Women's Health – Biomarkers in Clinical Practice and Future Approaches

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Data presented is intended for purely educational use to provide the participant with scientific, evidence-based, fair and balanced data in compliance with FDA guidelines.
Agenda

- Oncology – Breast and Ovarian Cancer
- Bone Health - Osteoporosis
- Pregnancy Complications - Preeclampsia
## Leading Causes of Death in the US in 2013

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>Number</th>
<th>Percentage</th>
<th>Male to Female Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>all</td>
<td>2,596,993</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>1. Heart Disease</td>
<td>23.5</td>
<td>1.6</td>
<td></td>
</tr>
<tr>
<td>2. Cancer</td>
<td>584,881</td>
<td>22.5</td>
<td>1.4</td>
</tr>
<tr>
<td>3. Chronic Lower Respiratory Diseases</td>
<td>5.7</td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td>4. Accidents</td>
<td>5.0</td>
<td>2.0</td>
<td></td>
</tr>
<tr>
<td>5. Cerebrovascular Diseases</td>
<td>5.0</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>6. Alzheimer's Disease</td>
<td>3.3</td>
<td>0.7</td>
<td></td>
</tr>
<tr>
<td>7. Diabetes Mellitus</td>
<td>2.9</td>
<td>1.5</td>
<td></td>
</tr>
<tr>
<td>8. Influenza and Pneumonia</td>
<td>2.2</td>
<td>1.3</td>
<td></td>
</tr>
<tr>
<td>9. Nephritis, Nephrotic Syndrome</td>
<td>1.8</td>
<td>1.4</td>
<td></td>
</tr>
<tr>
<td>10. Suicide</td>
<td>41,149</td>
<td>1.6</td>
<td>3.7</td>
</tr>
<tr>
<td>...</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death after Injury by Firearms</td>
<td>33,636</td>
<td></td>
<td></td>
</tr>
<tr>
<td>...</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnancy, Childbirth</td>
<td>1,138</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Survival improvements with some types of cancer

Though new cases with Breast and Prostate cancers remain high, death rates are lower due to early detection and advances in treatment.

On the other hand, many patients die with Ovarian or Pancreatic cancer because it is generally discovered at advanced stages (high mortality rate).
Breast and Ovarian Cancer – 5-year Survival Rates and Staging at Diagnosis

While 5-year survival rates have improved for both cancer types over the past years, Ovarian Cancer survival rates are only half as high as for Breast Cancer.

This is largely due to the fact that Breast Cancer is detected in earlier stages when the tumor is still localized.

SEER Cancer Statistics Review 1975 - 2012, National Cancer Institute
What is Cancer?

In the most basic terms, cancer refers to cells that grow out-of-control and invade other tissues. Cells become cancerous due to the accumulation of defects, or mutations, in their DNA. Certain inherited genetic defects (for example, BRCA1 and BRCA2 mutations) and infections can increase the risk of cancer. Environmental factors (for example, air pollution) and poor lifestyle choices - such as smoking and heavy alcohol use - can also damage DNA and lead to cancer.

Most of the time, cells are able to detect and repair DNA damage. If a cell is severely damaged and cannot repair itself it undergoes so-called programmed cell death or apoptosis. Cancer occurs when damaged cells grow, divide, and spread abnormally instead of self-destructing as they should.

Types of Cancer

Cancer can occur anywhere in the body. Broadly, cancers are classified as either solid (for example, breast, lung, or prostate cancers) or liquid (blood cancers). Cancer is further classified according to the tissue in which it arises.

**Carcinomas** are cancers that occur in epithelial (lining) tissues in the body. They comprise **80% to 90%** of all cancers. Most breast, lung, colon, skin, and prostate cancers are carcinomas.

**Sarcomas** occur in connective tissue like the bones, cartilage, fat, blood vessels, and muscles.

**Myelomas** are cancers that occur in plasma cells in the bone marrow.

**Leukemias** are blood cancers of the bone marrow.

**Lymphomas** are cancers of the immune system cells.

**Mixed cancers** arise from more than one type of tissue.

A tumor is an abnormal mass of cells. Tumors can either be benign (non-cancerous) or malignant (cancerous). Benign tumors grow locally and do not spread. Malignant tumors have the ability to spread and invade other tissues. This process, which is a key feature of cancer, is known as metastasis.

By definition, the term "cancer" applies only to malignant tumors.
Cancer Treatments
Overview and Classification

Local Treatment
- Surgery
- Radiation Therapy

Systemic Treatment
- Chemotherapy
- Hormone Therapy
- Biological or Targeted Therapy

Neoadjuvant
- Before Surgery - Chemotherapy or Radiation to shrink the tumor
- May include other systemic therapies
- Best case is a pathologic complete response

Adjuvant
- Following Surgery - Chemotherapy or Radiation to eradicate all cancer cells and prevent recurrence
- May include other systemic therapies
- Best case is a pathologic complete response

Various Functions with Diagnostic Testing – the Role of Biomarkers

- **Screening**: Checking for cancer (or for conditions that may lead to cancer) in people who have no symptoms.
- **Diagnosis/Classification**: Relating to, aiding in, establishing, or confirming a diagnosis. Arrangement into classes or groups based on common characteristics.
- **Surveillance/Recurrence**: Ongoing scrutiny or to watch. A return of the symptoms occurring as an event or trend in the natural history of the disease.
- **Prognosis/Prediction**: A forecast of the probable course and/or outcome of a disease. Indicative of the likely outcome.
- **Disease Monitoring**: Performance or analysis of routine measurements aimed at detecting a change in the health status of a patient or with the effectiveness of a treatment.
Breast cancers are malignant tumors that arise from the uncontrolled growth of cells in the breast. They occur primarily in the ducts and secondarily in the lobules. Each breast cancer will have its own characteristics.


Lab test online. 04-2011. [http://labtestsonline.org/understanding/conditions/breast](http://labtestsonline.org/understanding/conditions/breast); accessed 4/11/2016
**Early Detection**

*What the societies recommend*

<table>
<thead>
<tr>
<th>Optimism</th>
<th>American Cancer Society (ACS)</th>
<th>Universal Consensus?</th>
</tr>
</thead>
<tbody>
<tr>
<td>▪ Breast cancer that is detected and treated in its earliest stages can be cured over 90% of the time. The primary early detection tools are breast self-exams, clinical breast exams, and mammograms</td>
<td>▪ Women age 20 and older consider doing a breast self-exam every month</td>
<td>▪ U.S. Preventive Services Task Force no longer recommend screening mammograms for women under the age of 50 and they recommend routine mammography every 2 years for women ages 50-74.</td>
</tr>
<tr>
<td></td>
<td>▪ Women in their 20s and 30s should have a clinical breast exam at least every three years</td>
<td>▪ American Congress of Obstetricians and Gynecologists (ACOG) now recommend mammography screening be offered annually to women starting at age 40</td>
</tr>
<tr>
<td></td>
<td>▪ Women age 40 and over should have a yearly mammogram</td>
<td></td>
</tr>
</tbody>
</table>
TNM Staging for Breast Cancer

Cancer staging is the process doctors use to classify cancer according to its size, location, and extent of spread. Staging helps doctors determine the prognosis and treatment for cancer. The TNM staging system classifies cancers according to:

**Tumor (T):** Primary tumor size and/or extent

**Nodes (N):** Spread of cancer to lymph nodes in the regional area of the primary tumor

**Metastasis (M):** Spread of cancer to distant sites away from the primary tumor

Screening / Risk Assessment

- BRCA1 and BRCA2 are human genes that produce tumor suppressor proteins. These proteins help to repair damaged DNA.

- Specific mutations in BRCA1 and BRCA2 genes increase the risk of female breast and ovarian cancer because DNA damage may not be repaired properly.

- Mutations in the BRCA1 or BRCA2 genes are rare in the general population (0.2 to 0.3%), but the risk to develop cancer in the presence of these mutations has been estimated:

  [Graph showing lifetime risk to develop breast or ovarian cancer with and without BRCA mutations]

  - With no mutation: 12% for breast, 1.3% for ovary
  - With BRCA1 mutation: 60% for breast, 39% for ovary
  - With BRCA2 mutation: 45% for breast, 15% for ovary

Disease Monitoring
Patient management detecting a change in health status

Tumor markers as an aid in the early detection of recurrence
- CA 15-3
- CA 27.29

- A study that was published in 2008 found that increasing CA 15-3 or CA27.29 levels can pre-clinically detect distant metastatic disease in approximately 70% of asymptomatic patients.

- In a recently published study evaluating 813 patients in Germany with a median follow-up period of 63 months, a pre-defined increase in tumor markers based on individual baseline values that triggered whole body imaging was „...highly effective for early detection and localization of tumor recurrence.‟

- Another recently published study in Chinese patients retrospectively evaluated 284 patients that had developed metastatic breast cancer. Of those patients 57% showed elevated levels of CA15-3. This confirms previous study results where increased CA15-3 levels detected 40-60% of recurrences prior to clinical or radiological evidence of disease, with a lead time of 2-18 months.

Prognosis and Prediction Testing
Patient management following treatment

Gene expression profiling examines a set of genes in a tumor tissue

- Oncotype DX
- MammaPrint

- Gene expression profiling tests examine a set of genes in tumor tissue to determine the likelihood of breast cancer recurrence.
- Use of these tests is now recommended by the American Society of Clinical Oncology and the National Comprehensive Cancer Network for newly diagnosed patients with node-negative, estrogen receptor positive breast cancer.
- In 2015, the „Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group“ of the CDC analyzed 5 studies that assessed the clinical utility of the Oncotype DX assay. While they confirmed their previous statement that the evidence in these studies shows the clinical validity of the assay, they conclude that the clinical utility in improving patient outcomes has not been shown yet.
Ovarian Cancer

Basics

Most ovarian cancers (<90%) are epithelial cancers, it begins in the tissue that covers the ovaries

Rare forms of ovarian cancers begin in the germ cells of the ovaries or the stromal cells

Less than 20% of all ovarian cancers are detected in early stages when the tumor is still localized

TNM Staging for Ovarian Cancer

Cancer staging is the process doctors use to classify cancer according to its size, location, and extent of spread. Staging helps doctors determine the prognosis and treatment for cancer. The TNM staging system classifies cancers according to:

**Tumor (T), Sub Stages 0 to 3c:** Primary tumor size and/or extent

**Nodes (N), Sub Stages 0 to 1:** Spread of cancer to lymph nodes in the regional area of the primary tumor

**Metastasis (M), Sub Stagens 0 to 1:** Spread of cancer to distant sites away from the primary tumor

Early Detection
What are the challenges

- Although screening tests are available for early detection of breast and cervical cancer, there is a lack of reliable tests for ovarian cancer screening.
- Ovarian cancer is often diagnosed after the cancer has spread (metastasized), making it harder to treat.

Ovarian Cancer Risk Factors
- The pathogenetic mechanism(s) that explains the link between many of the risk factors and development of ovarian cancer have not been determined
- Risk factors for ovarian cancer include: older age at first birth (>35), family history of breast or ovarian cancer, BRCA mutations, hereditary non-polyposis colorectal cancer, Lynch syndrome, and primary infertility- ovarian stimulation

Signs of Ovarian Cancer
- Early Ovarian cancer may not cause any symptoms; when signs do appear, the cancer is often advanced
- Most women with EOCs are diagnosed between the ages of 40 and 65
- Symptoms:
  - Abdominal pain or swelling
  - Pain in the pelvis
  - Gastrointestinal problems such as gas, bloating or constipation

## Gynecologic Cancer Symptoms

*Ovarian cancer may cause one or more of these signs and symptoms*

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Cervical Cancer</th>
<th>Ovarian Cancer</th>
<th>Uterine Cancer</th>
<th>Vaginal Cancer</th>
<th>Vulvar Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>abnormal vaginal bleeding or discharge</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>pelvic pain or pressure</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>abdominal or back pain</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>bloating</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>changes in bathroom habits</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>itching or burning in the vulva</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>changes in vulva color or skin, such as rash, sores or warts</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
</tbody>
</table>

Patients need to **pay attention** to their body, and know what is normal.

The **earlier** ovarian cancer is found and treated, the more likely treatment will be effective.

![Roche Logo](image-url)
### Challenges with Early Screening

#### Recommendations for Ovarian Cancer Screening

<table>
<thead>
<tr>
<th>Professional Group</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>US Preventive Service Task Force (09/2012)</td>
<td>Does not recommend routine screening in asymptomatic women. There is &quot;...no new evidence about the benefits ... but some new data about observed harms of screening.&quot;</td>
</tr>
<tr>
<td>American Cancer Society (2016)</td>
<td>Does not recommend routine screening in asymptomatic women. Even in women at high risk &quot;...it's not clear that using these tests (CA125 and TV US) ... lowers their chances of dying from ovarian cancer.&quot;</td>
</tr>
<tr>
<td>American College of Obstetricians and Gynecologists (ACOG), Committee Opinion 2011</td>
<td>Does not recommend routine screening of low-risk women using CA125 and TV US and suggests to wait for long-term follow-up data. Recommends to offer surgical removal of ovaries and fallopian tubes by age 40 to women with BRCA mutation.</td>
</tr>
<tr>
<td>National Comprehensive Cancer Network (NCCN) (2015)</td>
<td>Does not recommend routine screening in the general population. Recommends CA125 monitoring and TV US every 6 months for high-risk women (BRCA mutations, family history), but &quot;...prospective validation of these tests remains elusive.&quot;</td>
</tr>
</tbody>
</table>
UK Collaborative Trial of Ovarian Cancer Screening [UKCTOCS]

Largest prospective randomized controlled trial on screening in ovarian cancer, follow-up up to 14 years

Final results were published in March 2016 in „The Lancet“

Results:

- A reduction in death from ovarian cancer (primary endpoint) of 11% / 15% was observed in the screening groups that used VU alone or CA125 + VU
- Although these reductions are statistically not significant, an earlier detection of ovarian cancer could be shown
- The authors conclude that „... Further follow-up is needed to assess the extent of the mortality reduction before firm conclusions can be reached on the long-term efficacy and cost-effectiveness of ovarian cancer screening.“

Early Screening Methods, Products and Algorithms for the Assessment of Suspicious Pelvic Masses show Inconsistent Results in Studies

<table>
<thead>
<tr>
<th>Algorithm</th>
<th>Description</th>
</tr>
</thead>
</table>
| **Risk of Ovarian Cancer Algorithm [ROCA]** | • Subsequent screening using CA125; risk score is based on changes over time in biomarker concentration after baselining each individual woman  
  • Studies show inconsistent results when tested in screening |
| **Risk of Ovarian Malignancy Algorithm [ROMA]** | • Biomarker algorithm using CA125, HE4 and menopausal status; several FDA-approved assays are available, algorithms are different depending on assays used  
  • Studies show inconsistent results, ranging from no difference to using CA125 alone to significant improvements in sensitivity when used for the assessment of pelvic masses |
| **OVERA®** | • Vermillion received 510(k) clearance in March 2016  
  • 5 biomarkers; proprietary algorithm for the assessment of suspicious pelvic masses; single risk score |
| **OvaSure®** | • 6 biomarkers, developed by researchers at Yale School of Medicine  
  • Marketed by LabCorp, received FDA warning letter in 2008, not available any more |

References:
Surveillance and Recurrence Testing

Patient management following treatment

Tumor markers for early detection of recurrence

- CA125

The overall likelihood of relapse after initial therapy for all stages of disease for women with EOC is 62 percent; it is 80 to 85 percent for women who present with stage III or IV disease.

For women who have completed initial chemotherapy, retreatment is based on signs and/or symptoms of relapsed EOC and not based on a rising CA-125 alone.

Summary

• Cancer is a term used for diseases in which abnormal cells divide without control and are able to invade other tissues.

• Depending on whether or not they can spread by invasion and metastasis, tumors are classified as being either benign or malignant.

• An estimated 232,000 new breast cancer cases/year with more than 2 million living with history of breast cancer in the US.

• Ovarian Cancer is the 5th most frequent cancer in women, generally affecting post-menopausal women.

• Although screening test are available for early detection of breast and cervical cancer, there is a lack of reliable tests for ovarian cancer screening.
Agenda

- Oncology – Breast and Ovarian Cancer
- Bone Health - Osteoporosis
- Pregnancy Complications - Preeclampsia
Definition of Osteoporosis

A skeletal disorder characterized by…

- Excessive osteoclast-mediated bone resorption
- Compromised bone strength
- Increased risk of fracture at all sites

“Osteoporosis is one of the most common and debilitating chronic diseases, and a global healthcare problem”

“Osteoporosis has financial, physical, and psychosocial consequences, all of which significantly affect the individual, the family, and the community”

Osteoporosis Prevalence and Burden of Disease

Growing prevalence from aging societies

- Affects over 200 million people worldwide, more than 80% are women
  10% of women up to the age of 60,
  20% of women between 60 and 70,
  40% of women between 70 and 80,
  and more than 65% of women above the age of 80 are affected

- The lifetime risk for hip, vertebral, and distal radius fractures is estimated at 40%, which is similar to the risk of coronary heart disease


JBMR Vol 29, No 11, November 2014, pp. 2520-2526
Osteoporosis Prevalence and Burden in the US

2 million osteoporotic fractures occur each year, resulting in more than half a million hospitalizations

- An estimate of 2.6 million office hours and more than 180,000 individuals placed in nursing homes are results of osteoporotic fractures

The burden of osteoporotic fractures is not perceived as an important health risk by many women and risk factors are not taken serious, compared to risk factors for cardiovascular disease or breast cancer

- Most important risk factors include reduced estrogen levels after menopause, low BMD, low BMI, previous fractures, family history of fractures, Vitamin D and/or Calcium deficiencies, lack of exercise, smoking, poor nutrition, alcohol abuse

Hip fractures are the most devastating and debilitating bone break (approximately 300,000 fractures per year)

- 50% of patients never reach their previous functional capacity
- 25% of patients end up in nursing homes
- **25% of patients die within one year after the fracture**

JBMR 22 (3) 2007, 465-475; Singer, Mayo Clinic Proceedings 2015, 90; 53-62;
Diagnosis of Osteoporosis Using Central DXA

WHO definition

• DXA = Dual Energy X-ray Absorptiometry
  • Used in clinical practice to diagnose osteoporosis
  • BMD measurement, mainly for spine and hip
  • T-score compares the patient’s BMD with the mean in a healthy young reference population

Osteoporos Int (2014) 25: 2359-2381
Pharmacologic Therapies

- **Anti-resorptive drugs prevent bone breakdown**
  - Bisphosphonates slow or stop the process that dissolves bone tissue
  - SERM (selective estrogen receptor modulators) or HRT (hormone replacement therapy) also act as anti-resorptive drugs
  - Anti-RANKL is a fully human monoclonal antibody that inhibits osteoclast-mediated bone resorption by binding to RANKL and preventing it from binding to the osteoclast receptor RANK

- **Anabolic drugs support the building of bone mass**
  - Teriparatide is a recombinant form of PTH which activates osteoblasts more than osteoclasts, leading to an overall increase in bone mass

Osteoporosis Therapies and Patient Adherence

Poor compliance and the need for patient management

Less than 50% of patients persist with their osteoporosis therapy for more than one year

- Patients initiating therapy
- Patients continuing therapy

**Side Effects**
- Safety concerns
- Health problems
- Lack of results

**Lack of motivation**
- Considered unnecessary
- Inconvenient dosing
- Cost

Adherence

Curr Opin Rheumatology 2009 July; 21(4): 356-362
Result of Poor Compliance

Poor compliance and persistence lead to compromised fracture risk reduction

Caro et al, 2004
N = 11,249

Siris et al, 2006
N = 35,537

Fracture Risk Hazard Ratio

<table>
<thead>
<tr>
<th>Fracture Risk Hazard Ratio</th>
<th>16% Risk Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Compliance</td>
<td>0.8</td>
</tr>
<tr>
<td>High Compliance</td>
<td>0.6</td>
</tr>
</tbody>
</table>

24 Month Fracture Risk (%)

<table>
<thead>
<tr>
<th>24 Month Fracture Risk (%)</th>
<th>Non-Persistent</th>
<th>Persistent</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>10</td>
<td>7.7</td>
</tr>
</tbody>
</table>

P < .001

Strategies for Improving Outcomes

How clinicians can use information to improve patient management

• General patient education, e.g. by providing an osteoporosis leaflet, did not improve adherence to treatment

• In contrast, personalized education, provided by the physician or a nurse, significantly improved adherence

• Patients that received bone marker information, were included in discussions around their DXA-results, or were included in discussions of treatment options were significantly more likely to adhere to therapy

• Patient reminder programs, regular calls, text messages or mails appeared to be beneficial as well

• Patient confidence in the health care provider was reflected in greater treatment adherence when the treatment was prescribed by a specialist vs. a general practitioner

Curr Opin Rheumatology 2009 July; 21(4): 356-362
Why Wait Two Years?

Complementing DXA – A bone marker can provide a feedback mechanism in 90 days to compliment bone density at 2 years.

Bone Density (% change) | