The Kronos Early Estrogen Prevention Study (KEEPS): Rationale, Design & Baseline Characteristics of the Study Population
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The KEEPS trial is a randomized, double-blind, controlled trial designed to test whether menopausal hormone therapy initiated within 3 years of menopause can delay progression of atherosclerosis, as assessed by common carotid artery intima media thickness (CIMT, primary outcome) and coronary artery calcium (CAC, secondary outcome) over 4 years of treatment. Additional outcomes of interest include cognitive function, menopausal symptoms, quality of life, lipids/CVD biomarker status, and mammographic breast density. Women (n = 727) were randomized to the following regimens: 0.45 mg/d oral conjugated estrogen (CEE), 0.05 mg/d transdermal estradiol, both with cyclic oral micronized progesterone (200 mg/d x 12 days/month), or placebo. Women 42-58 years old and 6-36 months from final menses were eligible. Exclusion criteria included: hysterectomy, body mass index (BMI) >35 kg², LDL cholesterol >160 mg/dL, CAC >50 Agatston Units at baseline, smoking >10 cigarettes/day, and history of diabetes, myocardial infarction, stroke, thromboembolic disease or cancer. Mean age (SD) at enrollment was 52.7 (2.6) years and mean years (SD) from onset of menopause were 1.8 (0.8). About 15% of participants self-identified as African American or Hispanic, and ~80% were Caucasian. More than two-thirds had a college education, a similar percentage had moderate-to-severe vasomotor symptoms, and mean BMI was 26.2 kg/m². KEEPS participants were at overall lower risk of CVD than Women’s Health Initiative (WHI) participants: lower mean systolic BP, lower mean BMI, more favorable lipid parameters (all P values <0.01). At baseline, CVD risk factors, as well as CIMT and CAC values, were comparable across groups. Mean baseline CIMT for all groups was 0.712 ± 0.09 mm. Thus, KEEPS has several design features that are distinctly different from the WHI design, including: enrollment of younger and generally healthier perimenopausal and recently menopausal women; administration of a lower dose of CEE (0.45 mg daily) versus 0.625 mg administered in WHI; one arm that includes estradiol and a transdermal route of delivery; cyclic administration of natural progesterone versus continuous therapy with synthetic medroxyprogesterone acetate in WHI; and inclusion of only those women undergoing natural and non-surgical menopause. KEEPS findings that will be presented at this plenary session include the effects of the interventions on atherosclerosis progression by CIMT and CAC and effects on cognitive function assessed by a comprehensive and detailed battery of cognitive tests.

Learning Objectives:
At the conclusion of this presentation, participants should be able to:

• Understand the rationale for the KEEPS trial and differences in study design compared to the Women’s Health Initiative (WHI)

• Describe the differences in the hormone interventions and in the baseline characteristics of the KEEPS study population, compared to WHI

• Recognize the strengths and limitations of the KEEPS design, including the use of vascular imaging (surrogate outcomes) rather than clinical CVD events
Plenary Symposium #1—Presidential Symposium

“New Findings from the Kronos Early Prevention Study (KEEPS) Randomized Trial”

Supported in part by grant funding from: Noven Pharmaceuticals, Inc.

Effects of Oral Conjugated Estrogen or Transdermal Estradiol Plus Oral Progesterone Treatment on Common Carotid Artery Intima Media Thickness (CIMT) & Coronary Artery Calcium (CAC) in Menopausal Women: Initial Results from the Kronos Early Estrogen Prevention Study (KEEPS)

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The KEEPS was a 4-year randomized controlled trial testing for effects of menopausal hormone treatment (MHT) initiated within 3 years of menopause on atherosclerosis progression. The primary endpoint was CIMT by high-resolution B-mode ultrasound performed twice at baseline and annually thereafter. CAC score by high resolution computed tomography measured at baseline and 48 months was a secondary endpoint. High CAC and clinical cardiovascular disease (CVD) were exclusion criteria. Additional endpoints included serum lipids, menopausal symptoms, and quality of life. Women [n = 772; 52.7 ± 2.6 (mean ± SD) years and 1.8 ± 0.8 (range 0.5–3.9) years from menopause] were randomized to either daily 0.45 mg/d oral conjugated estrogen (CEE), 0.05 mg/d transdermal estradiol, both with cyclic (200 mg/d x12 days/month) oral micronized progesterone, or placebo. At baseline cardiovascular risk factors including age, body mass index, blood pressure, smoking history, and lipid profiles as well as CIMT and CAC values were comparable among groups. Mean baseline CIMT for all groups was 0.712 ± 0.09 mm with a coefficient of variation (SD/mean) based on 2 pretreatment scans of 0.83 ± 0.98 %. Changes in CIMT were analyzed by intent-to-treat using calculated slope of the best fit regression line for all CIMT values from baseline to time of last scan in each subject having at least one follow-up scan with comparisons amongst groups by ANOVA. Additional post-hoc analyses adjusted for adherence to study treatments and use of other medications affecting cardiovascular risk, such as statins. Changes in CAC were also compared amongst entire groups with secondary analyses comparing subgroups with and without CAC score > 0 at baseline. As expected, the number of clinical CVD events (no myocardial infarctions or new onset angina; 3 episodes of transient cerebral ischemia; and no strokes) was too small for informative analysis. Up-to-date analyses of all endpoints will be presented, either during this session or separately, including effects of the interventions on cognition, menopausal symptoms, quality of life, mood, as well as adverse events observed.

Learning Objectives:

At the conclusion of this presentation, participants should be able to:

- Understand some limitations on interpretation of the cardiovascular outcomes of the WHI hormone trials
- Learn the effects of oral vs. transdermal hormone treatments on vascular imaging outcomes in KEEPS
- Appreciate the meaning and limitations of vascular imaging measurements as surrogates for clinical outcomes
The Kronos Early Estrogen Prevention Study: Results of the Cognitive & Affective Sub-Study (KEEPS Cog)
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The Kronos Early Estrogen Prevention Study (KEEPS) and the Cognitive and Affective Sub-Study (KEEPS Cog) concluded in 2012. The mission of KEEPS Cog, a randomized, double-blind, placebo-controlled, parallel-group design clinical study is to evaluate the differential efficacy of 4 years of therapy with transdermal estradiol (tE2) and conjugated equine estrogen (CEE) on cognitive and affective function of women within 3 years of menopause. The KEEPS Cog design included: 1) comparison of the cognitive effects of tE2 and CEE in a single study, 2) administration of low dose CEE (0.45 mg) 3) enrollment of healthy, younger perimenopausal women 4) cyclic administration of natural progesterone and 5) inclusion of women undergoing natural menopause. 662 women were enrolled in KEEPS Cog. Mean age at baseline was 52.7 years, 74% had a college education and 15% identified as African American or Hispanic. Mean Body Mass Index (BMI) was 26.4kg/m2 and 22% possessed at least one ApoE4 allele, a risk factor for Alzheimer’s disease. Mean plasma hormone levels (pg/ml) at baseline were: estradiol (20.2), estrone (23.3) and progesterone (335.7). KEEPS Cog employed a comprehensive battery of cognitive tests. A confirmatory factor analysis was conducted using four independent domain-specific factors, comprised of nine cognitive tests and a global cognitive measure. Factors included: Verbal Learning & Memory; Auditory Attention & Working Memory; Visual Attention and Executive Function; and Speeded Language and Flexibility. Mood indices included the Beck Depression Inventory and the Profile of Mood States. Analysis of baseline data revealed: 1) an inverse relationship between testosterone and verbal memory, 2) increased systolic blood pressure (BP) is related to adverse performance on working memory and attention, 3) based on cardiovascular risk markers (i.e., BMI, Framingham, carotid-intimal media thickness, systolic BP, LDL, HDL, triglycerides, fasting glucose) the latent profile analysis classified participants with a baseline coronary arterial calcification score of “zero” into two groups: i) those at “high-risk” for cardiovascular (CVS) disease and ii) those at “low-risk” for CVS disease, 4) the “low-risk” group performed better on tests of “global cognition” and “language and flexibility,” were better educated, and 5) the “high-risk” CVS disease group was older with higher prevalence of the ApoE4 allele.

Learning Objectives:
At the conclusion of this presentation, participants should be able to:

• Understand the key study-design differences between the KEEPS Cognitive and Affective Study (KEEPS-CA) and the WHI Memory Study (WHIMS)
• Discuss major findings of the KEEPS-CA study following analysis of both baseline and treatment phase data
• Review the potential clinical implications and new areas of hormone therapy research likely to emerge from findings of the KEEPS-CA study
Understanding & Communicating Risk

Vincent T. Covello, PhD. Center for Risk Communications, New York, NY

Risk communication is the two-way exchange of information about threats, including health threats. The goals of risk communication are to enhance knowledge and understanding, build trust and credibility, encourage dialogue, and influence attitudes, decisions, and behaviors. These goals apply to all four major types of risk communication: 1) information and education; 2) behavior change and protective action; 3) disaster warning and emergency notification; and 4) joint problem-solving and conflict resolution. To communicate risks effectively, programs should prepare a written communication plan in advance. Deciding ahead of time about many of the necessary communication decisions and activities allows for a quick and effective response during an emergency. Key elements include answering questions such as: What needs to be done? Who needs to know? Who is the spokesperson? And who needs to act? There are seven cardinal rules for effective risk communication: 1) Accept and involve the receiver of risk information as a legitimate partner, 2) Plan and tailor risk communication strategies, 3) Listen to your audience, 4) Be honest, frank, and open, 5) Coordinate and collaborate with other credible sources, 6) Plan for media influence, 7) Speak clearly and with compassion.

A fundamental concept of risk communication is that people experiencing stress typically: 1) have difficulty hearing, understanding, and remembering information, and, 2) want to know that you care before they care about what you know. A central theorem of risk communication is that people’s perceptions of the magnitude of risk are influenced by factors other than numerical data. Dr. Peter Sandman, a risk communication expert, has pointed out that there is low correlation between the technical seriousness of a risk (for example, how many people die from the risk) and its cultural seriousness (for example, how many people the risk upsets and how badly it upsets them). In research studies, the correlation hovers around 0.2, accounting for a tiny four percent of the variance. This often results in two problems: 1) risks that are likely to harm people do not upset them so they fail to take appropriate precautions, and, 2) risks that are not likely to harm people do nonetheless still upset them so they take unnecessary precautions. Many of the obstacles to effective risk communication derive from the complexity, incompleteness, and uncertainty of data. In addressing uncertainty, the following guidelines can help: 1) Acknowledge – do not hide – uncertainty, 2) Explain that risks are often hard to assess and estimate, 3) Explain how the risk estimates were obtained and by whom, 4) Announce problems and share risk information promptly, with appropriate reservations about uncertainty, 5) Tell people that what you believe either (a) is certain; (b) is nearly certain; (c) is not known; (d) may never be known; (e) is likely; (f) is unlikely; or (g) is highly improbable; and also tell them (h) what can be done to reduce uncertainty, 6) Tell people that what you believe now may turn out to be wrong later. The overarching objective of this presentation is to prepare participants to communicate more effectively about high concern issues related to age-related diseases and menopause. The specific goals of the presentation are to help participants: 1) craft and deliver messages responsive to audience concerns, 2) design communication strategies to enhance believability, trust and credibility, 3) develop new and innovative ways to communicate risk and benefit information proactively.

Learning Objectives:

At the conclusion of this presentation, participants should be able to:

• Craft and deliver messages responsive to audience concerns

• Design communication strategies to enhance believability, trust, and credibility

• Develop new and innovative ways to communicate risk and benefit information proactively
The Promise of Breast Cancer Prevention
Paul E. Goss, MD, PhD. Medicine, Harvard Medical School, Boston, MA

Breast cancer is increasing globally and is the commonest cancer and cause of cancer-related death in women on all continents. Screening, treatment and adjuvant therapies have made modest gains but there remains an urgent public health need to prevent this cancer. Lifestyle changes related to diet, exercise and weight control have resulted in modest reductions only in reducing risk, thus pharmacologic interventions with appropriate risk-benefit profiles remain attractive. Estrogens promote breast cancer in cell cultures and animal models, and high serum estrogen and testosterone levels are related to elevated risk. Both ultra-low and pharmacologically high levels of estrogens inhibit breast cancer growth in culture. Thus antagonizing estrogens specifically has been a logical approach. The ABC principal of prevention: Agent, Biomarker and Cohort, are at the heart of this endeavor. Tamoxifen and raloxifene decrease the risk of developing breast cancer by ~38% and both are FDA approved but the risk of endometrial cancer and thromboembolism have detracted from their use with only ~4% of US women eligible to take it, do so. The aromatase inhibitors prevent breast cancer in a number of estrogen dependent preclinical models and profoundly reduce contralateral breast cancers, a preventative effect, in breast cancer patients. Because of this record we examined the role of aromatase inhibitors in breast cancer prevention. Among three approved agents in common clinical use for cancer, we chose to test exemestane in prevention, because of its unique steroidal structure and possible mild androgenic benefit on bone metabolism. Our MAP3 prevention trial was a double-blind, placebo controlled clinical trial 4560 postmenopausal women. The median age of participants was 62.5 years and their baseline median Gail scores was 2.3 (>1.66 is the FDA approved GAIL score recommended for tamoxifen). At a median of 35 months of follow up 11 invasive breast cancers were detected among exemestane treated women and 32 in those on placebo, with a 65% relative reduction in the annual incidence (0.19% vs 0.55%). Adverse events occurred in 88% of the exemestane group and 85% of those on placebo (p=0.003). No significant differences between the groups in terms of skeletal fractures, cardiovascular events, other cancers, or treatment-related deaths were noted. Only minimal self-reported quality of life differences were observed. MAP3 provides a powerful tool to prevent breast cancer. The number-needed- to-treat (NNTT) to benefit one is comparable to statins preventing a cardiovascular event but still needs improving. Both the SERMs and the aromatase inhibitor cause profound reductions in breast cancer risk but the challenge is to improve risk identification. Numerous risk factors are well recognized and have been incorporated into risk identification algorithms such as the Gail, Claus, BRCAPRO, Jonker, IBIS or Tyrer-Cuzick and BOADICES models but unfortunately these models have been limited by the fact that some 60% of women who develop breast cancer are still not identified by these models. Intensive research on genetics, epigenetics, gene expression profiling and whole genome scans are underway to identify novel risk alleles that are associated with breast cancer. Genome-wide association studies have identified several common genetic variants, such as 2q35,16q12,5p12, 1p11, 14q24 and unique telomere dysfunctions are currently being examined as markers of risk. Including these and expanding the risk factors in the models to include mammographic breast density, pregnancy induced hypertention, alcohol intake, smoking history and other risk factors, may well narrow the Cohort of women most suitable for breast cancer prevention. In Summary, we have remarkable Agents to reduce ER+ breast cancer but novel agents capable of reducing ER-ve disease are needed. Anti-inflammatories and anti-hyperglycemics are promising. Mammographic breast density and plasma hormone levels have been disappointing as biomarkers of prevention and ongoing research is needed in this regard. For reasons outlined much work is needed to make breast cancer prevention as widely adopted by physicians and women as anti-hypertensive or lipid lowering medications.

Learning Objectives:

At the conclusion of this presentation, participants should be able to:

- Recognize that breast cancer is increasing globally and is the most common cancer and cause of cancer-related death in women on all continents
- Understand that much more work is needed to make breast cancer prevention as widely adopted by physicians and women as anti-hypertensive or lipid lowering medications
Plenary Symposium #2
“Chemoprevention of Breast Cancer in Healthy But High-Risk Women: The Clinical Conundrums”

Selecting Candidates for Chemoprevention & Choosing Among the Options: Tamoxifen, Raloxifene & Aromatase Inhibitors
Judy E. Garber, MD, MPH. Dana Farber Cancer Institute, Boston, MA

The original data suggesting that tamoxifen could reduce the risk of breast cancer development in women at increased risk came from the adjuvant treatment trials, in which women receiving tamoxifen were less likely to develop a second primary tumor than women who did not take the drug. The SERM agents, tamoxifen and raloxifene, as well as at least two others not being developed in the US for this purpose, have been shown to reduce breast cancer risk by about 50% when taken daily for 5 years. However, the side effect profiles have resulted in very poor uptake by women at risk and by their physicians. Raloxifene, which does not increase the risk of endometrial cancer as does tamoxifen, and which improves bone density which tamoxifen does not, is more acceptable to providers and patients. From the breast cancer prevention perspective, however, raloxifene is about 75% as effective as tamoxifen, but has about 75% the risk of adverse events, including venous thromboembolism and stroke in women after 60. Moreover, the benefit of tamoxifen persists for at least 10 years after completion of 5 years of the drug. The duration of benefit with raloxifene appears to be much more limited. Among premenopausal women, however, only tamoxifen is approved for use. There is an interesting manuscript from the NCI group (Freedman AN et al, J Clin Oncol. 2011;29:2327-33) in which the risks and benefits of tamoxifen and raloxifene are compared for women by age and level of breast cancer risk which we will review. Other SERM agents, lasofoxiphene and arzoxifene have been shown to have promise for breast cancer risk reduction but will not be developed for this purpose. Basically, tamoxifen is worth considering almost only in women without a uterus after menopause. The aromatase inhibitor Exemestane, as discussed by Dr. Gross, has also been shown to significantly reduce the risk of new primary breast cancers, initially in breast cancer adjuvant treatment trials, but subsequently also in a randomized placebo-control trial (the ExCel trial). These drugs also have side effects as bone loss and arthralgias and myalgias of varying severity. They are not good choices for women with existing bone loss. There are questions about potential adverse cardiac effects of the AI’s, but this has been studied in adjuvant treatment trials with reassuring results. Of concern, the manufacturer will not bring Exemestane to the FDA for a prevention indication despite the results of the trial. Other agents currently under study for breast cancer prevention include metformin because of data targeting the IGF-1 pathway, Vitamin D, and in a series of careful trials from the Italian group, low dose tamoxifen (5mg vs. 20mg) or tamoxifen with hormonal therapy. Low dose tamoxifen is also under study in women at increased risk based on therapeutic chest wall radiation, as for Hodgkin’s disease.

Learning Objectives:
At the conclusion of this presentation, participants should be able to:

• Become familiar with the risks and benefits of the existing risk-reducing agents, tamoxifen, raloxifene, and exemestane

• Become familiar with the adverse effects of these agents, and approaches that can help mitigate them

• Learn about the tools available to help weigh the risks and benefits of medication for risk reduction
Vitamin D & Calcium: Why Such Confusion?
Clifford Rosen, MD. 1Clinical & Translational Research, Maine Medical Center, Scarborough, ME; 2Medicine, Tufts University, Boston, MA

It has been almost two years since the Institute of Medicine issued Dietary Reference Intakes for calcium and vitamin D for the North American Population. The abundance of evidence reinforced by two independent systematic reviews reinforced the recommendation that individuals consume a total of 600-800 IU of vitamin D and 1000-1200 mg of calcium per day. Paradoxically, since that publication the, controversy about the role these two nutrients play in maintaining both skeletal and non-skeletal health has grown rather than subsided. For example, soon after the IOM report was issued, The U.S. Public Health Service Task Forces published a distinctly different perspective questioning the appropriateness of low dose calcium and vitamin D supplementation in any population. On the other hand, the Endocrine Society Guidelines published an analysis that suggested individuals should try to attain a serum 25OHD level of at least 30 ng/ml. More recently New England Journal of Medicine published another meta-analysis of vitamin D and fractures implying that greater supplementation with Vitamin D, beyond the IOM recommendations, was warranted to prevent fractures, particularly in older individuals. Furthermore, a wide range of Society guidelines as well as recommendations from ad hoc committees and an abundance of new meta-analyses from the same randomized trials used in the IOM report, has led to even greater confusion. In this talk, I will outline several major misperceptions that have emerged about calcium and vitamin D. In response to these issues we return to the evidence for clarification. My goal is to provide a roadmap for providers that ultimately will become part of any clinician-patient conversation.

Learning Objectives:
At the conclusion of this presentation, participants should be able to:

- Understand evidence-based approaches to vitamin D and calcium trials
- Define skeletal vs non-skeletal health outcome measures
- Understand the role of 25(OH)D as an exposure measure rather than a biomarker
Bisphosphonate Drug Holidays: To Be or Not to Be?
Nelson B. Watts, MD. Mercy Health Osteoporosis & Bone Health Services, Cincinnati, OH

Bisphosphonates have been widely used for treatment of osteoporosis and other diseases since the mid 1990s. Recent concerns about osteonecrosis of the jaw and atypical femur fractures as a possible consequence of long-term bisphosphonate therapy have been raised. Because of their unique properties (binding to and accumulating in bone), there is also evidence that sufficient drug may be present after 3-5 years of treatment to sustain fracture reduction over at least 1-2 years after administration of the drug is stopped. The evidence behind the concept of “drug holidays” will be discussed.

Learning Objectives:
At the conclusion of this presentation, participants should be able to:
- Become familiar with mechanism of action of bisphosphonates
- Understand the benefits shown in clinical trials
- Identify and put safety concerns into perspective
Plenary Symposium #3
“Controversies in Bone Health: Asking the Hard Questions”

Supported in part by grant funding from: Lilly USA, Merck & Co., Inc., Warner Chilcott

Abstract not available.

Learning Objectives:
At the conclusion of this presentation, participants should be able to:

- Describe the pharmacological agents approved for osteoporosis treatment
- Contrast the benefits beyond the bone for different classes of osteoporosis treatments
- Apply unique requirements of individual patients at progressive stages of life to selection of the most appropriate osteoporosis therapy
ABSTRACTS & LEARNING OBJECTIVES (continued)

Plenary Symposium #4
“The Female Heart—a Primer”
Supported in part by grant funding from: Astellas

What Makes Women Different? Getting to the Heart of the Matter
Puja K. Mehta, MD, FACC. Cardiology, Cedars-Sinai Heart Institute, Los Angeles, CA

Heart disease is the number one killer in women at all ages, and death rates in women ages 35 to 54 are increasing. While the overall trend in cardiovascular mortality, including heart disease, is on the decline compared to previous decade, a gender gap remains. Ischemic heart disease is a significant, under-recognized contributor to death and disability in women. Women face an adverse heart disease prognosis that is not fully accounted for by age, comorbidity, coronary atherosclerotic disease (CAD) extent and severity, or treatment gender gaps. There is a gender-difference in presentation, diagnosis, and treatment of heart disease. Women often have more atypical, milder symptoms of angina compared to men, and are also more likely to have open coronary arteries on angiography, which leads to false reassurance that they do not have heart disease. Data from the National Heart, Lung, and Blood Institute-sponsored, multi-site Women’s Ischemia Syndrome Evaluation (WISE) Study (Principal Investigator: C. Noel Bairey Merz, MD) indicate that microvascular coronary dysfunction (MCD) is prevalent and a mechanistic pathway of ischemic heart disease in women. MCD is defined as persistent symptoms of angina (typical and atypical), objective evidence of ischemia by stress testing, and no obstructive CAD by angiography. Currently, invasive coronary reactivity testing with vasoactive substances (adenosine, acetylcholine, and nitroglycerin) in the catheterization laboratory is used to detect abnormal coronary flow reserve, reduced coronary blood flow, endothelial, and coronary smooth muscle dysfunction. Non-invasive method of detecting myocardial hypoperfusion that can indicate MCD using cardiac magnetic resonance imaging is under investigation. Endothelial dysfunction and abnormal coronary flow reserve are both linked with adverse prognosis in women with ischemic heart disease and symptoms. Treatment of MCD includes traditional anti-anginal medications, and novel therapeutic options, such as alpha-beta blockers and late sodium channel blocker ranolazine. Aggressive educational efforts have made an impact in heart disease awareness in women but much work remains. Primary care providers and allied health professionals should utilize effectiveness-based guidelines for prevention of cardiovascular disease in women (updated 2011).

Learning Objectives:

At the conclusion of this presentation, participants should be able to:

- Recognize that ischemic heart disease is a significant, under-recognized contributor to death and disability in women
- Recognize that there are clear sex differences in the pathophysiology and presentation of heart disease, and there are unique cardiovascular risk factors specific to women
- Understand that coronary endothelial and microvascular dysfunction are key players in heart disease in women
Plenary Symposium #4
“The Female Heart—A Primer”
Supported in part by grant funding from: Astellas

Primary Prevention of Cardiovascular Disease: Nipping Common Risks in the Bud
Karol E. Watson, MD. Cardiology, David Geffen School of Medicine at UCLA, Los Angeles, CA

Cardiovascular disease (CVD) remains the leading cause of death in the United States and despite continued improvements in morbidity and mortality, CVD rates remain unacceptably high. Although awareness of CVD in women has lagged behind that of men, research on prevention in women is beginning to emerge, and these data show that there are several important differences between women and men. This is critically important for management of women at risk for CVD, since deaths from CHD have surpassed those of men since 1984. Although awareness of CVD in women is increasing, more attention is required to determine the most effective means of preventing cardiovascular events. Furthermore, guidelines for prevention in women are limited since women remain under-represented in clinical trials and gender-specific analyses have not been uniformly provided in major publications about CVD over the past 10 years. Some of the differences that have been elucidated in the pathophysiology of atherosclerosis are considerable between women and men. In addition, several risk factors exist that are completely unique to women and others hold greater risk for women as compared to men. The optimal preventive medications and strategies are active areas of investigation. Medications for primary prevention such as aspirin, statins and HRT have been the focus of intense investigation recently, and the data continues to emerge. There has been a significant shift in our approach to prevention of cardiovascular diseases over the past several years, especially in attention to differences between the sexes. In regards to women, the American Heart Association recently updated its guidelines for prevention of heart disease in women to reflect the new evidence. These guidelines recommend many lifestyle preventive measures such as more exercise and the consumption of oily fish at least twice a week. The new guidelines do not recommend hormone replacement therapy, antioxidants, or folic acid supplements for CHD prevention. Low-dose aspirin therapy is recommended for women >65 years, but not for younger women. Our current understanding of the most appropriate and effective strategies to prevent cardiovascular disease continue to evolve. In the future it is likely that further attention to lifestyle, including regular exercise, weight management and healthy eating will remain the mainstay of prevention.

Learning Objectives:
At the conclusion of this presentation, participants should be able to:

• Review the pathophysiology, epidemiology, and current recommendations for the prevention of cardiovascular diseases
• Review sex-based differences in cardiovascular risk, risk stratification, and management
• Discuss strategies in cardiovascular disease prevention and how they differ by sex
• Describe recent advances relevant to the care of women with cardiovascular disease
Move More, Sit Less: A First-Line, Public Health Preventive Strategy
Barry A. Franklin, PhD. Preventive Cardiology & Rehabilitation, William Beaumont Hospital, Detroit, MI; Physiology, Wayne State University, Detroit, MI

Although the inverse relationship between cardiorespiratory fitness, expressed as metabolic equivalents (METs; 1 MET = 3.5 mL O2/kg/min), and cardiovascular and all-cause mortality has been widely promulgated among physiologists and epidemiologists, the medical community has, to a lesser extent, embraced aerobic capacity as one of the strongest and most consistent prognostic markers in normal weight, overweight, and obese men and women, with and without other co-morbid conditions (e.g., hypertension, impaired fasting glucose, diabetes mellitus). Moreover, it appears that the least active, least fit, “high risk” patient cohort (bottom 20%) may especially benefit from structured exercise, increased lifestyle physical activity, or both, to improve survival. Recent studies have also shown that sedentary behaviors alone, especially sitting, independent of aerobic capacity or leisure time physical activity, are associated with higher rates of all-cause and cardiovascular mortality, obesity, type 2 diabetes, endothelial dysfunction, and metabolic syndrome as well as other physiologic derangements. Collectively, these data highlight the importance of avoiding prolonged uninterrupted periods of sedentary (primarily sitting) time, as well as increasing time spent in moderate-to-vigorous intensity exercise and lifestyle physical activity, in combating chronic disease. It is time for a new paradigm in exercise prescription beyond target heart rates and METs: move more, sit less.

Integrative Approaches to Prevention: Fact & Fiction
Mimi Guarneri, MD, FACOG. Scripps Center for Integrative Medicine, Los Angeles, CA

This presentation will approach the prevention and treatment of cardiovascular disease from a personalized, predictive, proactive perspective. The Interheart study has taught us the risk for 90% of acute myocardial infarctions. Modifying risk requires a combination of lifestyle change, nutraceuticals and pharmacologic therapy. Uncoding the human genome has pioneered the way to an understanding of genetic risk. However, equally if not more important is the revolution in elucidating the epigenome. Understanding why genes turn on and off is paramount to disease treatment and prevention. Research on the Amish community has demonstrated that lifestyle can trump your genes. Understanding the ApoE isoforms and the role of 9p21 are just examples of how we can use the human genome to predict risk and tailor nutrition therapy. This information will usher us into an era of medicine in which we truly have the opportunity to scientifically validate mind-body therapies, nutraceuticals and the concept of food as information. Already in cardiology genetic testing is being utilized to determine medication dosages, potential side effects and even the need for treatment. Diagnostic technology is allowing us to detect medical challenges long before they erupt into clinical disease. Tailoring programs of nutrition, nutraceuticals and lifestyle change based on genetic susceptibility and epigenetics is a paradigm shift for modern medicine.

Learning Objectives:
At the conclusion of this presentation, participants should be able to:
- Understand nutrition and its role in prevention of cardiovascular disease
- Review the link between stress and development of cardiovascular disease
- Understand emerging risk factors for heart disease
- Utilize your genetic makeup to develop a personalized and proactive guide to optimum health
Move More, Sit Less: A First-Line, Public Health Preventive Strategy
Barry A. Franklin, PhD. 1Preventive Cardiology & Rehabilitation, William Beaumont Hospital, Detroit, MI; 2Physiology, Wayne State University, Detroit, MI

Although the inverse relationship between cardiorespiratory fitness, expressed as metabolic equivalents (METs; 1 MET = 3.5 mL O2/kg/min), and cardiovascular and all-cause mortality has been widely promulgated among physiologists and epidemiologists, the medical community has, to a lesser extent, embraced aerobic capacity as one of the strongest and most consistent prognostic markers in normal weight, overweight, and obese men and women, with and without other co-morbid conditions (e.g., hypertension, impaired fasting glucose, diabetes mellitus). Moreover, it appears that the least active, least fit, “high risk” patient cohort (bottom 20%) may especially benefit from structured exercise, increased lifestyle physical activity, or both, to improve survival. Recent studies have also shown that sedentary behaviors alone, especially sitting, independent of aerobic capacity or leisure time physical activity, are associated with higher rates of all-cause and cardiovascular mortality, obesity, type 2 diabetes, endothelial dysfunction, and metabolic syndrome as well as other physiologic derangements. Collectively, these data highlight the importance of avoiding prolonged uninterrupted periods of sedentary (primarily sitting) time, as well as increasing time spent in moderate-to-vigorous intensity exercise and lifestyle physical activity, in combating chronic disease. It is time for a new paradigm in exercise prescription beyond target heart rates and METs: move more, sit less.

Learning Objectives:
At the conclusion of this presentation, participants should be able to:

- Summarize contemporary physical activity guidelines for all Americans, with specific reference to the duration (hours/week) of moderate intensity and vigorous exercise needed to evoke significant health benefits
- Identify high-risk and cardioprotective fitness levels expressed as metabolic equivalents (METs)
- Clarify the impact that sedentary behaviors alone, especially sitting, independent of aerobic capacity or leisure-time physical activity, have on all-cause and cardiovascular mortality
Motivational Interviewing: Helping Women See Their Health as a Daily Priority

Kathy Berra, MSN, ANP, FAAN. Stanford Prevention Research Center, Stanford University School of Medicine, Palo Alto, CA

"Having a working knowledge of and comfort in using "behavioral counseling" requires an understanding of the complexities of behavior, how to effectively and efficiently impart information in a clinical encounter, and how to evaluate its efficacy." 1 Cardiac and vascular diseases are the leading cause of death in women worldwide. Achieving healthy lifestyle behaviors plus compliance to important medical therapies significantly influences the development and severity of heart and vascular related illness. Motivational Interviewing (MI) is an effective technique for facilitating behavior change. It is based on empathetic and reflective listening, it deals directly with resistance, and supports self-efficacy. An important component of MI is showing appreciation for efforts made to change behavior, and showing confidence in the patient's ability to change behavior. 2 Building skills to effectively use MI in clinical encounters can improve patient behavior change. In addition, helping women appreciate the importance of their personal health as it relates to the health of their family is an additional motivation for women to improve healthy lifestyles. 3

Battle of the Weight Loss Diets: Is Anyone “Winning” (at Losing)?

Christopher D. Gardner, PhD. Stanford Prevention Research Center, Stanford University School of Medicine, Palo Alto, CA

While the “Low-Fat” diet was the predominant public health recommendation for weight loss and weight control for the past several decades, the obesity epidemic continued to grow. An alternative “Low-Carb” approach, although originally dismissed and even vilified, was comparatively tested in a series of studies over the past decade, and has been found in general to be equally if not more effective than Low-Fat for weight loss and for several related metabolic health measures. From a glass half full perspective, this suggests that there is more than one choice for a dietary approach to lose weight, and that Low-Fat and Low-Carb may be equally effective. From a glass half empty perspective, the average amount of weight lost on either of these two dietary approaches under the conditions studied, particularly when followed beyond one year, has been modest at best and negligible at worst, suggesting the two approaches may be equally ineffective. One could resign themselves at this point to focusing on calories and energy intake restriction, regardless of macronutrient distributions. However, before throwing out the half-glass of water, it is worthwhile to consider that focusing on average results may mask important subgroup successes and failures. In all weight loss studies, without exception, the range of individual differences in weight change within any particular diet groups is orders of magnitude greater than the average group differences between diet groups. Several studies have now reported that adults with greater insulin resistance are more successful with weight loss on a lower carbohydrate diet vs. lower fat, while adults with greater insulin sensitivity are equally or more successful with weight loss on a lower fat diet vs. lower carbohydrate. Other preliminary findings suggest there may be some promise with matching individuals with certain genotypes to one type of diet over another for increasing weight loss success. Future research to address the macronutrient intake component of the obesity epidemic should build on these recent insights and be directed toward effectively classifying individuals that can be differentially matched to alternate types of weight loss diets that maximize weight loss and weight control success.

Learning Objectives:

At the conclusion of this presentation, participants should be able to:

• Provide patients with an informed opinion on the comparative benefits of low-fat vs. low-carb weight loss diets
• Differentiate patients who might be predisposed to greater weight loss success with a lower carbohydrate diet due to insulin resistance
• Identify the pitfalls of oversimplifying “low-fat” and “low-carb”
• Provide potentially innovative strategies to patients for successful and lasting behavioral dietary change
Plenary Symposium #5
“Making Lifestyle Modification Work: Strategies to Meet the Challenges”

Motivational Interviewing: Helping Women See Their Health as a Daily Priority
Kathy Berra, MSN, ANP, FAAN. Stanford Prevention Research Center, Stanford University School of Medicine, Palo Alto, CA

“Having a working knowledge of and comfort in using “behavioral counseling” requires an understanding of the complexities of behavior, how to effectively and efficiently impart information in a clinical encounter, and how to evaluate its efficacy.” 1 Cardiac and vascular diseases are the leading cause of death in women worldwide. Achieving healthy lifestyle behaviors plus compliance to important medical therapies significantly influences the development and severity of heart and vascular related illness. Motivational Interviewing (MI) is an effective technique for facilitating behavior change. It is based on empathetic and reflective listening, it deals directly with resistance, and supports self-efficacy. An important component of MI is showing appreciation for efforts made to change behavior, and showing confidence in the patient’s ability to change behavior. 2 Building skills to effectively use MI in clinical encounters can improve patient behavior change. In addition, helping women appreciate the importance of their personal health as it relates to the health of their family is an additional motivation for women to improve healthy lifestyles. 3

Learning Objectives:
At the conclusion of this presentation, participants should be able to:

• Describe the importance of effective behavioral change counseling for lifestyle change in clinical encounters
• Define the counseling strategies of Motivational Interviewing for use in clinical encounters
• Understand motivators and barriers for behavior change in women
Kenneth W. Kleinman Endowed Lecture
“Changes in the New Healthcare Law and Their Effects on Practitioners”

Changes in the New Healthcare Law and Their Effects on Practitioners
Deborah E. Trautman, PhD, RN. Center for Health Policy & Healthcare Transformation, Johns Hopkins Medicine, Baltimore, MD

On June 28, 2012, the Supreme Court of the United States confirmed the constitutionality of the individual mandate and cleared the path for full implementation of the Affordable Care Act (ACA). This presentation will discuss implications of the Supreme Court Decision and the current status of the ACA implementation. The session will provide an opportunity to review key provisions in the ACA, with particular focus on changes in the law and their affect on practitioners. The presentation will include consideration of the challenges ahead in health reform.

Learning Objectives:
At the conclusion of this presentation, participants should be able to:

• Discuss key provisions in the Affordable Care Act
• Describe the current status of implementation and impact of the Affordable Care Act
• Identify challenges faced in effective implementation of the law
The obesity epidemic, while slowing in younger populations, is continuing apace in midlife women, with obesity rates approaching 50% and the most rapid increase in the BMI range between 30-35 kg/m2. Of the known increased morbidity and mortality associated with obesity, the acquisition of insulin resistance and metabolic syndrome is the most pernicious for the midlife woman. Adipose tissue is a rich source of chemical messengers and the development of an inflammatory macrophage phenotype and metastatic fat appear to be key features of the acquisition of an adverse metabolic profile. There is also a new appreciation of the effect of obesity on circulating reproductive hormones, which may have meaning in terms of menopausal symptoms that are experienced at midlife. There is a progressive relationship between obesity and reduced LH, FSH, estrogen and progesterone metabolites in perimenopausal women, with reductions of 30% in luteal progesterone and a marked tendency towards anovulation as a woman progresses through menopause. Adipose tissue also appears to favor androgen secretion and may be a peripheral source of the increased androgens observed in female obesity. While many pharmacologic treatments are under testing for use as a ‘magic pill’ to cure obesity, clinicians must provide rational advice for patients to help them avoid excessive weight gain or initiate a weight loss program. A basic behavioral model for clinical care of patients with modest weight loss goals of 5-10% of initial body weight includes frequent office visits, positive reinforcement, emphasis on multiple behavioral changes, and the provision of a ‘tool box’ from which patients may draw useful items as needed. Anticipation of recidivism is helpful. While there is no single dietary plan that is especially beneficial for all, patients may choose from a variety of methods that are suited to their lifestyle. For those who are morbidly obese, defined as a BMI>35 mg/m2, as well as those who have failed multiple attempts at lifestyle modification, behavioral methods are unlikely to work. For these patients, as well as those with lower BMI who have developed comorbidities such as type 2 diabetes or hypertension, surgical options will be presented. Finally, new research on circadian disruption, sleep loss, and regulation of body weight suggest that menopausal women may be particularly vulnerable to adverse metabolic consequences if they are rendered sleepless by symptoms.

Learning Objectives:
At the conclusion of this presentation, participants should be able to:

- Identify the relationship of BMI with morbidity and mortality
- Enumerate the medical risks associated with obesity in women
- Counsel obese women regarding sensible methods for weight loss and weight loss targets
- Counsel and refer patients appropriately for bariatric surgery
Plenary Symposium #6
“Obesity & The Menopausal Woman”

New & Emerging Weight Management Strategies
Louis J. Aronne, MD, FACP. Medicine, Weill-Cornell Medical College, New York, NY

There is a huge void in the current pharmacological treatment options for obesity. This gap is surprising given the high prevalence and associated costs of obesity. Many factors have prevented active drug development, including the poor safety and efficacy of earlier antiobesity drugs. However, there are now several compelling targets on the horizon. The new generation of antiobesity drugs offers hope for the management of obesity, but no single agent is likely to be a panacea. Rather, obesity will need to be managed like many other chronic diseases, with combination therapies and long-term treatment in order to achieve sustained success. New targets have arisen as more research has been performed to understand the complex circuitry that controls energy homeostasis. The goal of this review is to discuss the pathophysiology of obesity and the pharmacological agents that have recently been FDA approved for the treatment of obesity.

Lecture presented by:
Steven R. Smith, MD
Scientific Director
Translational Research Institute for Metabolism & Diabetes
Professor
Sanford-Burnham Medical Research Institute
Orlando, FL

Learning Objectives:
At the conclusion of this presentation, participants should be able to:

• Understand the pathophysiology of obesity
• Understand the mechanism of action and clinical aspects of pharmacologic agents used to treat obesity
• Learn how to evaluate the obese patient and, based on that evaluation, select an appropriate treatment plan
When Surgery is the Only Option
Kimberley E. Steele, MD. Johns Hopkins Center for Bariatric Surgery, Johns Hopkins Bayview Medical Center, Baltimore, MD

The Centers for Disease Control (CDC) has described the American tendency toward unhealthy food choices, overeating and inactivity as “obesogenic.” The prevalence of obesity in the U.S. has risen such that over half of the adult population will have a body mass index >30 by the year 2025. Among American women of reproductive age (20 to 34 years old), 31.4% are obese. This percentage increases with age, peaking at 42.4% among women aged 55-64 years, then decreasing for women age 65 years and older. Obese women are at risk for multiple medical co-morbidities and pregnancy-related complications. Obstetricians and gynecologists should be familiar with current approaches to the prevention and management of obesity. The etiology of obesity is multi-factorial and includes genetics, behavior and environment as they affect metabolism, activity, and dietary intake. Acknowledgment of the problem and appreciation of the risks of obesity and its associated diseases is essential. Informal office counseling is usually the initial approach to managing weight. When this fails, structured weight loss programs that include diet modification, medications, exercise, and behavior modification may be utilized. However, due to the limited long term effectiveness of these modalities bariatric surgery is increasingly becoming a preferred option. Several surgical approaches are available. Primary care physicians should be familiar with the advantages and disadvantages of each procedure and the importance of long term management of these individuals. To date, surgery has been the most successful option for long term weight loss success. This session will focus on the surgical approaches to morbid obesity

Learning Objectives:
At the conclusion of this presentation, participants should be able to:

• Become familiar with the criteria used to determine if a patient is a candidate for surgery
• Understand the preoperative, perioperative, and postoperative management of a bariatric patient including nutritional requirements
• Describe the various surgical options including laparoscopic adjustable gastric banding, sleeve gastrectomy, and Roux-en Y Gastric Bypass
• Discuss new and emerging weight loss techniques
Plenary Symposium #7

“WHI+10: The New Practice Paradigm in Hormone Therapy”

Supported in part by grant funding from: Teva Pharmaceuticals, Inc., Novo Nordisk, Inc.

Estrogen Therapy: Dose, Delivery, Duration
Robert L. Reid, MD. Obstetrics & Gynecology, Queen’s University, Kingston, ON, Canada

Estrogen therapy is the most effective treatment for menopausal vasomotor symptoms and associated manifestations that adversely affect quality of life during and after the menopausal transition (sleep disturbance, irritability, mood changes). Both systemic estrogen, in sufficient dosages, and topical estrogen can alleviate vulvovaginal atrophy. Estrogen therapy remains one of the most effective means to prevent osteoporosis and is first line treatment in symptomatic menopausal women. Estrogen therapy results in delayed development of coronary heart disease in recently menopausal women. Risks of menopausal estrogen therapy include venous thromboembolism, cholelithiasis, rare cases of ischemic stroke and a probable increase in breast cancer with longer durations of use. Currently there are inadequate data to demonstrate greater efficacy or safety with any particular estrogen so that known benefits and risks should be considered class effects. Contemporary data indicate that low and ultra-low dose therapy, after 3-4 weeks, can relieve many menopausal symptoms and will prevent the accelerated bone loss typical of the postmenopausal period. These low dose estrogen formulations appear to lower the risk for stroke and possibly VTE. They can also be expected to reduce the progestin requirement for endometrial protection. Route of administration needs to be determined by patient preference and clinical circumstances. Specific circumstances may suggest that a particular route of delivery is optimal (such as transdermal therapy for cigarette smokers or for some women with low libido). While observational data indicate that transdermal estrogen may reduce the risks of VTE and stroke it is presently unclear whether these apparent benefits result from differential actions on hepatic clotting factors or whether they result from lower absorption (since higher dose transdermal products may be associated with an increased risk of both VTE and stroke). Given that the benefits of estrogen therapy to health and quality of life outweigh the risks to most women duration of therapy should usually be determined by the persistence of menopausal symptoms or other health concerns.

Learning Objectives:
At the conclusion of this presentation, participants should be able to:

- Cite indications for estrogen therapy
- Quantify the material benefits and risks for women considering estrogen therapy
- Select the optimal dose, route of delivery, and duration of therapy for individual women
Plenary Symposium #7
“WHI+10: The New Practice Paradigm in Hormone Therapy”
Supported in part by grant funding from: Teva Pharmaceuticals, Inc., Novo Nordisk, Inc.

Progestogen Therapy: Dose, Delivery, Duration
James H. Liu, MD. 1Obstetrics & Gynecology, McDonald Women’s Hospital, Cleveland, OH; 2Reproductive Biology, Case School of Medicine, Cleveland, OH

In prescribing progestogens for women as part of hormone therapy, the overall goals are to prevent endometrial hyperplasia, improve compliance by reducing side effects related to vaginal bleeding, and reducing overall progestogen exposure. In contrast to estrogen-only treatment, lessons learned from the two companion WHI clinical trials suggest that the previously popular continuous combined estrogen-progestin therapy is associated with a small increase risk of breast cancer and coronary heart disease. The biologic effects of progestogens are mediated through two receptor isoforms, nuclear progesterone receptors A and B. Similar to estrogen receptors alpha and beta, the distribution of progesterone receptors are ubiquitous and have been localized to tissues such as uterus, breast, and brain. Progestogens are derived from either a 21-carbon or a 19-carbon skeleton. The bioavailability of natural progesterone is significantly influenced by route of administration. Oral progesterone formulations are: 1) rapidly converted to less active metabolites during the first pass through the liver; 2) are not well absorbed; and 3) must be micronized to enhance bioavailability. Transdermal progesterone creams are not sufficiently absorbed for clinical effects. In contrast, transvaginal progesterone preparations are preferentially transported to the uterus and endometrium and are well absorbed. Intrauterine delivery of progestogens via the IUD is the most direct and efficient option. Various prescribing patterns for estrogen-progestin therapy have been utilized. These include, cyclic estrogens on days 1-30 with progestogens on days 1-12; cyclic estrogen on days 1-25 with progestogens on days 14-25; continuous, combined estrogen-progestogens every day; and long cycle therapy consisting of daily low dose estrogen and progestogens every 3 months for 14 days. For women with estrogen-exposed endometrium, the minimal duration of progestogen treatment should be 12 days. Experience with these prescribing patterns, advantages, bleeding patterns, and possible side effects of these approaches will be discussed.

Learning Objectives:
At the conclusion of this presentation, participants should be able to:

• Identify the various progestogens used in clinical practice
• Understand the impact of route of administration on progestogen bioavailability
• Recognize the advantages and side effects of various progestogen treatment regimens in hormone therapy
It Takes 2 to Tango: Reviving a Languishing Libido
Sheryl A. Kingsberg, PhD1, Stanley E. Althof2. 1Reproductive Biology, Case Medical Center, Cleveland, OH; 2Case Western Reserve University School of Medicine, West Palm Beach, FL

Aging women and their partners often have to overcome several obstacles that threaten the quality of their sexual lives. While Western Culture seems to have finally given acceptance to the idea that women and men over 50 are still entitled to a sexual life, and, that some over 50 celebrities are still "hot" (e.g. Sigourney Weaver, Meryl Streep, Emma Thompson, Tom Cruise, George Clooney, Pierce Brosman, Daniel Craig), these obstacles continue to threaten midlife sexual self-esteem and satisfaction. Midlife women and men often face the sexual obstacle of declining sexual drive. Testosterone, which is known to have a strong impact on drive, declines in both men and women as a function of age. For women, circulating testosterone levels are, by age 50, half of what they were when a woman was in her early 20 due to declining ovarian function. Men too, may experience a decline in testosterone levels around mid life. If loss of testosterone wasn't enough of an obstacle for women, declining ovarian function also results in loss of estrogen and with it, VVA (vulvovaginal atrophy) as well as overall tissue changes resulting in aging. And aging men are faced with increasingly more unreliable erections as a result of aging, illness and medication. And finally, irrespective of age, sexual problems are highly prevalent. For women, almost 12 percent are likely to have a sexual dysfunction. For men, approximately 25 percent of men suffer from erectile dysfunction or premature ejaculation. It is fascinating to study the reciprocal relationship between male and female dysfunctions. Women partners of men with erectile dysfunction and premature ejaculation have more sexual problems than partners of men without male sexual dysfunction. It may therefore be relevant to inquire whether the patient's partner has any sexual dysfunction to determine if it has an impact on her. Similarly, women's sexual problems impact on the partner's sexual life as well. HCPs treating postmenopausal women should include questions about partner functioning when taking a sexual history and assessing sexual function. Given the high prevalence of sexual problems in both men and women, it is important to consider partner function when a woman presents with a sexual concern. In keeping with the awareness of sexual function in the context of the couple, treatment options may include some office based sex therapy for the couple as well as some individual counseling and/or pharmacologic options.

NAMS 2012 Hormone Therapy Position Statement
Margery L. Gass, MD, NCMP. The North American Menopause Society, Mayfield Heights, OH

In March 2012 the Board of Trustees of The North American Menopause Society (NAMS) updated the 2010 NAMS Hormone Therapy Position Statement because of new publications in the field and because of the growing recognition that estrogen therapy and combined estrogen/progestogen therapy have different risk profiles. It was concluded that these different profiles could affect recommendations on duration of use. Previous hormone therapy position statements from NAMS noted the improved safety profile when hormone therapy is used by younger postmenopausal women as compared to older postmenopausal women. The current position statement notes that the primary reason for recommending a 3-5 year maximum for use of combined estrogen/progestogen is the increase in invasive breast cancer that surfaces in that time frame. No increase in breast cancer was seen in the women using estrogen alone in the Women’s Health Initiative. That finding allows greater flexibility in duration of use for appropriately selected women. In July 2012 NAMS focused on demonstrating widespread agreement on a key component of the position statement. In collaboration with The Endocrine Society and the American Society of Reproductive Medicine, a strong statement was formulated on the acceptability and relative safety of using hormone therapy to relieve moderate to severe symptoms in recently menopausal women. Twelve other medical societies highly involved in women’s health endorsed the document. This unified statement from 15 medical organizations underscores the fact that experts in the field do agree upon the use of hormone therapy for menopausal symptoms.

Learning Objectives:
At the conclusion of this presentation, participants should be able to:

• Report the different rates of breast cancer that occur with use of estrogen therapy compared to combined estrogen/progestogen therapy

• Cite the risks of hormone therapy when used by younger postmenopausal women
Aging women and their partners often have to overcome several obstacles that threaten the quality of their sexual lives. While Western Culture seems to have finally given acceptance to the idea that women and men over 50 are still entitled to a sexual life, and, that some over 50 celebrities are still “hot” (e.g. Sigourney Weaver, Meryl Streep, Emma Thompson, Tom Cruise, George Clooney, Pierce Brosman Daniel Craig), these obstacles continue to threaten midlife sexual self-esteem and satisfaction. Midlife women and men often face the sexual obstacle of declining sexual drive. Testosterone, which is known to have a strong impact on drive, declines in both men and women as a function of age. For women, circulating testosterone levels are, by age 50, half of what they were when a woman was in her early 20 due to declining ovarian function. Men too, may experience a decline in testosterone levels around mid life. If loss of testosterone wasn’t enough of an obstacle for women, declining ovarian function also results in loss of estrogen and with it, VVA (vulvovaginal atrophy) as well as overall tissue changes resulting in aging. And aging men are faced with increasingly more unreliable erections as a result of aging, illness and medication. And finally, irrespective of age, sexual problems are highly prevalent. For women, almost 12 percent are likely to have a sexual dysfunction. For men, approximately 25 percent of men suffer from erectile dysfunction or premature ejaculation. It is fascinating to study the reciprocal relationship between male and female dysfunctions. Women partners of men with erectile dysfunction and premature ejaculation have more sexual problems than partners of men without male sexual dysfunction. It may therefore be relevant to inquire whether the patient’s partner has any sexual dysfunction to determine if it has an impact on her. Similarly, women’s sexual problems impact on the partner’s sexual life as well. HCPs treating postmenopausal women should include questions about partner functioning when taking a sexual history and assessing sexual function. Given the high prevalence of sexual problems in both men and women, it is important to consider partner function when a woman presents with a sexual concern. In keeping with the awareness of sexual function in the context of the couple, treatment options may include some office based sex therapy for the couple as well as some individual counseling and/or pharmacologic options.

Learning Objectives:
At the conclusion of this presentation, participants should be able to:

- Define the female and male sexual disorders
- Discuss the reciprocal relationship between male and female sexual dysfunction
- Outline techniques for assessment and diagnosis of sexual disorders
- Identify treatment options for women, men, and couples
Concurrent Session #3

“Special Issues in Midlife Women’s Care”

“Lesbian Women: The Health Impact of Civil Discrimination on Midlife Women”
Kate O’Hanlan, MD, FACOG, FACS, SGO. Gynecological Oncology & Surgery, Sequoia Hospital, Redwood City, CA

Although research confirms that homosexuality is a normal expression of human sexuality, established scientific studies are often not reflected in laws and judicial opinions for lesbians with regard to employment, taxation, pensions, disability, healthcare, immigration, military service, marriage, custody, and adoption. The expression of homosexual attraction or behavior is sometimes met by disdain or violence. Psychological and epidemiological research confirms that the public discriminatory attitudes and second-class legal status cause physical, emotional, and financial harm to lesbians, their families, and their children. Some lesbians experience discrimination in healthcare and avoid routine primary healthcare. The Women’s Health Initiative and the Nurses’ Health Study have provided conclusive evidence of disparate health demography and risk factor distribution for heart disease and many cancers. To decrease the harm, and improve the health of lesbians, medical institutions can include sexual orientation and gender identity in their nondiscrimination policies and offer domestic partner coverage in employment benefits. Our specialty societies should review current laws and judicial opinions and advocate for change. Further, specialty societies can effect change by issuing policy statements about issues of orientation and by writing orientation/identity curricula for public schools, colleges, and postcollegiate education to improve their accuracy, reduce sexually transmitted diseases, delay sexual activity, and reduce morbidity from homophobic violence.

Learning Objectives:
At the conclusion of this presentation, participants should be able to:

- Understand the social construct of stigma and its effects on culture and family
- Review the lesbian health demographic and risk factors in evidence from the WHI and NHS
- Formulate some solutions for the health disparities
**Concurrent Session #3**

**“Special Issues in Midlife Women’s Care”**

**Sexually Transmitted Infections (STIs) in Midlife Women**

Michael S. Policar, MD, MPH. Obstetrics, Gynecology & Reproductive Sciences, University of California, San Francisco School of Medicine, San Francisco, CA

Sexually transmitted infections are a concern for midlife and older women, mainly when a sexual relationships with new partner develops. Despite a recent media focus on this topic, rates of chlamydia, gonorrhea, syphilis, and HIV are very low in women of this age group, even when adjusted for the number of partners. No major organization, including the US Preventive Services Task Force (USPSTF) or the US Centers for Disease Control (CDC) recommends routine screening for gonorrhea, chlamydia, or syphilis in midlife women. Instead, they recommend a “targeted screening” strategy in which only women who disclose risk factors for infection are screened. Validated risk factors for targeted gonorrhea and chlamydia screening are a history of gonorrhea, chlamydia, or pelvic inflammatory disease in the past 2 years; more than one sexual partner in the past 12 months; a new sexual partner in the past 30 days; or reason for the patient to believe that her partner has had sex with another partner recently. Asymptomatic female patients who present with concerns that they have acquired a STI as a consequence of an unprotected sexual encounter should be offered screening for gonorrhea, chlamydia, syphilis, and HIV. However, in this circumstance, screening for herpes virus with serology or culture, hepatitis B or hepatitis C serologies, or human papilloma virus (HPV)DNA testing are not indicated and should not be performed. Most laboratories have switched to nucleic acid amplification tests (NAATs) for gonorrhea and chlamydia because they are much more sensitive and specific than older DNA probe and culture tests. The preferred genital site for NAAT sampling is from vaginal fluid, which has a slightly higher sensitivity than cervical or urine samples. In heterosexuals and women having sex with women, a single genital sample is adequate and oral or anal samples are unnecessary. According to the 2010 CDC STD Treatment Guidelines, individuals testing positive for chlamydia should be treated with azithromycin 1 gram orally and those who test positive for gonorrhea should be co-treated with ceftriaxone 250 mg IM and azithromycin 1 gram orally. If injectable drugs are not available, an alternative regimen is co-treatment with cefixime 400 mg orally and azithromycin 1 gram orally. However, in this case, the CDC now recommends a test-of-cure 7 days after completion of therapy, and if positive, a gonorrhea culture must be performed with antibiotic sensitivity testing. In addition, all patients treated for chlamydia or gonorrhea are advised to return in 3 months for re-testing in order to detect re-infection. Equally important is the fact that all sexual partners in the past 60 days must be notified and treated as well. The CDC strategy of “expedited partner therapy” is most effective, in which the infected patient delivers either the appropriate medications to the partner or prescription to be filled by him. Even though the partner may not been seen by the prescribing clinician, this practice is permitted in most states. National guidelines differ regarding HIV screening. In 2006, the CDC recommended that all adults between 13-64 years old receive a single HIV serology test, and if negative, be re-tested annually or more often on the basis of risk factors or engaging in risky behaviors. Alternatively, the USPSTF recommends HIV screening based on risk factors or engaging in risky behaviors only. Screening with a serologic test for herpes type-2 should be done only if HIV positive, if evaluating for sero-discordance within a couple, or if patient counseling determines that knowledge of a positive or negative serology result will cause the individual to change their behavior.

**Learning Objectives:**

At the conclusion of this presentation, participants should be able to:

- List four tests that should be offered to an asymptomatic woman who wants to be checked for STIs
- List four behaviors or risk factors that should trigger targeted screening for gonorrhea and chlamydia
Results from the MsFLASH Randomized Controlled Trial of Yoga, Aerobic Exercise & Omega-3 Supplementation for Relief of Vasomotor Symptoms

A. Z. LaCroix, PhD1, B. Sternfeld2, B. Caan2, K. M. Newton1, S. D. Reed2, L. Cohen1, H. Joffe5. 1Public Health Sciences Division, Fred Hutchinson Cancer Research Ctr., Seattle, WA; 2Division of Research, Kaiser Permanente Northern California, Oakland, CA; 3Group Health Research Institute, Seattle, WA; 4Obstetrics & Gynecology, University of Washington, Seattle, WA; 5Psychiatry, Center for Women’s Mental Health, Massachusetts General Hospital, Boston, MA

The Menopause Strategies: Finding Lasting Answers for Symptoms and Health (MsFLASH) clinical trials network, supported by the National Institute on Aging as a cooperative agreement, is conducting a series of randomized clinical trials designed to test new interventions for menopausal symptoms. Testing the efficacy of behavioral and complementary and alternative medicine (CAM) treatments was an important priority for the MsFLASH Network because these treatments are widely available, acceptable, low risk, and provide many additional health benefits. Our second trial was a randomized controlled 3 by 2 factorial design, 12-week trial that evaluated the following interventions: yoga, aerobic exercise, and omega-3 fish oil supplementation. With this design, 30% of the women were randomized to yoga, 30% to exercise, and 40% to usual activity. Within each of these groups, women were further randomized to active omega-3 supplementation capsules or matching placebo capsules. The primary aims of the trial were to compare the changes in self-reported menopause symptoms in each intervention arm to those in the respective control group (usual activity for yoga and exercise, placebo capsules for omega-3 supplements). Women were eligible if they were 40-62 years of age, in the late menopausal transition or postmenopausal, in good general health, having frequent hot flashes/night sweats (at least 14 per week for 3 weeks with at least 4 per week rated as moderately bothersome or severe), and not already regularly doing aerobic exercise, yoga or taking omega-3 supplements. The yoga intervention consisted of the class series, “Yoga for Mid-Life Women”, which included relaxing and restorative poses sequenced according to the principles of Viniyoga, breathing exercises, and yoga nidra meditation. Women attended class weekly and practiced at home daily. The exercise intervention was facility-based aerobic exercise training on a treadmill, stationary bicycle or elliptical trainer performed 3 times per week. All women had the same progressive energy expenditure goal, relative to body weight: 4 kcals/kg in week 1; 8 kcals/kg in week 2; 12 kcals/kg in week 3; and 16 kcals/kg in weeks 4-12. The omega-3 supplement contained omega-3 fatty acids from fish oils (manufactured by Nordic Naturals, Watsonville, CA). Each gel capsule had a total omega-3 dosage of 615 mg, which included the two major omega-3 components of ethyl eicosapentaenoic acid (EPA; 425 mg) and docosahexaenoic acid (DHA; 100 mg). Of 7,377 women who responded to mass mailings, 355 (4.8%) were randomized; mean age was 54.7 (sd=3.7), 26.2% were African American, 81.7% were postmenopausal, and mean baseline frequency of daily vasomotor symptoms was 7.6 (sd=3.8). The most common reasons for study exclusion were failure to meet VMS criteria (30.2%) and already exercising (11.2%), doing yoga/meditation (11.4%), or using omega-3 (9%). Primary (vasomotor symptom frequency, severity, bother) and secondary (sleep, mood) outcomes will be presented. The factorial design proved to be a highly efficient approach to studying multiple behavioral interventions in a single trial.

Learning Objectives:

At the conclusion of this presentation, participants should be able to:

- Understand the effects of yoga, exercise, and omega-3 fatty acid supplements on vasomotor symptom frequency, severity, and bothersomeness
- Understand the effects of yoga, exercise, and omega-3 fatty acid supplements on other symptoms associated with menopause including mood and sleep disturbances
The Paradox of Estradiol-Induced Breast Cancer Cell Growth & Apoptosis

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Estrogen is known to be the driving force for the development and growth of breast cancer (Jordan Cancer Res 2009; 69:1243-54). This knowledge is the scientific basis for the use of the anti-estrogen tamoxifen for the successful treatment of estrogen receptor (ER) positive breast cancer and for the use of the selective ER modulator (SERM) raloxifene to reduce the incidence of breast cancer in high risk postmenopausal women. However, through a study of antihormone resistance to SERMs and estrogen deprivation therapy (aromatase inhibitors) a new apoptotic biology of estrogen was discovered (Jordan Cancer Cell 2004; 5:207-213). Long term estrogen deprivation results in the reconfiguration of ER positive breast cancer cell signaling pathway so that reintroduction of physiologic estrogen triggers apoptosis rather than causes estrogen-stimulated cell proliferation. The sequence of molecular events has recently been described in model ER cell systems of antihormone resistance (Ariazi et al, PNAS 2011; 108:18879-86). These laboratory data, and the successful use of physiologic estradiol to treat aromatase inhibitor-resistant metastatic breast cancer (Ellis et al, JAMA 2009; 302:774-780) have recently been used (Jordan and Ford, Cancer Prev. Res. 2011; 4:633-37) to explain the significant decrease in breast cancer, all cancers and mortality in the Women’s Health Initiative trial of conjugated equine estrogen alone study in hysterectomized women (Anderson et al, Lancet Oncol 2012; 13:476-86).

It appears from laboratory data that long term estrogen deprivation subsequently causes estrogen induced apoptosis whereas short term estrogen deprivation growth will subsequently result in estrogen stimulated growth. An estrogen deprivation gap is required scientifically to cause estrogen induced apoptosis.

Learning Objectives:

At the conclusion of this presentation, participants should be able to:

• Understand the current endocrine therapies for breast cancer
• Recognize the evolution of acquired resistance to anti-hormone therapy
• Understand the science behind the new apoptotic biology of estrogen in breast cancer
Ovarian Cancer Screening: Why No Consensus?
Susan C. Modesitt, MD, FACOG, FACS. Gynecologic Oncology, University of Virginia Health System, Charlottesville, VA

Ovarian cancer is a devastating disease that is expected to impact 22,000 women in 2012 in the United States and most women will die of their disease. Women with early stage disease have upwards of 90% five year survival yet most women are diagnosed in advanced stages where the five year survival remains a relatively dismal 15-30%. Thus, the holy grail in gynecologic oncology has always been the pursuit of an effective screening mechanism for ovarian cancer. Yet, in order to have an effective cancer screening test, the screening modality must be technically feasible, have acceptable detection rates and positively impact the treatment and outcomes of the cancer in question. To date, there is not an accepted or recommended screening regimen for women with ovarian cancer although several modalities have been in screening trials for years including transvaginal ultrasonography, Ca-125 or other potential tumor markers (e.g. HE-4, leptin, prolactin, osteoponin etc), serum proteomics, and multi-modality testing. Unfortunately, to date, no screening mechanism has been proven effective in normal risk women for ovarian cancer screening and currently no major group endorses testing (ASCO, ACOG, SGO, USTPF etc) for normal risk women. The potential for harm (unnecessary testing and/or surgery for benign conditions) outweighs the potential benefits. Of note, the National Comprehensive Cancer Network does recommend screening (with ultrasound, physical exam and Ca-125) for women at high risk due to hereditary syndromes like hereditary breast and ovarian cancer or Lynch syndrome.

