old one day, because I think they deserve it.

And I'd just like to end one time with reading one of the patient testimonies to you. I am a T9 complete paraplegic. Before I received my lymphedema pump I had constant problems with swollen legs and feet. I had bleeding cracks between my toes that would not heal. In one month with my pump for one hour a day, all of these problems have gone away, and I can now see the bones in my feet and lower legs. This has been truly amazing.

Thank you very much.

DR. GOODMAN: Thank you. Next we welcome Deborah Gross from Lympha Press USA.

MS. GROSS: I'm Deborah Gross from Lympha Press USA. We manufacture pneumatic compression devices.

I would like to address MedCAC question number seven, the applicability to the

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Medicare population. The available evidence must be scrutinized in this respect: Studies

on MLD and bandaging examined professionally applied massage and professionally applied bandages. These do not translate into the same techniques performed by the patients by themselves at home or by their caregiver if they have a caregiver. Results in the clinic don't necessarily translate into results at home, and it's very important to consider this when you look at the available research. Pumps are a consistent and effective method for the patient to treat him or herself at home. They plug it into the wall, they turn it on, they get their treatment and they're done. Very very consistent, and the device takes care of most of the aspects of the treatment for them. As the Medicare population is frequently isolated and homebound even if they're in the middle of a big city, I ask for your consideration of the available research in this very important life. Thank you.

DR. GOODMAN: Thank you very much, Ms. Gross. Next is Saskia Thiadens, I apologize if I mispronounced that, from the National

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Lymphedema Network. Up after her will be Sherry Norris, Kim Neel and Jacqueline Berry.

MS. THIADENS: My name is Saskia Thiadens and I'm the executive director and founder of the National Lymphedema Network. I would first and foremost like to thank the CMS for bringing us here today to address the diagnosis and treatment for patients with secondary lymphedema.

As a nurse and patient advocate, I'm representing the millions of patients in this country and plead for your assistance in supporting them in maintaining their quality of life through timely and appropriate treatment for this often disabling condition. 21 years ago I founded the NLN and there were very few physicians or therapists with knowledge or interest in the lymphatic system, and patients were not appropriately diagnosed and treated. Today we are witnessing a growth of interest in lymphedema and lymphatic disorders, and we have tried to provide you with the most up-to-date evidence-based research which you have asked us for. I agree, there is still many, an untold number of questions, and it

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will take time to support more evidence-based research. We are heartened by the NCI and the American Cancer Society, and the many other studies on its way and that are already

sponsored here today. We would like to suggest that in the temporary absence of adequate high level evidence of the efficacy of the current lymphedema treatment protocols, that the clinical evidence of 50 years of treatment of tens of thousands of patients in the U.S., Europe and Australia not be ignored by Medicare coverage of the protocols which have been found effective for some subset of lymphedema patients, and allowing the selection of the specific treatments judged by each patient's physician to be indicated for that particular patient. Immediate help can be offered to today's cancer survivors, thereby avoiding serious complications, costly hospitalizations and ultimate disability. It is critically important for Medicare to continue paying for treatments that already are covered. As the executive director of the NLN, I owe my patients answers as to why

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all aspects of their treatment are not covered by Medicare. I sincerely hope that after today's meeting we can approve the Medicare coverage for the diagnosis and treatment for patients with secondary lymphedema.

DR. GOODMAN: Thank you, Ms. Thiadens, thank you very much.

(Applause.)

DR. GOODMAN: Sherry Norris is next, from Alala.

MS. NORRIS: My name is Sherry Norris. I am representing actually the patient here and also, I have secondary lymphedema caused from a hysterectomy of all things. I'm here today because I want to speak out for our Medicare patients who are not getting coverage for these compression garments. As compression garments are part of their planned care, these garments help maintain the reduction in limb volume. However, currently these items are not covered by Medicare. As a lymphedema patient, I am a walking hazard wearing bandages every day. You should have seen me walking in here. This is exactly what our older population is expected

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to do because of lack of coverage for garments. These garments can also be quite expensive and these patients are having to choose between their medications or their garments. This is not fair, to ask someone to choose between these two items. If we would follow the

standard of care and cover these items for these patients, it will overall bring down the long-term cost outlaid by the insurers.

I hope the panel will consider these things when they cast their votes on questions number five and six, and remember all the research and data presented today by our panel of experts and our speakers. Thank you.

DR. GOODMAN: Thank you, Ms. Norris. Next is Kim Neel, also from Alala.

MS. NEEL: My name is Kim Neel, I am a breast cancer survivor and also a lymphedema patient. Compression garments are not reimbursed by my health insurance company because of Medicare's guidelines, and my company is not the only one. I urge you to update the coverage for lymphedema to the CDT recommended here today.

And as a guidepost and keystone for

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medical reimbursement in the United States, I request that you reexamine the Women's Health and Cancer Rights Act of 1998 where it published a document that you all put out that says your rights after mastectomy, and it specifically includes reimbursement for lymphedema supplies resulting from mastectomy. Thank you.

DR. GOODMAN: Thank you, Ms. Neel. And then we have Jacqueline Berry, from Physician Medical Supply.

MS. BERRY: Thank you. Physician Medical Supply, I started it 20 years ago just to take care of these patients, and I was just amazed at how many people had it. I actually made a presentation here ten years ago because I was upset about patients not really getting what they need, and I was also extremely upset about the Office of Technology Assessment, which I believe doesn't exist anymore. They reviewed all of the lymphedema pumps in 1986, has it been that long? And I have dealt with all the different pumps on the market, I have dispensed brand new pumps to people and they break after the people use them two times. So

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I think we really need to do a better job and really review what pumps you're paying for and what pumps you're not.

I frequently dispense the Lympha Press, not because I'm making any money doing it, in fact it costs more money for me to buy those pumps, but they're kind of like Mercedes, they last forever, and they have the sizes of

the sleeves that fit everybody. And they've also come out with a new pump that's only four chambers, and I think Dr. Rockson mentioned in his presentation, it's really the amount of pressure on each part of the limb that controls the reduction. And I really feel it works as well as manual lymph drainage, I don't really see a difference.

And a lot of my patients are Medicare, dual eligible is what you guys like to call them, and if their calf is more than 23 inches, and their ankle is more than 13 inches, they're not eligible for a non-custom compression stocking, which is almost up to a hundred dollars a pair. So when you have $800 to live on a month and your doctor says you need compression stockings or short stretch

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bandages, which are very different from Ace wraps that you buy at WalMart, those cost three dollars. I sell Lohmann & Rauscher, and BSN Jobst bandages, and to bandage one leg is really like 50 bucks.

DR. GOODMAN: Thank you very much, Ms. Berry.

MS. BERRY: Well, after you do all of that for that, and do physical therapy, you could buy a pump to begin with and you would probably be saving money, which is what I'm interested in.

DR. GOODMAN: We appreciate your input.

(Applause.)

DR. GOODMAN: Thank you. We have successfully heard some great comments and other good insight from 13 scheduled speakers and six nonscheduled speakers. We are scheduled to reconvene after lunch at one p.m. I know we're starting a few minutes after noon. At one p.m., let's put it this way, we'll start chasing you back in here. We're going to try to start just a few minutes after one. While we're contemplating and having

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lunch, I will remind the committee that you've heard some compelling comments today about the pathophysiology, epidemiology, and costs and so forth of this condition. Do remember that we're going to concentrate and really focus in on where is the evidence, how good is it, what does it tell us about diagnosis and treatment of this condition, that's where we're going to focus this afternoon.

Thank you. We will see you just about

at one o'clock.
(Luncheon recess.)
DR. GOODMAN: I want the McMaster, the EPC people, Mr. Walker, that's you, Dr. Oremus, that's you, and Dr. Armer in front as well, if you would. Thank you.
What we're going to do now is have questions from the committee to the presenters, and I would encourage the MedCAC to direct focused questions for presenters. If you really think you have an important question to address to someone else who spoke today, you need to be very specific about that, please.
And that's how we'll spend our time from now until about two o'clock, if necessary.

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Then the next session, for about 45 minutes, will be a panel discussion among the MedCAC folks, although if that has to spill over to a question back to our presenters, that's going to be okay.
Then we move into formal remarks and voting questions, a final open panel discussion if needed, and then closing remarks.
Now, sometimes these meetings end at 4:30 and sometimes they end early. I think what we'll do is have a midafternoon time check with regard to our progress, and then we'll decide then when, if or when to have a break, and try to project when we might be finished here, because I know some people are concerned about their flights, as I would be.
Okay then. Anything else procedurally at this point? So we're ready for questions.
I want to remind everyone as I did before the break, sorry to be redundant here, we are about answering these questions and all the panel is going to be asked to grade these or provide a vote for these, so I strongly encourage us to try to seek input for answering these questions despite all the interesting and important

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aspects about this condition.
I would also remind you and the folks here today that the MedCAC does not make coverage decisions, we don't even make coverage recommendations. It is our job to look at the available evidence as per our evidence questions, okay?
Let's start with Dr. Satya-Murti.
DR. SATYA-MURTI: Only one question.
We seem to have some doubts, or possibly a lack of data about the natural course of lymphedema unaffected by treatment and detection

technology. So I'm wondering, there are two panel members here who have included a study that was done preop and prospectively followed up, and some presenters also mentioned it today. So is there enough data, or if not, why is it very difficult to collect prospective data on every operative patient prior to surgery, including physical measurements, bioimpedance volume, and SF-36, and something like even an MMPI?
I know it's asking a lot, but then following them up prospectively at probably a little more frequent intervals, likes six weeks

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and so on, for about three specified times. So this would, I think, really answer some of the questions as to how this lymphedema behaves, it's sensitive to our detection technology, and why does it progress despite of the treatments?
DR. GOODMAN: Any of our three presenters care to reply to that? Dr. Armer.
DR. ARMER: (Inaudible.)
DR. GOODMAN: I'd prefer if you stood there and answer the question. If it's essential for someone else to speak, we can recognize them.
DR. ARMER: Okay, very good. We're one of the studies that does start a baseline measurement at preop and follow through postop at about two weeks, and three months, six, months, nine months, 12 months. And I think there's a difficulty with geographical placement of patients to get a preop measurement and then to follow. They're seen for preop visits to anesthesia, to x-ray, to EKG, and a preop assessment by a nurse practitioner perhaps, but then it's a different set of people that may be following them at postop.

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We have been very fortunate in our location in our cancer center, that's in one building and we're integrated in a research area near the clinic, but I know that with one of the CLGB trials that are trying to do the preop and the postop, they can be across the city from each other and it's difficult for the patients to do both of those, to do a preop measurement and to be seen in a surgical clinic where they may be followed from there. So that's, I think just geographically it's a logistical problem.
Now, the other part of your question?
Oh, the natural history.

DR. SATYA-MURTI: Well, it was sort of rolled into the same question. Had we done that either in clinical studies or as part of research, much of the evidence gap might have been filled is my contention, I could be wrong, but that would answer some of the natural history questions.
DR. ARMER: And our study is a natural history or an epidemiological study of lymphedema occurrence. We do the baseline before they have treatment and then follow from

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there. They do receive standard of care treatment and we record if they're diagnosed with lymphedema and if they're followed. They're not exited from our study but they are followed. So our study shows the emergence of the lymphedema and the sequel to that, but we do not exit them if they are diagnosed and treated, we simply record what that treatment is.
I don't know if that still answers the question, but it's not an intervention study, it is a natural history study with standard of care for the patients.
DR. GOODMAN: Okay. Dr. Umscheid is in next.
DR. UMSCHEID: This is just a follow-up to Saty's question. So if you've done that, do you have an incidence of disease over a given amount of time, and what is that incidence?
DR. ARMER: We do. That graphic that I showed during from my slides is from that data. At 30 months it's 41 to 91 percent, at 30 months depending on which of those four criteria, 200 mls, 10 percent, two centimeters

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or symptoms. So symptoms and 10 percent come together at almost the same rate at 30 months. Two centimeters is met earliest, two-centimeter girth change at any mapped anatomical point, and then in between there is 200 mls.
DR. UMSCHEID: And those are randomly selected patients?
DR. ARMER: They're consecutively enrolled patients that were diagnosed, and a very high enrollment rate among those.
DR. UMSCHEID: That were diagnosed with?
DR. ARMER: Diagnosed with breast cancer, followed before they had surgical treatment or radiation, and then followed for 30 months. Now they're being followed for

seven years in the NIH study.
DR. UMSCHEID: So that sounds like that answers Saty's question.
DR. SATYA-MURTI: Some of it, because she said depending on which method you use. So I'm wondering which method, then, is more amenable to therapy and which would actually improve, should we be treating the laboratory-oriented findings or symptom-based findings?

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DR. ARMER: I think if you made the fifth vital sign to be symptom assessment, that would be an economical way to get feedback for who needs to be triaged to be further assessed. But if you were to ask patients, have they noticed a change in this limb, and perhaps have they noticed swelling and heaviness that has come and gone, you could triage the answer to perometric measures that clinicians say are time consuming or costly. You know, either perometry or circumferences or water displacement or bioelectrical impedance, those have some cost to them in time or equipment, but you could triage perhaps in an appropriate way.
DR. GOODMAN: Thank you. Dr. Fischer.
DR. FISCHER: Thank you. As a follow-up to the question, several of the graphs that have been displayed show that lymphedema can emerge late in the course.
DR. ARMER: Yes.
DR. FISCHER: Do you have any data on patients that initially were treated, let's say with CDT, lymphedema regressed. Do we have any idea what their life history is? Are these

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people more prone to get lymphedema, let's say at three years after they initially had lymphedema and then regressed through treatment or not, or does that data exist?
DR. ARMER: We have not done our final analysis on this data so we have not looked at some of the sub-questions that could be asked of this data. What we do know in our survival analysis, once they meet a criteria for lymphedema they stay in that category. Hopefully they go to treatment and the edema resolves or at least reduces but they still have the diagnosis of lymphedema, just as if I had a diagnosis of diabetes, it stays even if my blood sugar is managed. So in the survival analysis we show new occurrence of lymphedema but we don't show them if they reduce to normal or near normal in that analysis.

DR. FISCHER: That was my question. Suppose they do go down to normal, I assume you continue to follow them?
DR. ARMER: We absolutely do.
DR. FISCHER: Right. So they're now normal. What happens to them two and three years later?

