MICHAEL KOWALKSI: I'm delighted to be speaking with you today at this Breast Center Grand Rounds about evidence-based acupuncture for cancer patients. In the past decade of my 33 years in acupuncture practice, I've taken a special interest in focusing on cancer patients. As I imagine you all know from your own experience, the needs of a cancer patient are greater, as is their gratitude for any help I can provide. When I give a talk to a breast cancer support group, their appreciation and welcoming attitude is palpable.

Throughout my acupuncture career it has always been my vision to integrate my practice of acupuncture with conventional health care providers in a patient-centered quality care model. And so I'm delighted to be part of the breast center team at Mayo Clinic, with the quality of care and the spirit of collaboration, which is so evident with everyone I have had the pleasure to work with here. Another reason I'm delighted to work at Mayo is my passion to participate in acupuncture research, to advance the evidence-based practice of acupuncture.

So let's start with the learning objectives for this Grand Rounds presentation-- define key acupuncture terminology; differentiate traditional acupuncture from evidence-based practice; analyze current acupuncture research for managing symptoms of breast cancer treatment; understand how integrating traditional acupuncture with evidence-based practice improves patient outcomes and patient satisfaction, and refer appropriately to acupuncture for cancer treatment symptom management. I would like to acknowledge Mayo Clinic Jacksonville's innovative leadership in integrative medicine, led by Dr. Dawn Musallem and colleagues in the Breast Center. Mayo Clinic Jacksonville is the first cancer center in North Florida to integrate acupuncture in their cancer care program.

Acupuncture's history predates modern recordings. In the top image you see animal bone acupuncture needles. More primitive versions were the bian stone needles, excavated from ruins in China, dating back to the Stone Age, 10,000 to 4,000 years ago. That makes acupuncture the oldest known system of medicine. A page from the world's oldest known medical text is in the lower image-- *The Yellow Emperor's Classic of Internal Medicine.* It describes acupuncture during the era of the Yellow Emperor-- 2700 BC-- and was written in its current form in 300 BC.

Between 2002 and 2007, the US Census Bureau surveys found a nearly doubling of the use of acupuncture during that five-year period, from 3.4% to 6% of Americans either using or have used acupuncture as part of their health care. The latest US census survey found that there was a small but significant linear increase in the use of acupuncture between 2007 and 2012. Interestingly, the 2012 census survey also found that while only 25% of Americans had some insurance coverage for acupuncture, use rates for acupuncture among people who had no insurance coverage increased, suggesting an increased willingness to pay out of pocket.

The growing body of evidence on acupuncture's effectiveness has driven much higher demand for acupuncture among cancer patients than in the general public, especially among breast cancer patients. This study from *The American Journal of Surgery* found that integrative medicine therapies are used consistently by 84% of breast cancer patients, versus 66% of patients with other types of cancers. Oncology acupuncture is a growing field of acupuncture treatment that is specialized to the needs of cancer patients.

From 2009 to 2016, the percentage of NCI designated comprehensive care centers that provide information on acupuncture on their websites has increased from 59% to 89%. So nearly all the major cancer centers now recommend acupuncture on their websites. Interestingly, 73% of these cancer centers now provide acupuncture onsite. Clearly acupuncture is being integrated into conventional cancer care to meet the needs of cancer patients.

Much scientific research has focused on the biomedical mechanisms of action of acupuncture, showing that healing occurs by stimulation of neuropeptides. Endogenous opioid peptides are considered major candidates for a role in acupuncture's pain-reducing actions. Bai and colleagues reviewed nine publications exploring the neurophysiologic mechanisms of acupuncture. They found that real acupuncture can induce more increased activity in the somatosensory cortex, limbic paralimbic system, and basal ganglia compared with a sham group.

In the past 10 years there has also been robust research on acupuncture mechanisms in the area of functional brain imaging. Claudia Witt of the University of Zurich and her team reviewed 779 papers, and 34 were eligible for mera-analysis. 10 meta-analyzes were performed to evaluate brain response to acupuncture across studies and contrast verum and sham acupuncture. Differences in brain response between verum and sham acupuncture from subtraction analysis showed more activation in the sensorimotor, affective/cognitive processing brain regions for verum acupuncture over sham. The results of the other meta-analysis were homogeneous.