Risks & Benefits of Elective Oophorectomy: Data vs Dogma
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Elective or prophylactic procedures should clearly benefit the patient; without the procedure there should be a significant risk of developing disease. Prophylactic oophorectomy is performed in order to prevent the subsequent development of ovarian cancer and is performed for 55% of all US women and 78% of women between ages 45-64 who are having a hysterectomy for benign disease. The lifetime risk of ovarian cancer, excluding those women who have high-penetrance gens for BRCA or Lynch syndrome, is < 1%. While ovarian cancer leads to 15,000 deaths per year in the US, coronary heart disease accounts for 350,000 deaths per year. Oophorectomy in premenopausal and postmenopausal women results in immediate reduction of ovarian estrogen and androgen blood levels. Early reports from the Nurses’ Health Study found that oophorectomy for women who never used estrogen doubled the risk of myocardial infarction (RR 2.2 95% CI 1.2, 4.2) compared with age-matched premenopausal women. A study published from the Mayo Clinic found a statistically significant association between bilateral oophorectomy before age 45 and cardiovascular mortality (HR 1.44; 95% CI 1.01-2.05) and the risk was significantly increased in women who were not treated with estrogen through age 45 or longer. A 2009 NHS study found that oophorectomy was associated with an increased risk of coronary heart disease for all women (HR 1.17 95% CI 1.02, 1.35) and the effect was greater for women having oophorectomy before age 45 (HR 1.26 95% CI 1.04, 1.54). That analysis also found an increased risk of death from CHD (HR 1.28 95% CI 1.00, 1.64). A specific analysis of women who had never used postmenopausal hormones found an increased risk of incident coronary heart disease (HR 1.98 95% CI 1.18, 3.32) for women having oophorectomy before age 50, and the risk of stroke was higher (HR 1.85 95% CI 1.09, 3.16) for women having bilateral oophorectomy at any age. A recent NHS analysis submitted for publication found that oophorectomy was associated with higher mortality from coronary heart disease. A subset analysis of all women who were alive 15 or more years after surgery (without a prior CVD event) demonstrated that bilateral oophorectomy before age 50 years was associated with a higher risk of death from coronary heart disease, CVD (coronary heart disease or stroke) and death from all causes. It appears that the past dogma of routine oophorectomy for women having a hysterectomy is not upheld by current research and that this practice should be reconsidered.

Learning Objectives:
At the conclusion of this presentation, participants should be able to:

- Quantify the benefit of oophorectomy with regard to the risk of ovarian cancer
- Quantify the risks of oophorectomy with regard to the risks of coronary heart disease, lung cancer, colorectal cancer, neurologic conditions, and overall mortality
Ovarian Cancer Screening: Why No Consensus?
Susan C. Modesitt, MD, FACOG, FACS, Gynecologic Oncology, University of Virginia Health System, Charlottesville, VA

Ovarian cancer is a devastating disease that is expected to impact 22,000 women in 2012 in the United States and most women will die of their disease. Women with early stage disease have upwards of 90% five year survival yet most women are diagnosed in advanced stages where the five year survival remains a relatively dismal 15-30%. Thus, the holy grail in gynecologic oncology has always been the pursuit of an effective screening mechanism for ovarian cancer. Yet, in order to have an effective cancer screening test, the screening modality must be technically feasible, have acceptable detection rates and positively impact the treatment and outcomes of the cancer in question. To date, there is not an accepted or recommended screening regimen for women with ovarian cancer although several modalities have been in screening trials for years including transvaginal ultrasonography, Ca-125 or other potential tumor markers (e.g. HE-4, leptin, prolactin, osteoponin etc), serum proteomics, and multi-modality testing. Unfortunately, to date, no screening mechanism has been proven effective in normal risk women for ovarian cancer screening and currently no major group endorses testing (ASCO, ACOG, SGO, USTPF etc) for normal risk women. The potential for harm (unnecessary testing and/or surgery for benign condiditons) outweighs the potential benefits. Of note, the National Comprehensive Cancer Network does recommend screening (with ultrasound, physical exam and Ca-125) for women at high risk due to hereditary syndromes like hereditary breast and ovarian cancer or Lynch syndrome.

Learning Objectives:
At the conclusion of this presentation, participants should be able to:

- Understand the six basic criteria for a good cancer screening test
- Learn the limitations of current ovarian cancer screening options
- Assess the data for offering ovarian cancer screening in high-risk women
Emergence of Elevated Anxiety as Women Transition Through Menopause
Joyce T. Bromberger, PhD. Epidemiology & Psychiatry, University of Pittsburgh, Pittsburgh, PA

Anxiety symptoms and disorders are highly prevalent in women and are associated with substantial decrements in functioning, interpersonal relationships and high levels of subjective distress. The National Comorbidity Survey Replication reported that among the cohort of women aged 45-59, lifetime rates of any anxiety disorder was 36.3% and 12-month prevalence was more than 20%. Although studies of the menopausal transition have not examined prevalence of anxiety disorders, they have reported that a variety of anxiety symptoms are highly prevalent in midlife women. In a large community sample, over a two week period, 51% of women 40-55 years old reported any tension/nervousness or irritability and 25% reported frequent (>6 days in past 2 weeks) irritability or nervousness. However, the extent to which the menopausal transition confers an increased risk of anxiety symptoms is unclear as studies of the transition have reported inconsistent results. For example, some studies indicate no statistically significant differences in prevalence or risk for anxiety by menopausal stage despite high prevalence rates of anxiety symptoms during and after the menopausal transition, ranging from 19% to 53% during premenopause, 24% to 30% during early perimenopause, 19% to 40% during late perimenopause. Other studies report that early or late perimenopausal women have significantly higher rates of anxiety symptoms than premenopausal women. We found in an analysis of cross-sectional data from the Study of Women’s Health Across the Nation (SWAN), a 7-site multi-ethnic study of menopause, that the odds of frequent (> 6 days in past 2 weeks) irritability and nervousness each adjusted for multiple covariates in separate analyses were significantly higher among early perimenopausal (OR=1.33, 1.54, respectively) compared to premenopausal women. There are numerous potential reasons for the mixed findings regarding links between anxiety and perimenopause. Studies have used different designs, populations and anxiety symptoms as outcomes. ‘Anxiety’ is a general term that refers to multiple types of symptoms and disorders. Anxiety refers to varying symptoms characterizing different anxiety disorders, such as panic disorder (e.g., suddenly feeling fearful for no reason), social phobia (e.g., fear of social or performance situations), or generalized anxiety (e.g., excessive and uncontrollable worry, irritability). Such heterogeneity in anxiety symptoms and disorders is reflected in the literature, the vast majority of which includes diverse measures of individual anxiety symptoms such as “irritability” or “feelings of panic” making it difficult to compare studies and draw conclusions. Such symptoms are correlated with hot flashes which raises issues regarding the association of menopausal stage with anxiety independent of hot flashes. Nevertheless, the high prevalence of anxiety symptoms and disorders during midlife suggests the importance of conducting further longitudinal research to examine whether the risk for a syndrome of anxiety and/or anxiety disorders themselves is greater during the menopausal transition than before.

Learning Objectives:
At the conclusion of this presentation, participants should be able to:

- Describe the multiple anxiety symptoms that have been assessed in studies of the menopausal transition
- Discuss what is known about the relationship between anxiety symptoms/disorders and menopausal stage
- Identify risk factors for anxiety symptoms in midlife women
Plenary Symposium #10
“Menopause & Mood: Anxiety, Depression, & Beyond”

Treating Depression in Midlife Women
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Perimenopause is a time of heightened risk for depressive symptoms, with a 2-fold increase in new-onset major depression and a 4-fold increase in new-onset depressive symptoms. Increased variability of E2, FSH and LH relative to mean levels is associated with more depressive symptoms, as is a history of premenstrual dysphoria. Perimenopause may also heighten the neurophysiologic response to stress. Stressors that especially increase the risk of perimenopausal depression are those which are unanticipated, uncontrollable, and adversely affect self-esteem. In turn, depression increases the risk of early menopause, osteoporosis, cardiovascular disease, and diabetes. Antidepressant medications that cause sedation and orthostatic hypotension can increase the risk of falls and fractures in women with osteoporosis. Serotonergic agents can reduce bone density. Antidepressant medications such as paroxetine, fluoxetine, citalopram, venlafaxine and desvenlafaxine are effective for reducing vasomotor symptoms, although less so than estrogen. Cognitive-behavioral therapy can alleviate anxiety-linked hot flashes. Estrogen is not effective as monotherapy for major depression, but may augment antidepressant efficacy, and may alleviate subsyndromal depressive symptoms. Similarly, aerobic may alleviate depressive symptoms. Interpersonal psychotherapy is a time-limited therapy that can be useful for addressing midlife role transitions. Overall, multifaceted treatment for perimenopausal depressive symptoms can encompass one or more of the following: lifestyle changes, alleviation of contributory physical symptoms, support groups and networks, targeted psychotherapy, antidepressant medication, and estrogen supplementation.

Learning Objectives:
At the conclusion of this presentation, participants should be able to:

• Understand factors contributing to increased risk of depressive symptoms during perimenopause
• Review components of a multifaceted approach to treating perimenopausal depressive symptoms