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DR. ARMER: Their volume is reduced but they still do have lymphedema, and it may not have reduced to baseline.
DR. FISCHER: My question is, if they still have lymphedema, then they still have lymphedema.
DR. ARMER: Yes.
DR. FISCHER: But what if they no longer have lymphedema, if they're treated, you say it never happens?
DR. ARMER: There can be transient lymphedema that does resolve, and they may go into that latent stage, that zero stage. They still have latent lymphedema, they still have an impaired lymphatic system. If they undergo treatment, wear a garment, do bandaging, exercise, all the things that they should do, they still have a diagnosis of lymphedema and they have a heightened risk of the infection, of a progression of lymphedema if it's not managed appropriately.
DR. FISCHER: So once you have lymphedema, you always have it.
DR. ARMER: You do by definition.
DR. FISCHER: Even if, for example,

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all you had was a sentinel lymph node biopsy.
DR. ARMER: Once you do have lymphedema you do have lymphedema, and the chronic lymphedema by CDC definitions would be six months or longer, and then acute or transient could be that that comes and goes over a period of time. It could reverse with elevation of the limb even, and appearing to be normal, but they still do have a transient lymphedema. The chronic lymphedema is a state that is of six months duration or longer.
DR. GOODMAN: Okay, thank you. Dr. Pauker is next, and before Steve, before you proceed, let me just remind all here today, if someone in our audience today has a very important absolutely laser on-focus answer to a question, don't shout it out. Come to the front of the room, stand in the queue, and we will do our best to recognize you in a timely fashion. Okay, Dr. Pauker.

DR. PAUKER: I have two questions. Question one regards the technology assessment. We heard from Dr. Rockson and I gathered from my reading that there was a study very well done in lymphedema in Europe, Germany,

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et cetera. Given that knowledge, why did the tech assessment exclude non-English articles? I understand it's sometimes difficult but if there's reliable data there, how come you didn't look?

DR. OREMUS: So, it's true that exclusion of non-English articles was one of the elements we pursued. Part of the reason for the exclusion was simply the practical difficulty of translating a series of articles that could be in many different languages, so that was part of it. The second issue is while the physician who presented after us did indicate that a great deal of the research was in fact done in Europe, systematic review research suggests that a lot of the non-English evidence that is significant will diffuse itself into the English language literature in one way or another.

DR. PAUKER: My second question, which is somewhat unrelated, to go back to the earlier discussion we had about natural history. I'm interested in not only the people who are diagnosed as having lymphedema as 25 or 30 or whatever percent, the people don't have

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it. If you look at them and manage their postoperative limb volume measurements, what is it? That is to say if people, everyone in the world including the ones with lymphedema, what is it, because the people, including the perioperative period you may get some swelling, so how do we distinguish?

DR. ARMER: We're very much aware that there's postoperative swelling that's common after surgery and for our analysis, the two-week measurement postop is not ever in that analysis, it's lifted out. So the definition of lymphedema is one that comes at three months after baseline, six months, nine months, 12 months. And when we look at postop swelling in that immediate postop measurement, that's where we were able to actually look at the fact that there's a higher risk ratio, 1.4 risk ratio for someone that has immediate postop swelling that goes away without treatment, but then at three, six, nine, 12, 18 months, they have a higher risk for developing lymphedema of a chronic

lymphedema nature.
DR. PAUKER: So you were not able to recognize, if you wait for three months or
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something, we can't recognize it earlier?
DR. ARMER: I wouldn't say that's true. For the purpose of our analysis we lifted out that data, because I think it takes a clinical examination, and in that case I don't think you can go just by anthropometric measures, you need to examine the skin, the color, the turgor of the skin, and that takes an experienced clinician to do that. I can say that volume changes and volume may even have changed in both limbs because of retention of fluid after surgery. So the limb on the affected side may have increased but also the limb on the other side increased, and it will resolve as the edema resolves after the surgery.
DR. PAUKER: What about in limbs that don't eventually get edema?
DR. ARMER: I would call on our experts who use bioelectrical impedance. My understanding is it reflects the volume in the limb, so if there were increased volume in both limbs the ratio would also be a number that has changed, but it's a comparison of the two limbs.
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DR. GOODMAN: Thank you, Dr. Armer. Dr. Alvarez, do you have an answer for the question on the table?
DR. ALVAREZ: Not that particular question but the one before.
DR. GOODMAN: Okay, if you would address that briefly, thank you.
DR. ALVAREZ: I believe that the technology assessment research methodology is seriously flawed. If I were to submit an NIH grant by singly indexing lymphedema to obtain funding for research, I would not be granted for the poor research of the literature that I conducted. I feel that singly indexing is not only wrong with lymphedema because it's so poorly diagnosed, but cellulitis was never involved. Neither of the particular modalities should be singly indexed like IPC or manual lymph drainage or any of the other modalities. In addition to that, chronic venous ulcers, fibrosis was never indexed. I think you're going to miss a lot of the populations, and at least four or five good papers that I know of with wound healing were missed here.

Thank you.

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DR. GOODMAN: I would remind all here, though, that we're not a biomedical research institution, not necessarily talking about NIH grants. We're looking for the availability of rigorous scientific evidence pertaining to a question, the locus of that evidence is almost always found in the peer reviewed journal literature, and that's the body of evidence upon which we're going to focus.

If I may, I need to ask back to something that's going to help us answer question number one. The McMaster people, we're facing in question one an issue regarding the sufficiency of evidence to determine if a set of diagnostic strategies can reliably do two things, reliably identify and, not or, and reliably stratify the severity of secondary lymphedema. In the set that we were given there were four imaging techniques, five quantitative tissue techniques including tissue tonometry, perometry, circumferential measurements, water displacement and bioimpedance, patient reporting, patient-reported symptomatology, physical exam and other. So there are quite a few, there's a

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large set of subsets of techniques to identify and stratify the severity.

Is there in your judgment, based on your technology assessment, sufficient evidence to determine if any of those can be used to determine reliable identification and stratification among that whole set, does any single one emerge as having sufficient evidence?

DR. OREMUS: In terms of severity, I can say that in the articles we abstracted, the answer is no, because there were only three articles that attempted to grade severity of lymphedema. As I had indicated in the presentation, those three grading schemes were most likely developed by the authors of the studies and they made no attempt to indicate how those schemes were developed, nor did they make any attempt to validate those schemes. So there's really no specific evidence to address that issue based on our technology.

DR. GOODMAN: So there were I believe 31 studies of diagnosis, was it?

DR. OREMUS: Yes.

DR. GOODMAN: And only three hold

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anything that looks like severity?
DR. OREMUS: Only three tried to employ some kind of grading scheme to look at severity of secondary lymphedema, that's correct.
DR. GOODMAN: So they weren't good, then, at identifying or stratifying it, they didn't address severity; if only three addressed severity, the balance did not at all then?
DR. OREMUS: That's correct.
DR. GOODMAN: So none of the four imaging techniques, five quantitative techniques, patient-reported symptomatology, physical exam, did that?
DR. OREMUS: That's correct.
DR. GOODMAN: Save for three studies.
DR. OREMUS: That's right, save for three studies, and they were all author-developed instruments specifically.
DR. GOODMAN: All author-developed instruments, and so they weren't the same?
DR. OREMUS: That's correct, they were all different. For example, one of them was developed by the two physical therapists who

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were involved in the study, and it was a grading scheme, there was one grading scheme developed for imaging, but again, it was all developed for those studies, and there was no attempt to assess the validity or provide scoring rules or any sort of a guidepost for someone who wanted to come in and employ those scales.
DR. GOODMAN: Okay, thank you.
Dr. Gorelick.
DR. GORELICK: Thank you. As I'm looking at the big picture here I see two camps that have formed, the technology assessment gives one picture of the story and our speakers give another picture of the story, and it's very different. When you read one thing and you read the other, you're in two different worlds.
So I have a question for Dr. Armer, and the McMaster group may wish to chime in if this dovetails with your expertise. I'm looking at the PEP criteria, and you gave a lovely presentation of stop, caution, go, so on, and I'm just wondering, is there a substantial difference in the rigors of the

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criteria that have been set down here? So I'm looking at, for example, the comment about

having a randomized controlled trial and at least a hundred subjects. I mean, that to me doesn't necessarily mean that we've got the right clinical trial going, it means that there were at least a hundred subjects. So, are we getting into a difference of where we're setting the bar here between how one approach is being taken and how the other approach is being taken?

I know that the one world is very strong in their conviction and I happen to suspect that this probably works, but you know, the other issue is what's the level of the evidence, if you wouldn't mind.

DR. ARMER: Those levels of evidence were used throughout the ONS project, so across other symptoms as well as lymphedema. But I think one of the key differences as I reviewed the technology assessment is that the ONS criteria permitted the review of more than randomized controlled trial, but also expert opinion and meta-analysis of the literature. I think that's one of the reasons our conclusions

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are different between those two sets of findings.

DR. GORELICK: I guess there is a difference obviously. I mean, once you start getting into expert opinion in most of the evidence grading scales you start getting quite a bit lower down. How heavily that expert opinion weighs into this in terms of your highest level of evidence or green evidence, you know, I can't tell you, and you guys sat down and hashed it out in a room and fought over this in e-mails, and I just don't know.

DR. ARMER: Right. And I think there is some clinical judgments involved always when you have clinical experts, as well as research judgments, and it was by consensus that those levels of evidence were assigned, so there was a give and take there.

DR. GORELICK: So this is not a system that I've used before when we've graded evidence, it's very different. And so, is this a system that's being used frequently or was this one that was designed by the group?

DR. ARMER: It was actually from Bernadette Melnick's work at Arizona, it's a

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cited source, and I think it more resembles probably the Australian review of literature than the Cochrane, the Joanna Briggs Institute. So I think it's a very accepted standard,

clearly spelled out. The levels of evidence and the documentation for how those were arrived at are documented actually in the chapters and at the web site, so it's a very rigorous process.

But I agree, somewhat different criteria, and I think in our field the literature is not as great as they are in some other areas, and when we pare it down to perhaps 30 studies, we may be missing some evidence-based practice guidelines that are very valuable for our patients, and as we move forward and build the research, we don't want to throw out what we have but we want to build on that.

I think one thing that's very clear from the activities of today and the reports from today are that there will be clear direction for the research that needs to be done to further build our literature and to build our levels of evidence, and I'm hopeful

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that we won't throw out those smaller studies that build to those more rigorous studies, because that's what we have.

DR. GOODMAN: Thank you, Dr. Armer. I would just remind the group that I don't believe that the literature search was intended to or did detect practice guidelines, you were looking for evidence, not guidance; is that correct?

DR. ARMER: Right, and it was expert consensus and practice guidelines.

DR. GOODMAN: Right. And expert consensus is very helpful in evidence-based medicine but does not comprise evidence.

DR. ARMER: Right.

DR. GOODMAN: Thank you. I believe it's Dr. Gerber next.

DR. GERBER: Dr. Armer, thank you very much for your presentation this morning. I found it very enlightening but it also raises a number of questions. One of them is trying not to (inaudible). And for example, in our question number, first of all on part B, where we're asked to determine the difference, or the confidence that we have with those five

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measures with respect to determination of limb volume or skin elasticity, do you consider those two the same and do you consider them basically primary signs of lymphedema?

DR. ARMER: I'm offering you my opinion here, not an evidence-based result. I

think those are two different criteria, volume is different from skin turgor or skin elasticity. And another parameter that's different is the experience of the patient; a patient with very mild changes can have significant distress from lymphedema, so that's a difference.

DR. GERBER: So, permit me one other final question, and that is, you spent a good deal of time talking about the benefits of psychosocial support, the evidence for that, as well as exercise and the evidence for that, for management of lymphedema. Is it your belief that that management strategy addresses limb volume, skin elasticity, or other information that is important for the management of lymphedema, and if so, what do you mean by lymphedema?

DR. ARMER: To get to the beginning of

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that, I think that the self-management education begins at the time the person comes to be at risk, so it's a risk reduction self-management as well as management of lymphedema once it emerges. And as far as addressing psychosocial aspects and how that would relate to the management of edema, I think the integration of the self-management practices for risk reduction and progression, if lymphedema has emerged, is very important and deserves support.

DR. GERBER: It is important, absolutely, but I'm asking for a metric. So you say the evidence is available that this is an effective strategy for the management of lymphedema, and the metric of that, is it a volumetric, is it skin turgor, is it scintigraphy, is it lymphatic architecture, is it range of motion? I mean, which domain are we talking about? This is a confounder, I think, when we're trying to determine either effectiveness or efficacy.

DR. ARMER: Sure. I better understand your question now, thank you for repeating that. I think the most simple measure perhaps

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will be volume change. I think an additionally important measure is symptom expression of the patient, because sometimes you will see the symptom change before you see a reduction in volume or the other way, so I think those are two important metrics to follow.

DR. GOODMAN: Did I see Dr. Cormier's hand? No. Dr. Umscheid is next then.

DR. UMSCHEID: I have one question and one comment. The question is for the McMaster group. A lot of the comments about the TA and some of the alleged limitations of the TA are based around the language. I looked in your trial flow diagram and I didn't see the numbers of exclusion for language, but do you know offhand about how many abstracts were excluded for not being in the English language, even a rough estimate?

MS. WALKER: If they were not in the English language they would have been excluded at the first level, so if I remember correctly it's 3,000 something, the first level, and then down to about 400. I honestly couldn't give you an exact number. I could probably get the number for you.

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DR. UMSCHEID: I think that number would actually be important, because what a lot of people are saying is that a lot of important studies that would have otherwise met your inclusion criteria were excluded because they were in French or German, and so if your numbers suggest that you didn't exclude a lot of studies for language alone, then that would actually counter that argument.

MS. WALKER: I mean, the thing is they would have been excluded at the first level, that's why they were never documented, but I'm sure we could find them for you.

DR. UMSCHEID: I understand, thank you.

My comment is, I'm a bit concerned that as a group we're taking a very dogmatic approach to having this base of evidence. Usually we talk about high levels of evidence like randomized controlled trials when we're very uncertain about the benefit, there are known risks, or there's strong theoretic rationale for risks. Here we're talking about very different things where I think the prior probability of something like compression of

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working is much higher, we would all guess that it probably works without even seeing a lot of strong data, and the harms of it might actually be lower than let's say a procedure.

So I'm concerned that people are looking for RCTs in an area where perhaps they don't need RCTs. You know, there are classic examples like seat belts in cars, parachute, where all I need is one case study to show me that parachutes work. And I'm not saying that

all we need is one case study here, but I'm very concerned about this search for not only RCTs but large high quality RCTs, multiple RCTs looking at areas where there may not be a lot of risks, the benefit may be based on observation alone if there are reasonable observational trials or even one controlled trial, that may be enough to support its use unless there is evidence otherwise to suggest that it may be harmful.

DR. GOODMAN: Might I ask the McMaster team, your research was not confined to RCTs, was it?

DR. OREMUS: Yes, we included observational studies as well. The major

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criterion when it came to including study types was excluding studies that did not have a comparison group, so if the study had a comparison group, it could have come in had it met our other inclusion criteria.

DR. GOODMAN: So observational studies such as cohort or prospective --

DR. OREMUS: Case control, cohort, they could have been included.

DR. GOODMAN: So if you had some base of comparison, it was included?

DR. OREMUS: Precisely.

DR. GOODMAN: Did not have to be an RCT.

DR. OREMUS: Precisely.

DR. GOODMAN: Did not have to be a large RCT?

DR. OREMUS: We didn't have number restrictions, so an RCT alone would have permitted the study to come in.

DR. GOODMAN: Thank you. Dr. Cormier.

DR. CORMIER: Would a preimposed treatment have been included in that, if they are preimposed are they their own comparisons?

DR. OREMUS: It would depend on the

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structure of the study. I don't believe we included -- no, we did, if it was an observational pre-post study then we would not have included it, but if it was specifically designed maybe as a crossover RCT, it might have come in.

DR. GOODMAN: Dr. Janjan.

DR. JANJAN: Thank you. I have a comment and a question. First of all, being a symptom researcher, I understand all the issues that you're facing as far as the issue of is there subclinical lymphedema. We know just as

standard practice, we don't do blood pressures, we don't draw blood from an arm that's been operated, so that I think is a moot issue. But that being said, I think the data about the cost of cancer care demonstrates that there's more cause through disability and lost productivity than there is from direct care itself. The things that I'm concerned about since patient symptoms are part of our question here, I didn't see a great emphasis on patient reported outcomes, and if you're going to be developing quality analysis on these patients, what factors would you include in the quality

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of life calculation to develop a quality outcome?

DR. CORMIER: Am I allowed to answer?

DR. JANJAN: You know, we talked about pain, we talked about functional outcomes --

DR. GOODMAN: Dr. Cormier is confident that she has a good response. Dr. Cormier.

DR. CORMIER: Andrea Cheville has actually performed a prospective study with lymphedema patients at the University of Pennsylvania where she collected, using the time tradeoff methods, utilities for patients with various stages of lymphedema. It was a well designed study with over 200 patients and she has actually, it's currently in press in I believe the Annals of Internal Medicine, I am a co-author for that study. So we have utilities specifically for that reason, so that we can define qualities in the future.

DR. JANJAN: Thank you. Because what we're talking about is for this type of therapy is not a survival outcome, it really does go to the bottom line of symptom care. This is what this treatment is all about and I guess, I wonder if that abstract was, your abstract was

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published, and whether or not that was included in the assessment.

DR. CORMIER: It would have followed well after the time line.

DR. OREMUS: It wasn't part of our mandate to look at the economic aspects, so even if it was published before our cutoff in March, we wouldn't have included it because it wasn't within our scope.

DR. GOODMAN: Thank you. Thank you for your help there, Dr. Cormier. Dr. Eng is next.

DR. ENG: This is a question for the McMaster group. Was age part of the factor?

Because one of the questions that we need to answer is not only is the evidence adequate, sufficient and of appropriate quality, but how applicable is it to the Medicare beneficiaries, the over-65 population. And the studies that were presented, as well as the studies that we were given to read could not determine what the, you know, whether there were studies in just older patients.

DR. GOODMAN: Dr. Oremus.

DR. OREMUS: Indeed, one of the things

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we looked at was age, specifically for these reasons, and in one of the sets of studies we found that the age criteria, although specified, were not clearly specified. And in those studies that specified age criteria, the range of people included was very large. For example, we found many studies where the age criterion was simply 18 years or older, and many of these studies actually didn't provide a mean or median age of the actual population that was enrolled.

In fact, one of the poorest elements of reporting in the studies we looked at was the patient characteristics. Many studies didn't bother telling us who their patients were, some did, but many didn't. So if a study had an inclusion criterion of 18 or over, that's all they gave us. Other studies, it was under 70, but we don't know how many people were 65 to 70, versus below 65. In ten of the studies in one of the groups the median age was over 50 years, but again, we don't know how many people were over 65 or where they fell on the spectrum. So there was very poor reporting in that respect in these studies.

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DR. GOODMAN: Thank you.

Dr. Satya-Murti.

DR. SATYA-MURTI: Some of the patients do not develop overt lymphedema according to many of the presenters. It may be in the 30, 40 percent range, it may be even higher. If we start looking, we might find more. Like Dr. Pauker was also saying, my question is, there ought to be some kind of a protective mechanism or something inherently that precludes or impedes their progression. Unless we know that, I don't know if we can address that any of our treatments have successfully altered the occurrence, the preclinical treatment.

So I really think there is that big

gap of who does not progress to symptomatic and detectable edema. Finally, I think this would be a good time to have some kind of a consensus statement as to what lymphedema is, is it something -- some of you are talking about Stage I when you can perceive it, and some in the preclinical stage. So as with many things, with sleep apnea and then metabolically active residual cancer and so on, I think it might be

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time to come up with a consensus statement as to what might represent lymphedema, including if there is a preclinical detection capability.

DR. GOODMAN: Thank you. Dr. Cox.

DR. COX: I guess I have a frustration, and I echo what was just said. As an oncologist in staging systems, staging systems that describe a disease are only useful if they're able to stratify groups that have either prognostic meaning or outcome meaning. And when I get a look at question number one, looking at all these techniques, when there's not an agreement about what lymphedema is in a descriptive term, what the different levels of severity are, how it's staged, and all this comes with the lack of natural history data, then it's very difficult when held to Dr. Goodman's criteria of valuable evidence, to answer any of these questions. So I hate to, without posing a question, continue to be a little bit frustrated in a comment.

DR. GOODMAN: Thank you, Dr. Cox. Yes, Dr. Kuebler, or Ms. Kuebler.

MS. KUEBLER: I think what's confusing, as a member of MedCAC for the past

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four years in looking at the evidence on various issues is that here we're looking at medical levels of evidence and nursing levels of evidence. Our presenters have established their own levels of evidence and McMaster uses a different level of evidence, so I think that may be part of the confusion.

DR. GOODMAN: Dr. Umscheid.

DR. UMSCHEID: I just wanted to comment, since the question says sufficient evidence, so for a dangerous pill that has potential side effects, for me that's multiple RCTs. For something that has minimal side effects, again, that might be one observational trial, so it's sufficient evidence, not high level RCTs.

DR. GOODMAN: Dr. Kato.

DR. KATO: I'm just kind of curious

why -- you know, you seem to have a very large group of people here who are in support of, or who are involved in the treatment of lymphedema. One of the exercises that some of the medical societies have done and I have been involved in too is, and this has been mentioned before, is getting together, putting down in

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writing, developing a consensus statement identifying or defining certain things, then throwing it out in the public domain to have criticism, and then come back to it, revise the consensus statement, and then move on. Because a consensus statement by writing everything down will allow you to say, what is our level of evidence and what do we need in order to firm this up? And so it's an iterative process.

I'm just kind of curious why, you know, you have patients, I mean, they're out there. And despite the fact that we have improved, minimized the surgical invasiveness of breast cancer therapy, you know, six percent are still having lymphedema by whatever definition you use. So what has been the barrier to the societies or your groups of developing those statements and moving along in the process that other societies clearly have done for cardiovascular disease, you know, pulmonary disease, things like that?

DR. GOODMAN: You can start, Dr. Armer.

DR. ARMER: I think you make a really

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good point. The International Society of Lymphology consensus was dated 2003 and updated just this fall in 2009, so that's an international guideline, but it's not a numeric guideline, it's based on clinical assessment as well. There's been a recommendation actually out of Nicole Stout's research at Bethesda on how to quantify those stages. But I think we're at a point now in our field where we've got a collaboration in our Lymphedema Framework Project, bringing together the Lymphology Association of North America, the National Lymphedema Network, different partners in the area of lymphedema management and care provision. And we're updating the best practices document from the United Kingdom as a part of our international collaboration.

So I think that we're at a point where we're going to be able to more closely state a consensus that would be acceptable in our

country and perhaps in the international forum. That's been a difficulty with some of our garments being different, even for garments, the way limits are measured in our different countries that are moving forward with research

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in this area, and we need to come to some agreement on what those metrics should be and how they're achieved.

DR. KATO: But is it just that people, the participants refused to agree, or are there other barriers out there? I come from the cardiovascular perspective and you read these guideline statements of the American Heart Association, American College of Cardiology, the Heart Failure Society, Heart Rhythm Society, and on and on, the European Society of Cardiology, all getting together and putting the words on paper. And even if it's a consensus document, at least it's a starting point to say we all agree about this, and then you can move on.

And again, I'm just curious. You know, lymphedema has been around, you know, when I was a general surgeon in training decades before, and we're still looking at the same issues, and it's not for lack of patients.

DR. ARMER: Right.

DR. KATO: So I'm just trying to figure out why is the organizational structure such that you haven't built that process.

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DR. ARMER: I would say there are some factors here in the last two decades with, Saskia's efforts with the National Lymphedema Network have come to a much greater awareness. But in those misconceptions that I addressed today and what was just said by Dr. Janjan, I get probably monthly phone calls or e-mails saying now that we have sentinel lymph node biopsy, my doctors say we can now do blood pressures and we can draw blood and we can give IVs on this affected side because lymphedema doesn't exist anymore. And there are so many misconceptions, it's been such a problem in large numbers, but it's been also felt to be in the past, and it isn't. I think it's also an area where there has been an interest on the international, in the international communications to keep it open to debate and to try to move forward best practices in third world countries versus more developed countries, because our causes are very different from filariasis to cancer.

DR. GOODMAN: Thank you, Dr. Armer. I just want to remind our panel, we've got eight questions to answer, we've got a

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limited amount of time to address them. Our job today is not, unless you want to address it during the discussion period which is question eight, is not to psychoanalyze one of the very important sectors in medicine today, in nursing. It's a very important issue but we've got to look at the evidence as it is now. Later on if we have time at the end of the day we'll try to determine maybe some suggestions about how to get better evidence, if this panel thinks that evidence is needed. Okay. Back to the issue at hand. Dr. Pfalzer.

DR. PFALZER: Thank you. I'm not sure who wants to address this, but relative to question four that we have to address, there are multiple domains listed here, and let me just refresh your memory. In clinical studies of treatments for secondary lymphedema, how confident are you that there is sufficient evidence that improvement in each of the following measures is or is not strongly associated with improved health outcomes? And then the interventions are affected limb circumference, affected limb volume, symptom

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assessment, affected limb function, strength, endurance, range of motion, sensation, et cetera, ADL, activities of daily living abilities, frequency of skin breakdown or ulceration, frequency of occurrence of local infection, quality of life, and then other. And so in looking at the technology assessment, because of the limited number of studies, this is my take on this, many of these domains were not measured from the perspective of this review of the literature. Jane, given your work, because you just documented treatment interventions and you used multiple criteria for diagnosis and how you're following these folks over time, have you done any kind of measurement on the functional level as far as activities of daily living, looking at frequency of recurrence of cellulitis or infection, those kinds of things?

DR. ARMER: I thank you for the opportunity to answer that question. We have the scale, the SF-36, but we have not yet looked at it except as total outcomes. We've looked at it with quality of life, with

symptoms and volume change, like I shared
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today, but we are just now cleaning and analyzing the 30-month as everyone has exited the study, so that's an interim record as people had passed 12 months. As far as recurrence of infection or one-time infection, we collect that data, but again, until everyone has completed the 30 months, we wouldn't have analyzed the infection data. The other sources were two though three, 20 to 30 percent had recurrence of infection from other sources, not from our data.
DR. GOODMAN: Thank you, Dr. Armer. Anything to add, Dr. Oremus, yes, on that question?
DR. OREMUS: Just to respond to your comment, I wouldn't say that the literature search was limited, it was in fact extensive, but it was governed by the questions that we were designed to answer, and within that scope we didn't find that any of the studies dealt with many of those specific issues.
DR. GOODMAN: Thank you. Mr. Weiss, did you have an answer?
MR. WEISS: I have a laser answer to that question.
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DR. GOODMAN: We'll take it. Thank you very much.
MR. WEISS: I would just commend the questioner to chart 12 in my submittal which is labeled lymphedema cellulitis. You have about a dozen and a half references to literature on that subject and this has to do with the health impact of lymphedema.
DR. GOODMAN: Do you happen to know how many of those are randomized controlled trials or otherwise studies with comparators, direct comparators?
MR. WEISS: Yes, sir, probably zero.
DR. GOODMAN: Thank you. Dr. Fischer.
DR. FISCHER: Since we're moving along in the questions, and five, six and seven I assume will occupy us in the future, I would just like to ask a simple question about pneumatic compression devices. Is anybody aware of a randomized prospective trial in which compression garments or CDT has been randomized against pneumatic compression devices.
SPEAKER: No.
DR. GOODMAN: Hold on. If someone has
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an answer to the question, they have to come to the microphone and I will be glad to recognize them. Who might that be?
SPEAKER: Can you repeat the question?
DR. GOODMAN: I thought someone said yes or no.
SPEAKER: I didn't hear the question.
DR. GOODMAN: Repeat the question, please.
DR. FISCHER: The question is, the current -- everybody seems to have accepted that a complex decongestive therapy is the standard of care at the present time, and we're going to be dealing with pneumatic compression devices as a question. All I want to know is, has there been a randomized prospective trial of complex decompressive therapy versus pneumatic compression devices?
DR. GOODMAN: Let's start with McMaster and/or Dr. Armer. Do we have an answer to that question?
MS. WALKER: Maybe one.
DR. GOODMAN: There may be one, I am told.
MS. WALKER: I would have to check for

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you, but I believe there is one where there's, complex decongestive therapy is used in both instances and then IPC is added on to one group. So it's not separate, it's not just IPC versus CDT.
DR. GOODMAN: It's not head to head one on one, it's a combination versus one; is that correct?
MS. WALKER: Yes, but I would have to double check.
DR. FISCHER: Is it a crossover trial?
MS. WALKER: I don't know that.
DR. OREMUS: I think I recall seeing it on the slide and I don't believe it was a crossover trial. It was two arms and it was combination therapy, and I think IPC was added as a third element, but we'd have to look back to be sure.
DR. GOODMAN: I'd like to see if you might find that in the hard copy of your slides, if that's possible, we would appreciate that. Any questions of the panel with regard to these? Dr. Satya-Murti.
DR. SATYA-MURTI: The McMaster panelists, on the table of diagnostic tests

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that you had put out, there was one that spanned across all the studies, and namely when

the diagnostic study was used, the index test and the reference standards were not blindly assessed, you kept repeating that, and also in the tabular form. So it really brings up the issue of validity if you were to be the person doing the bioimpedance or perometry and also subsequently had been privy to what the clinical diagnosis was, certainly the quality of assessment goes way down. Is that not correct?

DR. GOODMAN: Dr. Oremus.

DR. OREMUS: Indeed that's the case. If you're going to be doing a diagnostic testing study, the most preferable approach to conducting such a study is to have the individuals who are rating or assessing the test results to be blinded as to the patients' true diagnosis. And if it's multiple raters, you also want the ratings to be done independently, precisely to avoid knowledge of the true diagnosis or knowledge of someone else's rating to influence your own rating. So certainly if the independence or the blindness

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is violated, it can certainly affect the validity of a diagnostic testing study's result.

DR. SATYA-MURTI: Okay.

DR. GOODMAN: Thank you. Other questions on this issue? Dr. Umscheid.

DR. UMSCHEID: For IPC we heard from a lot of the presenters that the actual device itself matters, and I know there were a number of, I think it was RCTs that looked at IPC, and I think it was something like four showed benefit, one showed harm compared to laser, and then five didn't show any benefit. Were there any sensitivity analyses that were done by the McMaster group about, for those IPCs that were beneficial, were there certain characteristics of them that were different than the ones that were not shown to be beneficial in studies, for example multiple chambers or different compression rates?

DR. OREMUS: The studies that employed IPC did use in many cases different IPC regimens, you might have had an X chamber versus a Y chamber RCT, but they were in two different studies and the studies were too

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heterogeneous in terms of patient populations, outcome measures, so it was impossible to draw any general conclusions about which type of device would be better based on the studies

that we examined, so it's inconclusive.
DR. GOODMAN: Okay, thank you. I saw that Dr. Stewart wanted to comment. If you could remind us of the question that you're going to address, and do so in a concise fashion, please.
DR. STEWART: I was actually going to address his question and then back up to another question.
Regarding the pumps, I made the point in my lecture that single chamber pumps should not be used in lymphedema, they can cause harm to the patient by refluxing the fluid into the affected limb. There are multi-chamber compression gradient pumps that end at the roots of the limb and these are associated with fibrosis forming at the root of the limb and causing additional problems with increasing lymphedema over time. The newer pumps that are lower compression and include truncal pieces can actually move the fluid beyond the root of

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the limb and into the trunk where there are functioning lymphatics. Again, I also made the point that these are considered adjunctive devices to CDT. I hope that answers your question.
The comment that I was interested in making was regarding the actual infancy of lymphedema. While you may have been encountering lymphedema for decades, the treatment was introduced by Dr. Lerner just two-and-a-half or three decades ago, and so our country is very new to the treatment of lymphedema as introduced by Dr. Lerner from Europe using CDT. Prior to that watermark, the only treatment approaches that were utilized in this country were pumps, or completely ignoring the problem and telling patients that there is nothing they could do, they had to learn to live with their lymphedema. So we've come a long way in a mere 25 or 30 years.
And we're in the process at this moment of creating an international consensus with our colleagues in Europe, Australia, Canada, New Zealand, Japan, in trying to create a consensus as to diagnostic criteria and

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treatment for lymphedema, and I'm proud to be a member of the American Lymphedema Framework Project, and that is exactly the mission we've set for ourselves.
DR. GOODMAN: Thank you, Dr. Stewart.
I believe Dr. Whitworth wanted to make a brief

comment.
DR. WHITWORTH: An answer to a question, laser answer to one question, and that was, does this apply to the Medicare population? In the American College of Surgeons oncology group Z-10 study, 5,300-plus patients, there was a statistical association with increasing age, and that is in agreement with all of the other research that's been done.
DR. GOODMAN: An association between what and what?
DR. WHITWORTH: Development of lymphedema and increasing age.
DR. GOODMAN: So that's the natural course of the disease.
DR. WHITWORTH: No. If a patient is operated on at age 75 --
DR. GOODMAN: Oh, once there's been an

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intervention, thank you.
DR. WHITWORTH: Exactly. So there's a definite association in that large study, and that corroborates many previous studies. The other association is body mass index, which is not necessarily Medicare population.
The other brief comment I will make is that there are components of lymphedema diagnosis that resemble the same thing with regard to pain, we've had a lot of difficulty with pain over the years because people would say what's your diagnostic criteria for pain. We finally had to end up saying, if I say I have pain, I have pain. It's not that simple with lymphedema because we have objective measures, but I think you're hearing some consensus in this group that it's just not completely nailed down.
DR. GOODMAN: Thank you. Dr. Eng, did that help answer your earlier question?
DR. ENG: Thank you, but there isn't enough.
DR. GOODMAN: Ms. Thiadens, do you have a specific answer?
MS. THIADENS: I would like to add to

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Dr. Stewart's comment. In addition to the limitations that we have and continue, the main reason why we are struggling in this country and why we are so behind is because the lymphatic system is not taught in medical school, it's not part of the medical school curricula. So that's why the majority of the various disciplines have actually no knowledge

or interest in the lymphatic system, because they are not educated in the lymphatic system. That's what I'd like to add to this.

DR. GOODMAN: Thank you. That's not directly relevant to the evidence, but it may be relevant to generation of future evidence. Thank you very much.

Further questions at this time from the panel on any of the evidence questions in particular? All right. We'll try to be flexible about our agenda. Our agenda tells us that by now we should be having our initial open panel discussion among ourselves as a panel, which I suggest we do. However, if during this discussion you would like to inquire of any of our presenters, that's quite all right, so it's not going to be really just

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amongst ourselves, do feel free to ask further questions of them if you would like.

With that in mind, let me suggest that there's no better place to start than our own question one, and we might have a question about that, unless Dr. Pauker has another comment.

DR. PAUKER: I had a comment about questions one and two together. Looking at these questions now, I've been reading question one and two, and I am now confused.

DR. GOODMAN: You must be the only one, Dr. Pauker, or the only honest man in the room.

DR. PAUKER: Questions one and two have tacked onto the end three words, including subclinical disease, and it seems to me that the answers to one and two might be different for clinical disease. The problem in voting on answering that question, had I realized it before I would have pointed it out, and I think questions one and two are misphrased with that error, but I just raise the question, and I hear mumbling down here, so I'm probably not the only one.

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DR. GOODMAN: Thank you, Dr. Pauker. Well, we can, let me suggest two ways we might approach this, and we would be interested in your counsel on which you would like. The broader encompassing question would allow that if any of these diagnostic modalities could both reliably identify and reliably stratify the severity of disease, even including subclinical, if you had a yes, that's a very expansive and generous way of phrasing the

question. Or we could phrase it more specifically and for the moment just cross out including subclinical disease, answer the question about non-subclinical disease, and then having answered that, we could affix some additional comments about your impression with regard to whether any of these would be useful for subclinical, we could do that as well.
DR. PAUKER: Because if you look at them by themselves, there might not be good evidence, or impressions. If there is evidence, it would be evidence of clinical disease, so putting them together doesn't add anything to this issue but I think may be more confusing, so I suggest we break them apart.

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DR. GOODMAN: You want to break them apart.
DR. PAUKER: That would be nice.
DR. GOODMAN: Okay. So Dr. Pauker's Boolean algebra says not or, he wants them separately addressed; is that correct?
DR. PAUKER: Yes, sir.
DR. GOODMAN: Thank you. Anything else before we proceed to question one? Dr. Stewart, did you have a very important point to make before we proceed?
DR. STEWART: I just wanted to say that bioimpedance is relatively new and it can in fact diagnose subclinical disease in the upper extremity, at this point, we are limited to the upper extremity. By its nature, subclinical disease is not well diagnosed with the usual medical history, physical exam.
DR. PAUKER: That's why I asked the question.
DR. GOODMAN: Thank you, Dr. Stewart, for that.
Okay. Let's have a go, then, at question one, and I will start, if you don't mind. What I heard from the technology

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assessment was that of all the 31 included studies on diagnosis, exactly three said anything at all about severity. I see the McMaster people nodding their heads. I heard that of those three that addressed severity, none did so using the same scale or approach, correct? Okay.
Now I will make it tough for you at McMaster. Can you tell us of those three, did any stand out as actually being able to reliably identify and stratify the evidence, was there any one of those that did well for

that dimension?
DR. OREMUS: It was really not possible to conclude that because they were all, as I said before, author-developed scales employed in the author's own studies. So we have no way of independently validating whether those scales work or not.
DR. GOODMAN: Let's be real generous right now. Let's say that the author-generated scales, let's take for granted for the sake of argument that those are valid scales. Did the authors themselves using their own self-generated scales, find that any of these

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was good at not only identifying but stratifying severity?
DR. OREMUS: The authors didn't specifically comment on the goodness of their scales for doing that. I think that they had developed their scales to allow them to do that but they weren't really thinking about evaluating the scales themselves.
DR. GOODMAN: Okay, thank you. Dr. Gerber.
DR. GERBER: I'm still having a bit of confounding difficulty with understanding what we mean by lymphedema. I'm sorry to be a dog with a bone, but I am having a problem. For example, scintigraphy may be terrific at identifying lymphatic architecture; is that what we mean by lymphedema? Bioimpedance may give us some very important information about volume. Is that what we mean by lymphedema? I am concerned that we are confounding a technological measurement of something around which we haven't yet reached consensus and that is a problem. Because if we say we have confidence, that we have confidence that, let's say that lymphoscintigraphy is a reliable and

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valid instrument, against what gold standard, against what diagnostic criteria? That's what we have not yet been able to nail down as far as I can tell.
DR. GOODMAN: Thank you, Dr. Gerber. I will try to help and then maybe other panelists can kind of chime in. First of all, the three examples you gave would be, if the data were there to support them, would be surrogate measures of a clinical concept, where the clinical consent is a perhaps as yet not well defined lymphedema, whether it's bioimpedance or what you see on a screen from lymphoscintigraphy or what have you, those are

surrogate measures of data that may or may not be well associated or sufficiently well associated with this clinical concept, so that's for starters. Go ahead.
DR. GERBER: So then we need a matrix which gives us necessary and sufficient conditions, and we have heard from Dr. Armer very eloquently that it's symptoms, and Dr. Janjan that it is symptoms as well as appearance. I mean, most of us who have spent our lives in the clinic know it when we see it,

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I hate to use that hackneyed phrase. But the question of being able to agree that there is a measurement tool that universally defines this diagnostically, as opposed to can be used as an outcome measure, to reliably identify significant change is a very different matter.
DR. GOODMAN: Thank you, Dr. Gerber. And at this point though, Dr. Gerber, insofar as the inevitability of our asking you to vote on this question, do you think that there's not enough information upon which to base your vote, or something else?
DR. GERBER: It's that I could not base my vote on what I have read and what my options are on here because without calling the question, I can measure severity, that I don't have a problem with, but severity of what? And then we get into is lymphedema a combination of symptoms, physical findings, and the objective, bioimpedance and perhaps architectural measurements all come in together with some metric that tells you this is sufficient, one of these or two of these or three of these, or whatever. We're not there yet. So I would have great trouble putting a number in terms of

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expressing my confidence as applying this to the measurement of lymphedema.
DR. GOODMAN: So you have little basis upon which to be confident?
DR. GERBER: Right.
DR. GOODMAN: That suggests to me how you might answer the question, but of course that's yours to answer.
Yes. Would you like to identify yourself.
MS. MCBETH: Maureen McBeth from Mercy Medical Center. I don't think there is anyone in this room who would disagree with the definition, I'll read it directly, that every student going through CDT training would know. That is, lymphedema is the abnormal

accumulation of a protein-rich fluid in the interstitium which causes chronic inflammation and reactive fibrosis of the affected tissue. And yes, the question is which metric do we use to measure at what level of the disease, and Stout, et al., did bring something up with breast cancer patients for example, they proposed a wonderful diagnostic criteria. But we're looking at many different things and

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that's the problem, but I would say that this definition is common to all of them, whether that's the subclinical accumulation, the little 83 milliliters, or whether it's the gigantic elephantiasis. It's just, you're measuring apples and oranges.

DR. GOODMAN: Thank you, Ms. McBeth, that's very helpful. Dr. Pauker, and then Dr. Satya-Murti.

DR. PAUKER: Very quickly going back to question one, because the question says identify, and we don't know what identify means, how do we -- do we just put them together and say no?

DR. GOODMAN: Yes. We did go over these questions as best we could about a month or so ago. In this case I think we need to go with the Boolean and, which is, you need to satisfy both in order to be confident for the purposes here. Thank you. Dr. Satya-Murti.

DR. SATYA-MURTI: Ms. McBeth, listening to you then, the question of subclinical versus testing is relevant, because you just gave more of a pathophysiologic definition than a clinically oriented one, and

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yet, just about all the evidence that either McMaster analyzed or was presented to us treated the condition as clinical and preclinical, so none of the evidence applies to any of the questions we could answer if we took your definition that it is just an altered pathophysiologic status with no, it's no respecter of clinical appearance. So actually question one then is a bit circular. If you say if it is subclinical then only these tests would identify it, it lifts any clinical concerns, wouldn't it?

DR. GOODMAN: Thank you, Dr. Satya-Murti. Other questions, or points I should say, about question one? Dr. Gerber.

DR. GERBER: I just wanted to make a comment about the Stout report, that we both -- Cindy Pfalzer and I were co-authors on that.

We measured volume, we did not measure lymphedema in this generic multiple named set, and what we were talking about there was very simple, it was a change with respect to time in limb volume. It doesn't address the issue of physical exam or symptomatology.
Apropos of what Dr. Satya-Murti had

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just mentioned earlier, I do want to just comment that if we wanted to be successful in taking successive measurements in that population, and we had our fair share of trouble with that, even though it was in a military hospital, and the rigor and the attention to reporting for duty at your assigned clinics is high, we had many lost to follow-up, and we did it even within the context of addressing the issues of function.
If one were to look only at limb volume as the measurement of choice, I think the likelihood of getting repeated measures successfully would be much lower. So I think this is, this is not a trivial issue in my opinion, it is the issue of addressing a very complex physiological and biopsychosocial model. And by putting the context as we have in question one makes it extremely, there are two many ands and dependent clauses here, and unfortunately, it sets up a matrix that we need to look at as potential contributors to a complex biological and social problem, which is that of lymphedema. That was my comment about that.

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DR. GOODMAN: Thank you. I would suggest that the best that we're going to be able to do today by mid to late afternoon is forge our way through the storm as best we can with your best understanding of the concept of lymphedema. I did think we clarified the "and" with regard to reliably identifying and stratifying, we've got to be able to do both, and we will also address as a sidebar but no less significant sidebar, of subclinical disease, we'll be able to do that.
Let's talk now, if you don't mind, about question two a little bit. Remember that question one was is there sufficient evidence out there upon which to base any sort of finding. It sounded as though there was at best limited evidence depending upon your perspective. Question two would say if you thought there was an item in question one for which there was sufficient evidence, do any of

them actually do this? In other words, you've got enough evidence, whatever you deem sufficient. Do any of these among those that have evidence actually reliably identify and stratify severity of secondary lymphedema, and

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perhaps do the same for subclinical disease? Any comments by the panel at this point about identifying any one of those diagnostic modalities that does both identify and stratify the severity? Comments, questions? Dr. Umscheid.

DR. UMSCHEID: And we're assuming here that the individuals performing the task are qualified to perform it, that's an assumption that we're making.

DR. GOODMAN: Well, we're looking at the evidence that's on the table, your judgment insofar as how well the performers of those peer reviewed studies, how well qualified they might have been, yes. So that is not an explicit question here. Any questions or comments or discussion that we have among the panel, and/or questions relevant to this for our presenters or others? I don't see any. Okay. Thank you. Now remember, we will come back and vote on these, of course.

DR. STEWART: May I make a comment?

DR. GOODMAN: Dr. Stewart would like to make a comment pertaining to which question,

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Dr. Stewart?

DR. STEWART: I was going to state that the clinical evidence for the medical history and physical exam allows the physician or the treater to both assess the presence of lymphedema and stratify it, which is why that is used primarily as our tool for assessing lymphedema.

DR. GOODMAN: So an individual clinician with a particular patient you're saying can make that judgment in that clinical situation.

DR. STEWART: Correct. The only state that we have difficulty would be the subclinical, and then we would need to depend on other measures such as subjective reporting, which might then lead to bioimpedance testing.

DR. GOODMAN: Thank you. So a physician with a patient would make his or her clinical judgment based upon his or her understanding of available evidence, and apply it for that individual patient in that setting.

DR. STEWART: Correct.
DR. GOODMAN: Thank you. Let's look at question three now, if you don't mind.

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Let's talk about that as appropriate. Question three asks, how confident are you that secondary lymphedema can be classified into prognostic stages of severity, that is, staging that is useful to guide choice of therapy or predict response to therapy? So again, we're looking at these diagnostic modalities and trying to understand what their prognostic power is, especially insofar as staging is concerned. I know that we had several presentations that talked about staging, whether it was I, II, III, or zero, I, II, III. Comments, questions about prognostic capabilities here? None on that.
DR. STEWART: May I make another comment.
DR. GOODMAN: Just a moment. Dr. Cox first.
DR. COX: This I guess from my background in oncology comes into play. Is there any document or any presentation or even the consensus panels that have met, that have sought data to answer that question? Because I didn't see any in the reading or the like, that you could validate a staging system for

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lymphedema that would predict outcomes or response.
DR. GOODMAN: Thank you, Dr. Cox. Dr. Stewart.
DR. STEWART: The 2006 best practice framework study from the International Lymphedema Framework study that was published in Britain actually makes an effort, and it is a consensus document. These are the leading experts in lymphedema and lymphology in the world coming together and saying this is correct, this is the way, this is what we see clinically. And there is on page 44 on a horrible copy in the handout I gave you, of the various stages of lymphedema and the recommended CDT protocols that would follow based on the staging of the lymphedema. And so I think that as we are moving forward with our framework projects, we are agreeing and having greater consensus on how the staging is useful to help us choose our therapies and move forward.
DR. GOODMAN: Thank you, Dr. Stewart. So Dr. Stewart, that was a consensus statement,

correct?
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DR. STEWART: Correct.
DR. GOODMAN: So Dr. Cox, that was a consensus statement; is that okay?
DR. COX: Well, I hear what you're saying, I saw that. It resonates to me in a sense what Dr. Fife says, because I treat patients with this disease and I know there's effectiveness in it, but it seems like we're caught betwixt evidence and what we do in practice, efficacy. And so when I hear that you have a consensus staging but we don't have any data that underpins it, that says that it prospectively did predict these different outcomes.
DR. GOODMAN: Thank you, Dr. Cox. Let's look now at question four, please. Now we're moving into treatment, into therapy, and we will want to have any discussion as needed at this point on the following: In clinical studies of treatment or treatments for secondary lymphedema, how confident are you that there is sufficient evidence -- again, this is a question of whether there's evidence in the first place, not about what it says yet. How confident are you that there is sufficient
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evidence that an improvement in each of the following measures is or is strongly associated with an improved health outcome? And there follows a set of eight measures and a ninth category called other.
Let me point out to the panel, as I recall when we were discussing questions a month or so ago, perhaps it was longer, that we added to an original draft question not only that there was an improvement in each of the following measures, we said or is strongly associated with, so this allows consideration of validated surrogates, not just the more strict or hard to obtain outcome measure.
Dr. Pauker.
DR. PAUKER: Yes. As I now review this question in terms of quality health outcomes, is the change in quality of life assessment an improved health outcome, is a change in symptoms an improved health outcome, is any of that relevant to whether or not the modality changes these benefits in fact if that change is connected to a definition of what is an improved health outcome improvement. So again, I'm concerned about this, and I
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apologize.
DR. GOODMAN: No apologies required, Dr. Pauker, of course. Our understanding is if one looks at the literature, what impact these therapeutic interventions have is measured in various ways, and they fall loosely under the rubric of outcome measures. And so sometimes one might think that something's a true outcome, some others might think that measure is a surrogate outcome, and I think that some of these are sort of grouped together here in this setting and it is your judgment to make whether or not there's any impact.
DR. PAUKER: I guess I have a problem here because clearly it's not saying does the treatment improve the outcome necessarily. If one of these things is improved, is outcome improved, and is management improved, so in some perverse sense, it's an illogical question.
DR. GOODMAN: I think I get what you're saying.
DR. PAUKER: If IPC improves health outcomes, is health improved? And that's not a question about lymphedema, it's a question

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about quality of life assessment or ADL assessments, so do you understand why I'm confused?
DR. GOODMAN: I think so. I would take, for my perhaps more simplified way to look at this, I would consider that there is a set of interventions and there's a set of possible outcomes, and we're asking ultimately whether or not there is enough evidence that any of those interventions has an impact on any one of the eight listed items there, and nothing more than that. Dr. Singh.
DR. SINGH: Again, to clarify this question, I think, are we asking that on any of the treatment modalities improve the following health outcomes, is that what the question is, because these are health outcomes, limb circumference, limb volume, symptom assessment, limb function, ADL, progressive skin breakdown, these are to me health outcomes. Isn't that what the question is? There isn't like a separate health outcome that's outside the nine or ten health outcomes that you're looking at. I think what you're trying to ask is are any of the different modalities associated with an

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approved health outcome listed below itself, so that is the question.

DR. GOODMAN: That's how I would interpret it.
DR. SINGH: So it's not a separate health outcome, these are the outcomes.
DR. PAUKER: So on each one of these we could vote four or two or one.
DR. GOODMAN: That's correct.
DR. PAUKER: Okay.
DR. GOODMAN: And some of those we might consider primary endpoints and some might be surrogates, but these are the outcomes about which we care.
Dr. Jacques, did you have a comment?
DR. JACQUES: Yeah. Louis Jacques, from CMS. When we were first crafting that question, what we were looking at is essentially trying to get at your recommendations as to what ought to be the preferred or desirable outcomes if someone were going to do a clinical trial on lymphedema treatment, assuming one has a case definition of lymphedema, which I'm not sure of based on how far the meeting has gone today.

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So essentially if one looks at, for example in treatment of diabetes, people thought that hemoglobin A1c or glycohemoglobin was a good surrogate outcome. As it turns out, if you tightly control hemoglobin A1c you probably kill 25 percent more patients than you would otherwise. So when one looks at these particular potential outcomes for a clinical study, do you think there's enough evidence that some of these actually correlate to what we might call meaningful patient-oriented health outcomes, versus gee, Mrs. Jones, your foot is 250 cc's smaller than it was before, but by the way, you still can't walk and you have an ulcer on your foot, and you can't stand up straight. So we're trying to get some valuation from the panel around that issue.
DR. GOODMAN: Yes, and that valuation will be very useful in the subsequent question. Dr. Singh, and then Dr. Pfalzer.
DR. SINGH: What Dr. Jacques just said is very different from what we were talking about. I think what you just said is do any of these things mean anything, but that's not how at least a minute ago Steve and I were

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interpreting the question. We were interpreting it that any of the treatments were going to make any change in one of these eight measures, and Dr. Jacques just said no, that's

not right.
DR. UMSCHEID: That's question five.
DR. JACQUES: Yeah, that's question five. Question four is really a prelude to questions five and six.
DR. SINGH: But I think what you just asked, or what you just said in your comment is no, that's not what I want to know, I want to know something else, a platonic health outcome, that even if I improve your limb volume, if you die, that's not a great outcome. So, are you like now talking about another health outcome that's not listed, a platonic health outcome as it were?
DR. JACQUES: No. The point of question four quite literally, because in question five and question six we essentially ask you, do these treatments essentially affect or improve health outcomes. So logically, because there are many different types of outcomes that might be measured in clinical

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studies that one might assign differential evidentiary weight to.
So for example if you were doing a cancer trial and a patient in a particular treatment arm not only had improved survival but improved symptoms and decreased burden of their disease, would you value that more than someone whose outcome was, well, your PET scan doesn't glow as much as it did before. Both could have been very well designed methodologically rigorous trials, but one might consider them differently in making a decision, whether about treatment or policy, simply because the outcome is more important in one than the other.
DR. SINGH: So Steve was right, you really want us to look at outcomes beyond these that are listed.
DR. JACQUES: What we were just saying is look at those. If the panel believes that there is some other outcome that is worth conversation and voting, then clearly it is up to the discretion of the panel to do that. We simply put those out there to have a list because if we didn't have anything, there would

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be no starting point.
DR. SINGH: So right now what we are supposed to do is to see if any of these measures are associated, enough evidence to suggest that any of those will affect a change in these outcomes, it's not really changes in

another platonic outcome that might exist such as happiness and life and so forth.
DR. JACQUES: The only point of question four is, do you think these are desirable outcomes in clinical trials? I mean, if you were to reword the question, hopefully you would answer that based on evidence.
DR. SINGH: That's a very different wording now.
DR. GOODMAN: Dr. Singh, you have to speak in sequence for the benefit of our reporter. I'm sorry that we should do that, but we need to do that. So, what Dr. Jacques has so kindly clarified, is that question four does not ask about the impact of any particular intervention on an outcome. He is saying, do these one through eight or nine concepts or constructs comprise something that you would recognize as an improved health outcome. And

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then we will use that information in the two subsequent questions.
DR. SINGH: Okay. So let me repeat then. What you're saying is that the question four says, do any of these listed measures comprise what we might consider as a relevant health outcome? Is that now what the question is?
DR. JACQUES: Let me use the metaphor for diabetes. So if I gave you a list and I wanted to know if any of the following potential reported outcomes reflected improved health outcomes for patients with diabetes, and I said random blood glucose, fasting blood glucose, hemoglobin A1c, et cetera, whether they were biochemical markers or whether it was, you know, reduction in ulceration, improvement in diabetic retinopathy, et cetera, et cetera, improvement in glomerular infiltration. So the question is essentially, if someone is going to do a trial, should they spend their time on some surrogate outcome that the panel does not believe truly would reflect an improved patient-oriented health outcome, or should they in fact if they're going to do the

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trial, do it, quote-unquote, right the first time, with an important outcome.
DR. GOODMAN: So we're being asked to say on a scale of one to five how confident we are that any of these eight represents what we would consider to be an important endpoint.
DR. SINGH: Right. That is a very different question from what I understood.

DR. GOODMAN: Thank you.
DR. SINGH: Thank you too. I think the two of us didn't understand the question. The third time is the right time.
DR. GOODMAN: You were hardly alone. Thank you, gentlemen. Okay. Now that we've clarified the nature of the question, would anyone like to address it? Yes, Dr. Gerber. Or Dr. Pfalzer, were you first? I couldn't tell from this end of the room.
DR. PFALZER: That's all right. So this actually, the clarification certainly helps but it doesn't get rid of one of the fundamental problems, and I will use limb volume just as an example here where I could really use some help in trying to see my way

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through this. Because if I think about a hundred milliliter reduction in limb volume you may say well, that's not important because they can get their shoe on, they can fit into their sleeve, that volume change is not clinically significant. But that limb volume change may be a fact even with subclinical lymphedema, be predictive of lost physiological capacity in the lymph system and so it could be highly significant.
And I really struggle with trying to sort out this issue of when is it important and when isn't it around something such as limb volume. And while it's probably our oldest measure, it is a highly functional measure when it's of volumes seriously impaired from a quality of life and function perspective. It may also be predictive in a subclinical population of further problems downstream. So, does anyone care to address this issue of what kind of marker it is and when it's important?
DR. GOODMAN: Any takers on that question? On that question, Dr. Pauker, question four?
DR. PAUKER: I'm looking at question

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four. The question says is there evidence. What do we mean by evidence, do we mean evidence in outcomes or evidence of quality of life is important. I don't know if I can believe it's important, but when we have evidence of importance of the measure -- I guess the question is phrased in a rather odd way.
DR. GOODMAN: Dr. Jacques, are we looking for evidence of the importance of these

measures?
DR. JACQUES: Let me go back to diabetes again, and let's go back to hemoglobin A1c. One might before the publication of the ACCORD trial have felt based on whatever the prior evidence base was that hemoglobin A1c was in fact an important relater of improved health outcomes in a diabetic trial. After the ACCORD trial results were published someone's opinion, I hope, would have changed. So in the same way, I realize that at some point the panel members are simply going to have to make an individual judgment. Our hope is that judgment would be informed by evidence. I realize that in some cases, because it is an individual

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judgment, that individuals may weigh that evidence or consider that evidence differently.
DR. GOODMAN: Thank you. And so, Steve, sort of a bivariate answer there. Basically there is evidence to be considered and then there's your judgment of the confidence that you've got in it.
So, so anything more on question four?
Dr. Umscheid.
DR. UMSCHEID: I just wanted to reiterate my point earlier. I think it's really important that the committee does not take a dogmatic approach to evidence-based medicine. Here the question is sufficient evidence. If such evidence is your experience, your clinical experience over 30 years that quality of life assessments are important, then you have high certainty, you don't need an RCT for that. If hemoglobin A1c, you've never heard of it and you want to have a study to associate lower hemoglobin A1c with outcomes that you think are important, then you do need an RCT.
So I really recommend that people look at the phrase sufficient, and think about

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clinical experience as a part of that evidence, even if it's on the lowest rung.
DR. GOODMAN: Now remember, we are not here treating patients, which is a good thing, but evidence-based medicine, I will go back, evidence-based medicine is the application of evidence in a clinical setting. We're not in a clinical setting. Our charge is to look at the body of evidence, not to treat patients here today. Okay. Dr. Gerber.
DR. GERBER: I would just like to address number nine, and if I heard Dr. Armer

correctly earlier, she spoke about the number one phenomenon, which was marginalization of patients who had lymphedema -- I'm sorry, Sheila, sorry. See, I give you credit for everything because you gave such a great presentation, so right. It was about marginalization, it was about loss, and fundamentally about social integration. So I think that the issue of application of the international classification of function might be a useful construct here, in that social integration and the context of activity, not just limb activity but person activity, should

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be added under the other as a health outcome.
DR. GOODMAN: Dr. Gerber, state one more time exactly what the other should say.
DR. GERBER: So the other, another improved health outcome ought to be social integration and societal participation, or something that looks at both activity and participation if you use the ICF rubric.
DR. GOODMAN: Does anyone on the panel object to that suggestion? Do keep in mind that we're still going to be looking for evidence that that's a useful construct as an outcome, of course. Thank you, Dr. Gerber. Dr. Eng.
DR. ENG: In the geriatrics literature we use the term IADL as the surrogate for integration with societal function, such as transportation, money management, housekeeping and so forth. And I think I myself, if we were to add another outcome to this list, would be the IADLs. I personally don't like the term IADLs, but that's what it's come to mean in the geriatric literature.
DR. GOODMAN: Could you just define the distinction between that and ADL?

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DR. ENG: The ADLs are the personal functions that a person needs to do for just living in a certain environment, such as bathing, dressing, grooming, toileting, walking, eating. The IADLs are things that, activities that allow a person to perform activities outside of, what we call the social activities such as money management, transportation, shopping, housekeeping.
DR. GOODMAN: And the I in IADL stands for?
DR. ENG: Instrumental.
DR. GOODMAN: Could I suggest that that might fall within the suggestion that Dr.

Gerber just made insofar as the social integration and participation are concerned? Would that be close enough, Dr. Eng?
DR. ENG: It's up to Dr. Gerber.
DR. GOODMAN: Okay. Dr. Gerber.
DR. GERBER: IADLs basically have as their focus the instrumental, the accent is on instrumental, you need to use implements and interactions in a way to enable you to do essentially the executive functioning in your life, balancing your checkbook, making your

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appointments, et cetera, but that is not really at the same level that I was referring to, because socialization and societal participation is fundamentally about the quality of your interaction with other people, not so much about whether or not you can take care of the usual activities in your life. IADLs' focus is almost on the cognitive and your ability to utilize your executive functioning, the other one is more social and interpersonal and interactive, so there are differences between them.
DR. GOODMAN: Thank you. Dr. Janjan.
DR. JANJAN: The McMaster talked about 60 studies. Did any of these studies involve social integration or IADLs?
DR. GOODMAN: Dr. Oremus?
DR. OREMUS: No.
DR. GERBER: There is a literature certainly on this, it may be that you didn't search for it, but there certainly is literature that looks at the quality of life issues and the social integration and the participation, so I would say that it may not be listed but it's out there.

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DR. GOODMAN: Thank you. Dr. Fischer.
DR. FISCHER: We asked them to do a technology assessment, they went and reviewed a large number of papers. The papers were imperfect, they did the best they could. But in the future when you do another one of these, look at the abstract at the end of most articles in the foreign literature, they're usually in English. Having said that, if we discard everything of evidence, which is what I'm hearing, we don't have any purpose in being here. Theoretically this is an evidence-based exercise. The evidence may not be very good. People are talking about meta-analysis of consensus. I'm not the world's greatest

statistician, but I have never heard of a meta-analysis of consensus. So if we're going to throw out everything in an effort to reach a certain outcome, there's no point in being here. We asked for a technology assessment, they've done the work. It may not make everybody happy, but to keep on going on through these and bringing in other factors which may have no relevance and no evidence, I

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think is wrong.

DR. GOODMAN: Thank you, Dr. Fischer. I just want to make a suggestion about how we handle this other category. I fully appreciate the difference between the concepts of IADL and the concept that Dr. Gerber brought up. Given that we have had a prior look and expect to see nothing or close to nothing, I would just suggest that we rename number nine as social integration and other social operations or activity, social integration and/or IADL for now. In our discussion later on, if anybody thinks that this is an important area to address for further evidence generation and construct validation, that will be just fine, but I don't want to get too far into developing a list of things that some day could be useful if we know now that it's probably not in the current body of evidence, though we might wish otherwise.

Dr. Singh.

DR. SINGH: I was just going to raise more or less a process question. As I look at these questions and I studied the total number of questions, because we have to vote on each

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one of them, there are 48 of them. And if we start going around the table and voting on each one of them, and even if it takes us three minutes or four minutes per question, that's 160 minutes plus.

DR. GOODMAN: It won't take us that long, but I appreciate that.

DR. SINGH: There are 48 questions, not seven questions.

DR. GOODMAN: Understood. Now if the panel thinks any of those can be answered with one vote, we can do that too. I want to forge through right now to question five, which has to do with a set of six interventions, or treatment strategies, and this one asks whether there's sufficient evidence, again, not whether they work or not, but whether there's sufficient evidence upon

which to make that kind of determination. Does anyone want to comment on question five? I don't want to go back to the previous questions now. Question five.
DR. FISCHER: We're talking about evidence now, not what people think.
DR. GOODMAN: Sufficient evidence. It

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says sufficient evidence, not sufficient opinion, sufficient evidence.
DR. SINGH: Sufficient evidence in your opinion.
DR. GOODMAN: In the voter's opinion, of course. That's why we have you here and not computers. Now, Dr. Pauker first, briefly.
DR. PAUKER: I guess I have a problem, because are we voting on what we heard presented and what we have read in this stack of things or are we voting on things based on whatever we want?
DR. SATYA-MURTI: All of it.
DR. GOODMAN: You are being asked as a professional about your level of confidence, and I hope it would not exclude the body of evidence presented to you today and what you read leading to the meeting. Thank you.
DR. PAUKER: Thank you.
DR. GOODMAN: Was it Ms. Kuebler that had her hand up, or Ms. Kendig? I'm sorry, I have problems seeing raised hands there.
MS. KENDIG: That's all right. Just a point of clarification. When we are rating those, because the report I believe is broken

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out into looking at single therapies as well as the combined therapy. Are we rating confidence of evidence of those as single therapies?
DR. GOODMAN: Yes. It says each of the following treatment strategies, right? Okay.
MS. KENDIG: Thank you.
DR. GOODMAN: Dr. Pfalzer.
DR. PFALZER: So that leads to the follow-up question, what about actually the more standard combined therapies such as decongestive physical therapy, where is that combined?
DR. GOODMAN: Do you see that listed in any of one through five?
DR. PFALZER: No.
DR. GOODMAN: Okay. Say it one more time, what are you calling Roman VI?
DR. PFALZER: Decongestive physical therapy, or CDT, I'm sorry, complex

decongestive therapy.
DR. GOODMAN: CDT, otherwise known as complex decongestive therapy. Does anyone on the panel object to entering that as Roman VI under question five. No objection.

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Any other points to be made about question five at this point? Remember, this is a sufficiency question.
If not, let us turn to question six. Question six will already have considered the answer to question five, which is whether there's sufficient evidence for any of those. For those where there is a score of 2.5 or greater, we'll ask about whether these do actually produce clinically meaningful improved health outcomes. So this is, if you thought there's enough evidence to make a judgment on question five, among those for question six, do any of those actually work based on the available evidence?
Questions based on these? Discussion on any of these? Now I would presume, Dr. Pfalzer, that Roman numeral VI would say CDT once again. Okay. Let's enter CDT there.
Question seven deals with the generalizability to the Medicare beneficiary population. We had some very useful discussion earlier, particularly Dr. Eng's comments and others. Any further discussion about the generalizability to the Medicare population?

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Dr. Janjan.
DR. JANJAN: Does this also include Medicaid and Medicare disability?
DR. GOODMAN: I would say Medicare refers to the people aged 65 and over and those who are disabled, Medicare beneficiaries, not Medicaid, unless they are dual eligibles. I think I answered that correctly.
Any comments on the generalizability to the Medicare beneficiary population. Recall that from an epidemiological standpoint it sounds as though there may be about two million people in the United States who have this. It sounds as though there might have been as many as a half a million who are cancer survivors. It sounds as though the rising prevalence of obesity may be starting to push that number of two million up, something to keep in mind. Any other comments about generalizability? Okay. I want to hold question eight for later after we have voted.
Okay. We have a charge to the front

microphone. Please remind us of your name.
DR. FIFE: Dr. Caroline Fife, from the University of Texas Houston. You don't need to
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be reminded of your charge, but the role of the committee is to determine whether the scientific evidence is of adequate quality to draw conclusions about the effectiveness of interventions in routine clinical use for Medicare beneficiaries, and that's one of our great concerns. The majority of our patients don't have, who are Medicare beneficiaries don't have upper extremity lymphedema, they have lower extremity lymphedema. And virtually all of the RCTs involve upper extremity patients because that's who's easy to do RCTs on.
So this entire group of patients who we are worried about aren't included in the data that you are going to be evaluating, and that raises great concern about the generalizability and whether you can draw conclusions about these for the vast majority of Medicare beneficiaries.
DR. GOODMAN: And restate, because the vast majority of beneficiaries --
DR. FIFE: Have a lower extremity lymphedema, not upper extremity lymphedema, so they weren't reflected in these RCTs.
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DR. GOODMAN: Thank you for that important point and clarification. We are reminded as well about the distinction between efficacy and effectiveness, by the way.
Is there anything else about question seven that anyone wants to address at this time? Okay.
Why don't you pull out your Olympic Game cards here, one through five, I believe.
DR. KATO: Excuse me. Did you refer to a question eight?
DR. GOODMAN: Yes. Question eight, if you look at the green folder you got this morning, you might miss it right at the bottom of question seven, and question eight does not have grades assigned to it, so we're going to discuss clinically important evidence gaps.
Dr. Janjan, do you want to show Dr. Kato where it is.
DR. KATO: Okay.
DR. GOODMAN: Good. Let's return to question one. And, hello, Dr. Pauker.
DR. PAUKER: This question number one and number two, are we adding categories for

other? I know we changed two of the others, so
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are we doing that with these?
DR. GOODMAN: At the time we discussed them, none of those were raised, as far as I know, there is no other for these now.
DR. PAUKER: Then we should strike it.
(Discussion off microphone between Dr. Goodman, Ms. Ellis and Ms. Syrek Johnson.)
DR. GOODMAN: The question was, are we going to discuss the need to collapse any of our multiple Roman numerals into one, and I will broach that at the beginning of each question. I haven't heard anything strongly in that direction at this point.
So, question one is going to ask about four imaging techniques and five quantitative techniques to determine limb volume and skin elasticity, and two other concepts. So I think we'll do this one by one unless anybody objects, starting with the imaging techniques, and let me read the question just to remind us. Number one is, how confident are you that there is sufficient evidence, not whether it works or not yet, is there sufficient evidence to determine if the list of diagnostic strategies can reliably identify and stratify
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the severity of secondary lymphedema, including subclinical disease. And we agreed before in our first go through this that we were not going to talk about subclinical, so this is about identifying and stratifying the severity of secondary lymphedema.
Under imaging techniques the first is lymphoscintigraphy, otherwise known as lymphangioscintigraphy. On a scale of one, where one is low confidence and five is high confidence, can you raise your cards, please?
(The panel voted and votes were recorded by staff.)
MS. ELLIS: Also, remember to circle your scores on the handout sheets that I gave you with your name on it.
DR. GOODMAN: I would suggest that while you're holding it up or before you hold it up, do circle your score sheet and then hold it up. Let's go to MRI CT.
(The panel voted and votes were recorded by staff.)
DR. GOODMAN: Thank you. Ultrasound.
(The panel voted and votes were recorded by staff.)
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DR. GOODMAN: And I won't say it in its long version, or I guess I'll try it once, Tc-hexakis-2-methoxy isobutyl isonitrile, or MIBI scan.
(The panel voted and votes were recorded by staff.)
DR. GOODMAN: Thank you. Now we're going to move to these quantitative techniques to determine limb volume or skin elasticity, the first of which is tissue tonometry. Again, remember, this is the sufficiency of evidence, not whether it works as intended.
(The panel voted and votes were recorded by staff.)
DR. GOODMAN: Next is perometry, one to five.
(The panel voted and votes were recorded by staff.)
DR. GOODMAN: Thank you. Next is water displacement, or pardon me, circumferential measurements.
(The panel voted and votes were recorded by staff.)
DR. GOODMAN: Now, water displacement. Is there sufficient evidence to determine if

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they reliably identify and stratify, just to keep in mind, water displacement.
(The panel voted and votes were recorded by staff.)
DR. GOODMAN: Next is bioimpedance. Now I know we heard about some multiple versions of this but take it broadly, bioimpedance broadly, not necessarily a particular version of it.
(The panel voted and votes were recorded by staff.)
DR. GOODMAN: The next is patient-reported symptomatology, one through five, sufficient evidence.
(The panel voted and votes were recorded by staff.)
DR. GOODMAN: And finally for this question is physical exam.
(The panel voted and votes were recorded by staff.)
DR. GOODMAN: Now before we go on, you remember subclinical disease. Is there anyone on the panel that considers that they would have had a high confidence for any of these in subclinical disease, anything that would be

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let's say 2.5 and above, subclinical disease, sufficiency of evidence? Dr. Eng?

DR. ENG: I was thinking about bioimpedance based on what we heard earlier.
DR. CORMIER: I would vote to phrase the question the other way around, is there any one that we might think there might be sufficient evidence, because I think most of them we have heard no evidence at all.
DR. GOODMAN: Right.
DR. CORMIER: But I think the emerging evidence, and certainly the Stout trial, I mean, we've heard repeatedly that bioimpedance is the one measure, and I think patient symptoms, and we didn't get a chance to hear all the data behind the LBCQ and how it was validated, but we all saw in our packets the heaviness that one patient assessment system has shown over and over and over, that that symptom can predict, show subclinical lymphedema long before we might see volume measurements.
DR. GOODMAN: So what we might do then is ask, are there any of these for which there is sufficient evidence upon which to make a

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judgment pertaining to subclinical disease, am I saying that correctly? And I heard one, bioimpedance as one. Are there any others?
(Discussion off microphone between panelists and presenters.)
DR. GOODMAN: So we have three now. Let's go to perometry now, sufficient evidence for perometry, sufficient evidence for perometry vis-a-vis subclinical evidence. Again, sufficient evidence that perometry can reliably identify and stratify severity of subclinical disease, and this is for perometry only now.
(The panel voted and votes were recorded by staff.)
DR. GOODMAN: Dr. Armer, did you have a point to make?
DR. ARMER: Not an opinion, but a statement of fact. The Stout article used perometry and it was just misstated by someone, but it used perometry, so I just wanted to say that.
DR. GOODMAN: Not bioimpedance.
DR. ARMER: No.
DR. GOODMAN: Thank you. Subclinical

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disease, this is on circumferential measurements -- oh, excuse me -- bioimpedance. Bioimpedance for subclinical.
(The panel voted and votes were

recorded by staff.)
DR. GOODMAN: And finally, patient-reported symptomatology.
(The panel voted and votes were recorded by staff.)
DR. GOODMAN: So that finishes question one. Dr. Weiss, what important thing do you want to add now?
MR. WEISS: I just would like to point out for the record that there are two methods that aren't on this list that are being used extensively, I know in Denmark, for measuring secondary lymphedema.
DR. GOODMAN: Dr. Weiss, those did not come up in discussion with the panel, so we can't discuss them now.
MR. WEISS: Yeah. They were in the material I submitted, though.
DR. GOODMAN: We're grateful for that, we are. Thank you. The panel did not choose to address them. Thank you, Mr. Weiss.

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Now, I need to ask our staff, for those in question one, which ones achieved a mean score of at least 2.5.
(Discussion off microphone between Dr. Goodman and Ms. Ellis.)
DR. GOODMAN: We are going to vote B.III, B.IV, C and D, correct, all of which were graded at 2.5 or better.
So question two now asks not about the sufficiency of the evidence but whether or not these things do what they are supposed to do.
So how confident are you that each of the listed diagnostic strategies reliably identifies and stratifies the severity of secondary lymphedema? And we're going to look first at circumferential measurements. Or perometry? Did we say perometry or not? No.
Okay.
Circumferential measurements, reliably identifies and stratifies, okay?
(The panel voted and votes were recorded by staff.)
DR. GOODMAN: Now water displacement, which is B.IV, water displacement.
(The panel voted and votes were

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recorded by staff.)
DR. GOODMAN: Next is patient-reported symptomatology, item C, one through five.
(The panel voted and votes were recorded by staff.)
DR. GOODMAN: And finally, physical

exam.
(The panel voted and votes were recorded by staff.)
DR. GOODMAN: Thank you. Now we're going to move to subclinical disease, and Maria, would you remind us which of the items from number one scored 2.5 or greater for subclinical disease?
MS. ELLIS: It was the patient-reported -- it was the last question.
DR. GOODMAN: Which was patient-reported symptomatology, that was the only one that scored 2.5 or better among the voting members.
So, how confident are you that the patient-reported symptomatology reliably identified and stratifies for subclinical disease?
(The panel voted and votes were

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recorded by staff.)
DR. GOODMAN: So, that should do it for question two now, correct?
MS. ELLIS: Yes.
DR. GOODMAN: Let's move now to question three, unless someone has a really important point, and if you do, come to the microphone.
MR. BUTLER: Jack Butler with ImpediMed. By a very very rough tally, I thought both perometry and BIS were included in the subclinical measures at greater than 2.5.
MS. SYREK JOHNSON: Yes, but what we're doing is we're only calculating the voting members of the MedCAC, and some of the members are not officially voting members, so there's two separate scores. If you're adding every single one of them, you might get a different average than what we have.
DR. GOODMAN: Not all the scores you see are for voting members. We will record all the votes of all members of the panel, but not all are considered voting members for this purpose.
DR. SATYA-MURTI: And that is by

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charter.
DR. GOODMAN: That is by charter, yes. Thank you, Dr. Satya-Murti.
Question three is not intervention-specific as I understand it. How confident are you that secondary lymphedema can be classified into prognostic stages of severity, that is, staging that is useful to guide choice of

therapy or predict response to therapy?
(The panel voted and votes were recorded by staff.)
DR. SINGH: We didn't hear much evidence on this.
DR. GOODMAN: We may not have. I will leave that to your judgment.
(The panel voted and votes were recorded by staff.)
DR. GOODMAN: We're coming back to question four now. Remember, this was about the outcomes that matter, and there are items one through nine here, starting with limb circumference. Did you have a point, Mr. Cantor?
MR. CANTOR: Yes, I do. It's about question five, and I didn't know whether you

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wanted me to wait.
DR. GOODMAN: We're on question four now.
MR. CANTOR: Yeah. Did you want me to wait until we get to that?
DR. GOODMAN: Yes, sir.
Question four, as was clarified nicely by Dr. Jacques and our discussion with Dr. Singh and Dr. Pauker, had to do with the outcomes. It says, in clinical studies for secondary lymphedema, how confident are you that there is sufficient evidence that improvement in each of the following measures is, or is strongly associated with an improved health outcome?
So you recall that this is not intervention-specific, it deals with your judgment of the sufficiency of evidence as to whether or not these represent an improved health outcome in and of themselves or associated with, as the question states.
Affected limb circumference is the first, one through five.
(The panel voted and votes were recorded by staff.)

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DR. GOODMAN: Next is affected limb volume.
(The panel voted and votes were recorded by staff.)
DR. GOODMAN: Next is symptom assessment.
(The panel voted and votes were recorded by staff.)
DR. GOODMAN: Next is affected limb function. Examples given include strength,

endurance, range of motion, sensation, et cetera. Affected limb function. (The panel voted and votes were recorded by staff.) DR. GOODMAN: Next is ADLs, activities of daily living, abilities. (The panel voted and votes were recorded by staff.) DR. GOODMAN: Next is frequency of skin breakdown or ulceration. (The panel voted and votes were recorded by staff.) DR. GOODMAN: Next, the frequency of occurrence of local infection. This is item Roman VII, frequency of occurrence of local

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infection. (The panel voted and votes were recorded by staff.) DR. GOODMAN: Next, the quality of life assessment. (The panel voted and votes were recorded by staff.) DR. GOODMAN: Roman numeral IX we're calling social integration and/or IADLs. DR. ENG: I yielded to Dr. Gerber. DR. GOODMAN: Oh, Dr. Eng is yielding to Dr. Gerber to call it social integration. Any objection? Hearing none, we will call it social integration, please correct that for the record. Roman IX is social integration. (The panel voted and votes were recorded by staff.) DR. GOODMAN: So that completes question four. Now, question five gets to sufficiency of evidence, once again, this is not whether these following interventions work or not, it's whether there is sufficient evidence to make some sort of judgment. I think that Mr. Cantor was going to comment first, briefly I hope, Mr. Cantor.

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MR. CANTOR: Yes. In the list that we have here, we had other, Roman numeral VI being CDT. I believe there was also evidence in the presentations, an evidence base that there was a combination of CDT and pneumatic pump that was used in several of the clinical studies, and I submit that we should have a Roman numeral VII which would combine both CDT and pneumatic pump. DR. GOODMAN: Dr. Francis? DR. FRANCIS: Actually, I would like to expand upon what Mr. Cantor just said.

DR. GOODMAN: Expand briefly, please.
DR. FRANCIS: Yeah, I will. Many of the studies that you have been provided with have examined more than one modality at a time in terms of an intervention. In other words, some examined patients who wore compression bandages plus did IPC, patients who had MLD plus IPC, whatever, various combinations of therapy. So to me, it's a little bit outside on a lot of the evidence to completely singularize these interventions because many of them weren't studied as single therapies, in fact I would propose that most of them were not

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studied as a single therapy, so I'm not sure how you're going to do that.
DR. GOODMAN: We're going to integrate under the curve and use our judgment. For this item six which we started as having CDT, does the panel consider, keeping in mind what we already know is our prior here with regard to the technology assessment and the presentations, does the panel consider that in addition to adding CDT, you want to add CDT plus pneumatic compression, any strong sentiment for that? I'm not seeing any strong sentiment in favor of it.
Do you have --
MS. LINCOLN: I have one quick comment with the pump use.
DR. GOODMAN: Why don't you mention your name and affiliation.
MS. LINCOLN: My name is Kelly Lincoln, I'm a lymphedema therapist, and just with Roman numeral I with the pneumatic pumps, I think it's important because some of the research that we've looked at today shows that there are different types of pumps available, whether it be a distal to proximal sequence or

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whether it's the smaller chambered pumps, and some of the other research has shown that some of the other pumps should not be used, so is there a way to divide them?
DR. GOODMAN: Not unless the panel is inclined to do so. Again, thank you for your comment very much, it's in the record.
DR. GERBER: I would like to support the CDT plus pneumatic pumps. That's one of three studies that were done, and it should be included as a combined study for us to vote on.
DR. GOODMAN: Just to get our terminology correct, it's CDT plus pneumatic pump, or pneumatic compression? I want to use

the right --
DR. GERBER: I'm sorry, compression.
DR. GOODMAN: So CDT is Roman VI, and on the table is CDT plus pneumatic compression. Panel, do keep in mind that as I said, we have our priors, we sort of already know what's out there, and you may want to consider that. In addition to Dr. Gerber, does anybody want to add CDT and pneumatic compression as an item VII? I see at least four hands. Does anybody strongly object to adding CDT plus pneumatic

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compression? It doesn't look like it, I see no reason why we can't add that as an item, Roman VII.
All right, number five. How confident are you that there is sufficient evidence, again, sufficiency of evidence?
Dr. Umscheid, yes, sir.
DR. UMSCHEID: I just want to make two comments. If we start making these choices so specific, then I'm going to feel very uncomfortable voting on any of these unless it's a therapy regimen specifically that's been studied by the field, that's been examined appropriately. For example, if we have CDT plus pneumatic compression devices, then I'm going to vote very differently on just pneumatic compression devices.
So I don't know if that's your intent, and if it is, then I think we have to make sure that we have all the other relevant combinations that are out there.
DR. GOODMAN: None of Roman numerals I through now VI presuppose that they're being used in combination.
DR. UMSCHEID: But we also don't

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presuppose that they're being used in a single fashion, they're just being used.
DR. GOODMAN: They're being used. You might consider, what is their independent contribution to any improvement, and for this question, is there sufficient evidence to make that judgment.
DR. UMSCHEID: And the second thing is, I don't know if anyone feels strongly about adding laser to this. I saw a couple studies about laser.
DR. GOODMAN: You might have seen a couple studies. Is there any strong sentiment in favor of adding laser? I'm seeing more head shaking no than head shaking yes.
Okay, so let's proceed. How confident

are you that there is sufficient evidence to determine if each of the following strategies produces clinically meaningful improved health outcomes for patients with secondary lymphedema, sufficiency of evidence that the intervention results in improved health outcomes. Pneumatic pressure devices.
(The panel voted and votes were recorded by staff.)

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DR. GOODMAN: Next is exercise-based activities.
(The panel voted and votes were recorded by staff.)
DR. GOODMAN: Next is massage-based treatment.
(The panel voted and votes were recorded by staff.)
DR. GOODMAN: Compression bandaging/compression garments.
(The panel voted and votes were recorded by staff.)
DR. GOODMAN: Next, psychosocial support.
(The panel voted and votes were recorded by staff.)
DR. GOODMAN: Next is CDT only. CDT is the first entry under other, our sixth item.
(The panel voted and votes were recorded by staff.)
DR. GOODMAN: And finally, CDT plus pneumatic compression.
(The panel voted and votes were recorded by staff.)
DR. GOODMAN: Question six is answered

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only for those that were given a score of 2.5 or greater on question five.
MS. SYREK JOHNSON: I've got pneumatic compression devices --
DR. GOODMAN: Roman numeral I.
MS. SYREK JOHNSON: Roman IV, compression bandaging. And then I have other, VI, CDT, and VII, CDT and pneumatic compression.
DR. GOODMAN: So there are four items, correct?
MS. SYREK JOHNSON: Yes.
DR. GOODMAN: The first of which is pneumatic compression devices. So for pneumatic compression device the question is, how confident are you that each of the following treatment methods produces clinically meaningful improved health outcomes for

patients with secondary lymphedema? So this is resulting in improved health outcomes, pneumatic compression devices, one through five, please.
(The panel voted and votes were recorded by staff.)
DR. GOODMAN: The next is Roman IV,

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compression bandaging or compression garments, produces clinically meaningful improved health outcomes for patients with secondary lymphedema. Compression bandaging, compression garments.
(The panel voted and votes were recorded by staff.)
DR. GOODMAN: Next is CDT alone.
(The panel voted and votes were recorded by staff.)
DR. GOODMAN: And finally, CDT plus pneumatic compression.
(The panel voted and votes were recorded by staff.)
DR. GOODMAN: We will move to question seven now. Question seven has to do with the generalizability to the Medicare beneficiaries with secondary lymphedema. Note that when we talk about the generalizability for Medicare beneficiaries, we're going to have two categories of answer here, the first is going to be the diagnostic strategies, followed by treatment methods. So sort of separate that in your thinking.
DR. SINGH: But have we heard any data

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on that?
DR. GOODMAN: You may not have heard much data, Dr. Singh. We will leave that to our voting judgment.
And the question as you recall is, how confident are you that the conclusions regarding the diagnostic strategies as a group, and we'll stick with that now, diagnostic strategies as a group are generalizable to Medicare beneficiaries with secondary lymphedema? Remember that the diagnostic strategies as a group are those back in question two. Yes, Dr. Pauker.
DR. PAUKER: If I thought they were generalizable, but generalizable is a negative conclusion, I still show high confidence here?
DR. GOODMAN: Generalizability can work in either direction, Dr. Pauker. Okay.
How confident are you that the conclusions regarding diagnostic strategies as

a group are generalizable to Medicare beneficiaries with secondary lymphedema, diagnostic strategies generalizable to Medicare.

DR. STEWART: I have a question.

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DR. GOODMAN: Could you come to the microphone, and we'll recognize you.

DR. STEWART: I'm sorry. I was confused, I wondered if some of the members of the board would be confused as to whether or not you are voting on all of them or just the four that were found to be above 2.5, which would have been B.III, IV, C and D.

DR. GOODMAN: I don't know that that matters. Let's proceed with diagnostic strategies. We don't have the scores yet.

(The panel voted and votes were recorded by staff.)

DR. GOODMAN: Now treatment methods, how confident are you that the conclusions regarding the treatment methods as a group, question six, are generalizable to Medicare beneficiaries with secondary lymphedema? Treatment methods.

(The panel voted and votes were recorded by staff.)

DR. GOODMAN: Now, I know that some of you do have to absolutely run to a shuttle which is going to speed to BWI. We have one more question to address and we're going to

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address question eight in a moment, just want to make sure those who have to run out can, and MedCAC and CMS are very grateful to you members, including those who must run now. We're going to have a bit of discussion for question eight.

(Discussion off the record.)

DR. GOODMAN: Let's look at question eight. Question eight is not a voting question, but as was evident from the discussion leading up to this point, we have heard a lot and said some things about some apparent evidence gaps, some matters of definition and so forth. And in a constructive way, let's try to identify and summarize what you think might be any clinically important evidence gaps pertaining to the diagnosis and/or the treatment of secondary lymphedema. And when you talk about evidence gaps, if you have any trial designs or other means of generating relevant evidence that would support the closure of those evidence gaps, please

address those as well, if you would. So clinically important evidence. Dr. Fischer is first.

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DR. FISCHER: One of the things, I'm new to this game and I no longer do breast surgery, but it does seem to me that we know very little about the life history of lymphedema, and there is a readymade group of patients that should be available, and they're digitized, and it was paid for by the NCI, and this is the NASBP patients. And there are thousands of patients and they are very well characterized, they're around. Bernie Fischer who ran it, no relationship, is still around, just got an award. He's 93, still has all his marbles, I'm sure he would be happy to help. But I think we need to answer some questions like if you have lymphedema and then it goes away, do you still have lymphedema, and what happens to you three years later or five years later? And what's the very nature of why we have that exponential curve that increases in time, what's the issue there, is it the issue of dose in radiation? It clearly, I mean, unless you really are inept, the idea that you get eight percent lymphedema following a single node biopsy is frightening, it's frightening to me as a surgeon.

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DR. GOODMAN: Dr. Fischer, how would you phrase the evidence gap itself and how it might be addressed?

DR. FISCHER: The evidence gap is the actual life history of lymphedema and what are the characteristics that lead people who are heretofore seemingly without lymphedema to get lymphedema later on.

DR. GOODMAN: Now, would this be addressed like, for example, a longitudinal cohort study or some other approach that you might suggest?

DR. FISCHER: I think it would be addressed by a longitudinal study and I think there is a group of patients which is readily available, which has been paid for.

DR. CORMIER: But there's no lymphedema assessments in the original NSABP studies, there were no objective measures pre and post.

DR. FISCHER: That is correct, but if it doesn't work, if you can't get any meaningful data out of it, you'll have to do it, but there are still arms of the NSABP study

which are active, with thousands of patients.
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DR. CORMIER: Sure. But CLGB is ongoing, at least one if not two, and we're both collaborators on -- sorry.
DR. GOODMAN: That was Dr. Cormier, who did not identify herself, but that's who that was. Dr. Eng is next.
DR. FISCHER: Can I just add one more?
DR. GOODMAN: On this point, Dr. Fischer?
DR. FISCHER: No, on a separate issue.
DR. GOODMAN: Let's go to Dr. Eng, and we will return to you.
DR. ENG: I have four areas of knowledge gaps as I read the evidence, heard the evidence, and heard the discussion today. So the first one dovetails to the current comments. I think we need larger epidemiological studies to determine the trajectory from subclinical disease to the later stages of the disease. And these larger epidemiological studies have to take into consideration comorbid conditions. So the studies that we heard today, many of them excluded people who didn't have other conditions. This is very important for the
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Medicare population, because for Medicare populations it's not just breast cancer and post surgery, they come with stroke, they have vascular disease. Age is a risk factor that I think needs to be looked at rigorously, and there are other risk factors. So that's the first area.
The second knowledge gap is if treatments are started, what are the endpoints of treatment? Because today we don't know whether once lymphedema, always lymphedema, once pneumatic compression garments, always compression garments. So I think there are studies where we need to have knowledge about that.
The third is really in the area of health education. I think we have a really large gap in terms of educating providers, and I'm talking about at this point physicians, because I think there is a knowledge gap for physicians, surgeons and oncologists to really recognize that a condition exists, but I think that part of the health education of physicians is that you have to present evidence. I mean, to convince people that they should risk
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stratify their patients. So, it goes back to getting the data. And then health education for patients. So there's this thing with health education and it's especially important in Medicare beneficiaries because, once again, Medicare beneficiaries aren't just a single condition, they have to deal with multiple coexisting conditions, and here's just another one that comes along. And they really need, you know, information not in a technical way, but really health education. And the fourth one I think we did talk about, the knowledge gap in outcomes. And when you define what are the outcomes that we're going to study, you know, it doesn't have to be 20 outcomes, it has to be a defined maybe half a dozen, and everybody has to agree on them, right? So, I think those are the four that I wanted to comment on.

DR. GOODMAN: Thank you very much. Miss Kuebler.

MS. KUEBLER: I would just like to make a point that there was a lot of discussion

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on the technology assessment, and the majority of the literature seems to come from European countries, and maybe a meta-analysis of those studies would be useful in the U.S.

DR. GOODMAN: Thank you. I just wonder if you mean meta-analysis, which is a statistical combination of data and/or results, or if you mean a systematic review that incorporates European evidence.

MS. KUEBLER: Or both.

DR. GOODMAN: Or both, okay. I think we hear that it was not possible to do a meta-analysis because of the heterogeneity of the data, but either or both have been put on the table. Thank you. Dr. Pfalzer.

DR. PFALZER: I think we need to look at both efficacy and effectiveness. And so on the efficacy question, we do need to look at comparative effectiveness. It's not good enough just to compare treatment to control, but we do need more head-to-head studies comparing these different kinds of interventions, and I think that's very clear. So on the efficacy side of things, the comparative effectiveness does need to be

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looked at. On the effectiveness front, the large

cohort studies that are prospective are going to answer the effectiveness question better than any randomized controlled trial can, and prospective monitoring, just because of the nature of this beast, and I will call it a beast. Because of the multisystemic nature of lymphedema and the fact that we don't have currently good diagnostic markers, and I think it was pretty clear in this discussion today, we're working on it, we're working on trying to come up with some operational definitions that would give us more sensitive and reliable diagnostic measures but we're not there yet. And given that we're not there yet, then those large cohort trials going forward are one of the ways that you deal with that as you try to work that out.

DR. GOODMAN: Thank you, Dr. Pfalzer. I believe it's back to Dr. Fischer and then Dr. Janjan and then Dr. Pauker.

DR. FISCHER: I think one of the things that's lacking, at least to me, is a randomized prospective trial comparing CDT

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versus pneumatic compression devices, or a third arm can be added with CDT and pneumatic compression devices. There seem to have been enough patients that have tried CDT with a variety of pumps. I mean, one could have a combined -- I don't know if this is germane or not or whether it's okay to mention it, but it could be a CMS-industry type study where CMS would get to review the trial before it was carried out, and perhaps in return, and this is none of my business, perhaps those individuals who had pressure garments on their upper extremity could be paid for by CMS as part of the trial. I really think that, you know, having people get up and just tell us how wonderful things are when there's lots of patients available in this area is inappropriate.

DR. GOODMAN: Thank you, Dr. Fischer. Dr. Janjan.

DR. JANJAN: I guess the message that you're hearing over and over again is you need rigorous science and you need to have well defined criteria for your analyses. I think you also, what we heard a lot about was upper

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extremity post breast cancer, but we didn't hear very much given the volume of lower extremity lymphedema, especially post CABG. And there's a huge, especially in the Medicare

population, that have had CABGs that are not, have not been addressed at all in the literature.
The bottom line is what's important to the patient, and doing a lot of quality of life evaluations, you've got to get those quality of life outcome measurements well defined and evaluated. And where we are with CRE and qualities, you'd better figure out what's important to the patient and put that into a quality analysis.
The one thing I think you also need to do is a work force analysis, because all of this stuff is labor intensive, time intensive, and I don't know if we have enough folks out there who could deliver the care if you develop strict criteria for diagnosis and treatment. So that ought to be part and parcel of what you're doing.
DR. GOODMAN: Thank you, Dr. Janjan, very much. Dr. Pauker is next.

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DR. PAUKER: I think the category here is a huge, very diverse. Furthermore, besides that, you have to have comparative between activity studies. Therefore, you're going to need a very very large study, so you're going to need to have substantial funding, so the difficulty may not be only setting that up, but in figuring out how to fund it. But if you waste your time doing a study of a hundred, or 500 or 600 people, and you have small variations in outcome, it's going to come to no significant difference. To really make it worthwhile you have to have a mega-study. You've got lots of patients.
DR. GOODMAN: Thank you, Dr. Pauker. Dr. Kato, were you next?
DR. KATO: Just a quick comment. What I was impressed with was that there hasn't really been a lot of major developments in the past 30 years. And I look upon other technological advances, you know, one of my specialties is ICDs, pacemakers, and these things have been out since about 1991, and we're already seeing the third or fourth revision of the clinical practice guidelines,

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and so things are happening pretty quick. So to tell me that, you know, you're just kind of getting around to tightening up your consensus and you're trying to figure out your definition, and you've let 30 years go by, that's just a waste of time. And I think, you

know, if the government isn't going to be responsive, then you have an incredible obstacle. So get out and talk to your Congressman, that's where a lot of funding in research is, in a lot of the earmarks in all the legislation that comes through. You certainly have been able to galvanize a lot of support today, even though that wasn't part of what we were supposed to do, but that's, you know, you go out and get the money, and do the study.

DR. GOODMAN: Thank you, Dr. Kato. Dr. Umscheid.

DR. UMSCHEID: There were a couple of areas that I thought were important to future research. One, I agree with I believe Dr. Fischer. It seems like there are a large proportion of people who get lymphedema after these axillary lymph node dissections but there

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are also, the majority of these patients don't get lymphedema. And the question is, you know, what are the risk factors for those who get it versus those who don't, and can we predict who would get it, so I'm in favor of that. And the types of studies you could do for that would be something as simple as a case control study or a retrospective cohort study.

DR. GOODMAN: Dr. Umscheid, say that one more time. The evidence gap is?

DR. UMSCHEID: The evidence gap is understanding risk factors for getting lymphedema post op.

The other issue that I think obviously needs further study, the vast majority of the evidence that we talked about was in the breast cancer population. We obviously need studies in the non-breast cancer population.

Also in an analogous way, a lot of the data we heard was in the upper extremities. We need studies in the lower extremities because there was some at least anecdotal data suggesting that there were real differences in upper extremity versus lower extremity in lymphedema, and even the types of patients who

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had those types of edemas were very different, and we had heard some anecdotal evidence about compliance rates.

The last area I would mention is just, I did see, it looked like some small promising data about laser therapy producing lymphatic development in the TA report, and I don't know if that's another area for further research,

but I'd look at that.
DR. GOODMAN: Great, thank you, Dr. Umscheid. Dr. Satya-Murti is next.
DR. SATYA-MURTI: Lack of natural history is what I keep harping on, so have many others, so I think this would be an ideal spot for a registry, particularly if possible, I'm not here to tell how to do this, but if possible tagged and contingent on Medicare payment, a prospective preop assessment in multiple modalities, and then following interval based postop assessment. So a registry would provide us an enormous database, and very often a good incentive is payment, just as a side comment.
DR. GOODMAN: Thank you, Dr. Satya-Murti. Any other comments from the panel

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at this point about evidence gaps or how to address them at this point?
Just as a time check, we will be done by 4:20, if not a few minutes before. Okay.
Let me then, I will add a few comments then, and then we'll turn it back over.
Speaking as a nonvoting member of the MedCAC, I have a few observations with regard to evidence.
This is an extraordinarily large health care problem, it affects two million people and that number's not going down, it's going up. Among those two million people are at least half a million people with breast cancer. The rising prevalence of obesity is going to push that number up in the next decades.
We're also very impressed by the terrible personal clinical burden on these people. We normally don't spend a lot of time looking at case examples because we're looking at bodies of evidence, but inevitably many of the presentations seen today presented graphic evidence of what a terrible individual burden this is on patients and obviously their

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families and caregivers, and the system at large.
Given the extraordinary magnitude of this increasing problem, the body of evidence available to assess the diagnosis and treatment for this terrible clinical burden is far far from adequate. It isn't close, all right? Now as I think Dr. Kato suggested, 30 years is too long to be too slow. So for those that are truly concerned about the magnitude of this

problem, from a population standpoint, from an individual standpoint, clinically and economically, there is far more work to do than we're geared up to do now.

Furthermore, whether you look at the United States or globally, evidence requirements, and not always RCTs, but good studies that at least provide some basis of comparison to something used in practice, the demand for those is increasing and it is not decreasing. And at the rate at which this field has generated evidence over the last 19 years, which generated in the English peer reviewed literature not even 60 studies, divided equally between therapy and diagnosis,

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this field may be falling behind the evidence demand curve.

So, I hope that not only will you take into account, and not only will we and the Agency take into account the various scores you saw on these, but please do take very seriously the evidence gaps just identified and the ways we're addressing them. All right?

This is going to require in parallel, because consensus is not the same as evidence, expert opinion is not the same as evidence, in parallel achieving some consensus on basic terminology and which outcomes matter, A, and over what duration you measure these outcomes, and furthermore, how you assess costs, direct and indirect costs and productivity and so forth.

So just, one of the most valuable things that this MedCAC function performs, and I think we're very grateful to CMS for holding these open meetings with reams of evidence and a great amount of investment, that the government, that the Agency is putting into technology assessments with the cooperation of AHRQ and other federal agencies, and the fine

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fine work done by the evidence-based practice centers, including McMaster as presented today, with all that investment in trying to define what evidence is available and not, I hope that the signals that you heard, that we heard today, that the strong red flag, raise them high signals about the inadequacy of evidence is taken to heart, because if it isn't, we will be doing a great disservice to those two million and counting people who are victims of this terrible condition. So don't let us down.

Tamara, over to you for the

adjournment.
MS. SYREK JENSEN: That's a lot to take in, and we really truly appreciate the MedCAC guidance and your recommendations and your thoughts, and we at CMS have a lot of work to do, and to decide what we're going to do with your guidance and everything you've told us today and what our next steps are.
So thank you very much for taking time out to do that today. And thank you again for all the public input, we will consider all of that as well.
So with that, thank you very much. I

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hope everyone has a safe holiday next week.
Thanks.
DR. GOODMAN: Thank you all.
(The meeting concluded at 4:11 p.m.)