Their conclusions are that acupuncture not only stimulates moatosensory brain regions, but also affective and cognitive processing regions. This is especially important since the vast majority of acupuncture patients seek treatment for chronic pain and other chronic conditions. So the multiple areas of the brain in functional MR imaging can explain why acupuncture has so many long-term and varied health benefits.

Now let's consider how traditional Chinese medicine-- TCM-- theory explains the mechanisms of acupuncture. Patients are interested in learning how acupuncture works from a TCM perspective. So a basic understanding of this theory will improve communication about acupuncture with your patients.

According to TCM, vital energy, called chi, flows through your body beneath your skin in certain channels called meridians. When this vital energy flows freely and abundantly, you feel good mentally, emotionally, physically, and in every way. When energy flows become imbalanced or blocked, associated organ or other physiological function is compromised. Acupuncture corrects energy imbalance or blockage by needling key meridian access points. When correct energy flow is restored, related function and symptoms improve.

There is a meridian of chi energy which supplies the necessary energy to each of your vital organs for proper function. Each meridian has associated physical as well as holistic functions. As an example, let's look more closely at the pathway of the lung meridian, which originates deep in the lungs.

This diagram shows the left side of the superficial pathway from lung 1 just above the lungs to lung 11 down the arm to lung 11 in the thumb. Classical acupuncture texts refer to the function of the lung meridian as the receiver of pure chi energy from the heavens. According to traditional theory, the energy in the lung meridian not only provides the fuel for a healthy respiratory function, but emotionally allows you to let go and express grief. Mentally, it gives you the ability to be inspired and also to receive on a spiritual level the quality and essence in your life. Each acupuncture point on a given meridian has different functions, physically, mentally, emotionally, and spiritually.

So let's examine the clinical evidence and research on acupuncture as it relates to specific cancer treatment symptoms, especially for breast cancer patients. Over the last 40 years, thousands of acupuncture clinical trials have been conducted for diverse conditions. Specifically as an adjunct therapy in oncology, there are over 600 recent acupuncture clinical trials, systematic reviews, and meta-analyses. And for oncology acupuncture research there are over 900 NIH grants.

Many NCI clinical trials focus on efficacy, comparing real acupuncture on known acupuncture points to placebo or sham acupuncture using special placebo needles that don't actually penetrate the skin and are placed into non-acupuncture points just on top of the surface. It looks like the needle goes in with this device, but it doesn't actually go inside the patient. And the patients are blinded.

Interestingly, NCCIH has moved away from that design and prefers to fund acupuncture studies on comparative effectiveness. In my clinical experience, there are so many understudied or as yet unstudied health benefits of acupuncture. Peter Dorsher at Mayo Clinic has been a leader in acupuncture research. With the launch of this acupuncture pilot in the Breast Center, I see a big opportunity for us to become a leader in oncology acupuncture research. So I invite all the clinicians participating in this Grand Rounds to consider what symptoms and quality of life issues your cancer patients have other than the ones I will be presenting today which you would like to see studied. I would appreciate a collaborative discussion of your research ideas with myself and Dr. Mussalem.

Before we begin to examine the evidence, let's look at the enormous complexity of symptoms in cancer treatment. Between surgery, chemotherapy, radiation therapy, hormonal treatment, and immune treatment there is no other medical treatment as harsh on the body as cancer treatment. While tremendous innovations continue to be made in both treatment effectiveness as well as safety, there are many cancer patients who develop a cluster of symptoms, both during and after their treatment, which do not respond well to conventional medical treatment. These symptoms cancer patients suffer cause substantial impairment in their quality of life.

Let's consider some of the common treatment-related symptoms specific to breast cancer patients. These include nausea and vomiting, cancer pain, including musculoskeletal pain, chemotherapy induced neuropathy, hot flashes, anxiety and depression, poor sleep quality, and fatigue. Acupuncture is an effective adjunct therapy in managing these and other symptoms, both during cancer treatment and into survivorship.

Lorenzo Cohen, Kay Garcia, and their MD Anderson team did an excellent systematic review of the whole field of oncology acupuncture in 2013. They found clear evidence that acupuncture is effective for chemotherapy-induced nausea and vomiting. They also found promising, but not definitive, evidence of acupuncture's effectiveness for cancer pain, aromatase inhibitor-related arthralgia, chemo-induced neuropathy, post-operative ileus, xerostomia, hot flashes, anxiety and depression, sleep quality, fatigue, and lymphedema. Their findings were also important because they analyzed the limitations of many of the studies that had come before, especially many of the older studies were excluded due to poor study design.

For example, some studies had too small a sample size, so they were under-powered in terms of efficacy between real and sham acupuncture. In other studies, there were other issues, such as only one acupuncturist doing all of the treatment or the patients were not blinded between the real versus sham acupuncture. Or other high-risk of bias was noted. More recently, acupuncture research conducted at major cancer centers have had much better study design with much lower risk of bias.

I'd also like to point out that the interventions in these trials should be appropriate to what is being studied. The clinical practice of acupuncture has diversified as it has evolved over the centuries, encompassing many different diagnostic methods and treatment techniques. Even within the common styles of acupuncture practice, such as TCM, five element acupuncture, electro-acupuncture, trigger point acupuncture, and auricular acupuncture, there can be significant different perspectives on what constitutes a well-designed study.

So in 2001 STRICTA-- standards for reporting interventions in clinical trials of acupuncture-- guidelines were published to improve design and reporting of acupuncture trials. And they were updated in 2010. The guidelines standardize the way acupuncture studies report their design, treatment regimen, needling techniques, practitioner background, and what control or comparator interventions are used.

So let's look at some cancer-symptom specific trials. As early as 2000, Joni Shen of the NIH and her colleagues studied chemotherapy-induced vomiting in breast cancer patients. All patients received concurrent triple anti-emetic pharmacotherapy and high-dose chemotherapy and were followed for five days post-treatment. They compared electro-acupuncture to minimal needling acupuncture and to a control group who had anti-emetic medications only. The minimal needling group had real acupuncture with mock electro-stimulation.

The results show that over the five-day study period, the electro acupuncture group had five emesis episodes, while the minimal needling group had 10, and the pharmacotherapy-only group had 15. They concluded that in this study of patients with breast cancer receiving high doses of chemotherapy, adjunct electro-acupuncture was more effective in controlling emesis than the minimal needling or anti-emetic pharmacotherapy alone, although the observed effect had limited duration.

In 2013 Chong and colleagues at the Guangzhou school of TCM in China did a systematic review and meta-analysis of acupuncture for post-operative nausea and vomiting. They identified 30 randomized clinical trials, including 1,276 patients in the intervention groups and 1,258 patients in the control groups. Meta-analysis showed that acupuncture on acupoint PC 6 significantly reduces the number of cases of early vomiting post-operative, zero to six hours. This same treatment also reduced post-operative nausea 0 to 24 hours. They concluded that acupuncture for prevention and treatment of post-operative nausea and vomiting is worth popularizing for its efficacy, safety, cost effectiveness, and benefits. It also has analgesic effects and could serve as pain relief.

It is estimated that up to 40% to 85% of cancer patients suffer from pain. Even among cancer survivors who have lived more than two years from diagnosis, 20% of them have current cancer-related chronic pain. And 44% have experienced pain since their diagnosis.

In 2013, Lu and Rosenthal at Dana-Farber reviewed the latest evidence regarding the use of acupuncture for cancer pain and synthesized several actionable acupuncture protocols for specific cancer pain conditions. The studied cancer conditions included post-operative pain, chemotherapy-induced neuropathy, and aromatase inhibitor-associated joint pain. So I'm going to go through some of what they synthesized in their research now.

A randomized clinical trial was conducted to assess the effect of a massage and acupuncture combination versus usual care on post-operative cancer pain in patients who were undergoing cancer-related surgeries, including mastectomy, reconstructive surgery for breast cancer, abdominal surgery for intestinal and hepatic malignancies, pelvic surgery for ovarian cancer, and urological surgery for testicular, prostate, and bladder cancers, as well as head and neck cancer surgery. Acupuncture was provided along with massage at day 1 and day 2 post-operatively. The average pain score improved from a day 1 baseline to day 3 in the intervention group by 1.6 versus 0.6 in the control group. 43% of patients in the acupuncture and massage group improved their pain score at least two points, compared with only 26% in the control group. Meanwhile, the intervention group also showed a decrease in depressive mood, as compared to the control group, suggesting that acupuncture plus massage, in addition to usual care, reduces pain and depressive mood among post-operative cancer patients when compared with usual care alone.

Neuropathy is a common symptom of chemotherapy. Although chemotherapy-induced neuropathy is usually reversible, it may take months or years to recover. Up to 76% of patients reported neuropathic symptoms after chemotherapy. In one high quality randomized clinical trial cancer patients suffering from chronic neuropathic pain were treated with acupuncture implants in the treatment group. While noninvasive seeds were used in the placebo group. The implants were placed in specific ear acupuncture points. At the end of the second month the study group showed a significant decrease in pain intensity by 36% from baseline, while there was almost no change in the placebo group. This study is unique, as patients were required to have only two visits and one month apart, which is minimal compared to usual acupuncture care in terms of frequency and number of treatments.

A meta-analysis by Vickers reported a randomized clinical trial comparing acupuncture versus sham acupuncture for breast cancer patients treated with aromatase inhibitors and suffering from related joint pain. The median duration of aromatase inhibitor therapy was seven months. At six months, the end of the study, the mean worst pain scores were lower in the real acupuncture versus the sham arm. Moreover, significant differences between the two groups were found in pain severity and pain-related interferences, respectively.

This study is consistent with reported acupuncture for the treatment of non-cancer-related musculoskeletal pain, such as knee arthritis and chronic low back pain. This comprehensive review by Lu and Rosenthal concluded that accumulated evidence from clinical and animal studies suggests that acupuncture may be beneficial to cancer patients with pain. They added that acupuncture protocols generated from randomized clinical trials should be adopted by clinicians who are using acupuncture in the field.

Moreover, oncology acupuncture requires that clinicians possess knowledge and skills in both acupuncture and allopathic oncology. The current NCCN practice guidelines and its recommendations for using acupuncture as one of the adjunct integrative interventions for cancer pain should be followed and disseminated. As more clinical trials of acupuncture are being conducted, we expect a rapid growth of knowledge in acupuncture for cancer pain in the near future.

In the largest fatigue trial by Malassiotis and colleagues at the University of Manchester in the United Kingdom, they randomized 246 patients to compare enhanced usual care to acupuncture plus enhanced usual care for treatment of cancer-related fatigue, specifically in breast cancer patients. The enhanced aspect of usual care was that the usual care group received a booklet of information about fatigue and its management in order to standardize instructions across the study. The multi-dimensional fatigue inventory scores improved by 3.11 in the acupuncture treatment group over the control group. The study concluded that acupuncture is an effective intervention for managing the symptoms of cancer-related fatigue and improving patients' quality of life.

This parallel group randomized clinical trial studied the efficacy and effectiveness of ear acupoints for anxiety and pain. They randomly divided 180 hospital nurses into four groups-- control, seed, needle, and tape. The control group had no intervention. The seed group had taped beads applying pressure to the chosen auricular, kind of an acupressure technique. The needle group had a mini-needle taped and retained in the auricular points. And the tape group had adhesive tape over the auricular points as a placebo control.

The treatment consisted of 10 twice-weekly sessions for five weeks with duration of 5 to 10 minutes. The evaluation instruments were applied at the start and after 5 and 10 sessions. The results show a statistical difference for anxiety according to the repeated measures, with better outcomes in the needle group, which is shown by the dotted line. The second best outcome was in the seed group, depicted by the lower gray line. There

Was homogeneously in the results for pain measures. There was a reduction of pain of 36% in the needle group, which is again shown by the dotted line. In the seed group there was a 24% pain reduction, which again is depicted by the lower gray line. This study concluded that the APPA protocol reduced the anxiety level of nursing staff after 10 sessions of auricular acupuncture.

Hot flashes pose a considerable quality of life issue for many breast cancer patients. This large randomized clinical trial of 190 patients studied acupuncture as an integrated approach to managing hot flashes and breast cancer patients. They compared enhanced usual care, usual care with an instruction booklet, to acupuncture plus enhanced usual care. The results were that acupuncture plus enhanced self-care was associated with a significantly lower hot flash score than enhanced self-care at the end of treatment and at three months and six months post-treatment follow up visits. Acupuncture was also associated with fewer climacteric symptoms and higher quality of life in the vasomotor, physical, and psychosocial dimensions.

The effect of acupuncture is the yellow line. It shows that integrating acupuncture into your treatment plan for hot flashes is more effective for hot flashes than not integrating it. Interestingly, it also shows the durability of acupuncture's effect, even at six months after completing treatment. And if you notice, the line hasn't really completely flattened out yet after six months. The studied concluded that acupuncture is an effective and safe intervention for severe menopausal symptoms in women with breast cancer.

Even with all the evidence, some clinicians remain skeptical about acupuncture's effectiveness. Some prefer efficacy studies like the neuropathy and joint pain studies I presented earlier over a study like this one. But in terms of clinical decision making about whether or not to integrate acupuncture into your cancer care plan, I think a comparative study showing a clinically meaningful effect like this one for managing cancer treatment symptoms is more pragmatic.

So in the next portion of my presentation, I want to talk about how we can develop an evidence-based framework for our acupuncture practice. Evidence-based practice was originally defined back in the 1980s by David Sackett and his colleagues as the integration of best research evidence with clinical expertise and patient values. I believe wholeheartedly that this definition of evidence-based practice is in alignment with the patient-centered values and visions of Mayo Clinic.

We have examined the best research evidence in oncology acupuncture. Now let's consider the role of patient values and preferences in the evidence-based practice of oncology acupuncture. I can say with all sincerity how each and every one of you I've had the pleasure to work with here at the Breast Center mirrors these values which I hold so dear-- knowing your cancer patient as a whole person; respecting their unique set of values; understanding their unique preferences, and last but not least, putting the needs of your cancer patient first.

Jun Mao, of Sloan Kettering, and his multi-site research colleagues did a study funded by the American Cancer Society on how breast cancer survivors who are experiencing hot flashes make decisions to use acupuncture for managing their symptoms. When asked why individuals may choose acupuncture for managing hot flashes, most responses were centered not so much on what acupuncture is, but what it is not-- specifically, not a medication.

Interestingly, they endorsed using a treatment that is natural, even when effectiveness is uncertain. They noted that although breast cancer survivors expressed varied expected therapeutic benefits from acupuncture, they emphasized the natural appeal and avoidance of symptoms as key determinants when choosing to use acupuncture for their hot flashes. The study concluded that incorporating these factors in counseling breast cancer survivors may promote patient-centered communication, leading to improved hot flash management and quality of life.

I'd like to mention my own clinical experience in relation to these findings. Since I developed a special interest in treating cancer patients in my private practice about a decade ago, I have seen an increasing number of patients with all types of cancers, both during their treatment and in survivorship. I hear common themes as to why they choose to integrate acupuncture in their cancer care plan.

The most common reason I hear from cancer patients about why they are choosing to use acupuncture is that they're tired of taking so many pills. The second most common reason I hear is that they don't want to risk getting any more drug side effects. Some cancer patients have heard how much better their friends or family feel after receiving acupuncture, while others simply want to explore their holistic options. I've observed that when their conventional oncologist makes a referral appropriately for acupuncture, the patient typically expresses gratitude and admiration for their doctor's open-minded patient-centered approach, which deepens their trust in you and in their overall care plan.

We have examined the best research evidence as well as patient values and preferences on oncology acupuncture. Now let's consider how clinical expertise contributes to evidence-based oncology acupuncture practice. The traditional practice of acupuncture takes years of clinical experience to master, regardless of which style of acupuncture is practiced.

Our three acupuncture team members in this Mayo Clinic pilot program have over 62 combine years of clinical practice experience. We have each specialized in either the TCM or the Five Element acupuncture tradition. TCM acupuncture is the most prevalent style of acupuncture practiced in the US. TCM diagnosis requires a thorough analysis of the symptoms, as well as proficiency in Chinese pulse and tongue diagnosis. In TCM treatment, acupuncture points are loosely fixed, based on TC pattern diagnosis. The needles are typically retained for approximately 20 minutes.

In addition to requiring a thorough analysis of symptoms and Chinese pulse proficiency, Five Element acupuncture diagnosis requires the acupuncturist to also develop a keen sensory awareness to assess subtle cues about the patient's constitution. Interestingly, these subtle signs are used to diagnose and treat the original root cause of each person's energy imbalance according to their association with one of the five elements. Acupoint prescriptions are not fixed and customized to the individual needs of each patient. Typically the needles are inserted and removed immediately based on the strength or weakness of each patient's Chinese pulses.

In my recent publication in the *Journal of the Florida State Oriental Medical Association,* I addressed the need in my profession for an integrated evidence-based model of acupuncture practice. Some oncology specialist acupuncturists admit that they tend to abandon the traditional whole person treatment approach, focusing their practice almost exclusively on treating cancer symptoms using the best research evidence. Meanwhile, most acupuncture schools in the United States still do not include research studies in their curriculum. So most acupuncturists practice some version of traditional acupuncture without integrating the best research evidence.

With all due respect for acupuncturists who believe passionately in their own approach, in my 33 years experience in acupuncture practice and education, both of these practice models have outcome limitations. The evidence-based acupuncture model I have outlined is more effective in managing cancer symptoms while concurrently promoting a sense of well-being unique to the needs of each cancer patient. I think this combination of symptom-specific and global outcomes can have the most impact on the overall quality of life for our cancer patients. So in 2010 I founded the 5 Element Institute to advance post-graduate acupuncture education in evidence-based practice of acupuncture.

The 5 Element Institute is a Florida Board of Acupuncture-approved provider of continuing education, specializing in courses in evidence-based integrative acupuncture and oncology acupuncture. These courses train acupuncturists how to integrate their clinical expertise in traditional acupuncture methods with the best acupuncture research protocols.

Acupuncture is very safe. It has a low risk of minor side effects, such as minimal bleeding, dizziness, or pain in about 1% of treatments. Acupuncture needles are FDA-cntrolled devices. Although acupuncture is somewhat effective in mild to moderate neutropenia, it is contraindicated when the absolute neutrophil count drops below 500 per microliter leader and also is contraindicated in thrombocytopenia.

Because of the body of acupuncture research, the National Comprehensive Cancer Network has now recommended acupuncture in 5 of their 11 guidelines for supportive care-- adult cancer pain, cancer-related fatigue, anti-emesis, palliative care, and survivorship. Now NCCN has incorporated acupuncture in their supportive care guidelines, I hope this will change acupuncturist integration with conventional cancer care from empirical use to a more evidence-based standard of care. The American College of Surgeons' Commission on Cancer has also incorporated acupuncture into their accreditation standards for a cancer center's survivorship care plan.

By the end of 2017, survivorship care plans should be provided to at least 50% of eligible patients. And after the end of 2018, survivorship care plans should be provided to at least 75% of eligible patients. My acupuncture team members and I are here to support implementation of the survivorship care plan. The Commission on Cancer's standard for survivorship has adopted the American Society of Clinical Oncology's survivorship recommendations, which are specific for each type of cancer. For breast cancer survivors, ASCO recommends acupuncture specifically for musculoskeletal health and for pain and neuropathy.

Even with all the evidence of acupuncture's effectiveness for musculoskeletal and neuropathic pain, we need more quality research in the use of trigger point acupuncture for neuromuscular pain. In my clinical experience, trigger point acupuncture integrates extremely well with traditional acupuncture interventions for better pain management outcomes. Integrating acupuncture with conventional cancer treatment can measurably increase your patient's satisfaction with their cancer care plan. as an effective tool to measure to manage cancer symptoms, acupuncture improves your patient's quality of life, thus increasing their ability to be compliant with their cancer treatment. As an anecdotal example from my own practice, elevated liver enzymes can be reduced very effectively after acupuncture treatment on the liver meridian, thus preventing an interruption in the patient's chemotherapy.

For health care providers at Mayo Clinic Jacksonville, I and our acupuncture team are here to help you and our cancer patients. So after you correlate your patient's symptoms with the evidence on acupuncture's effectiveness, I am delighted to answer any questions you may have about making an appropriate acupuncture referral. When you evaluate your patient's needs and preferences, please consider their financial needs in regard to acupuncture insurance coverage or ability to self-pay. In communicating with your patient about acupuncture, I think it is important to point out that to make an acupuncture treatment referral that acupuncture treatment does not result in overnight success. It requires a commitment of at least 8 to 10 treatments to assess its effectiveness.

In conclusion, it is interesting to note that acupuncture's roots originate in the prehistoric past. With the evidence proving that acupuncture is effective, acupuncture will play an increasing role in supportive care in conventional oncology in the future. And the future is now. Thank you very much.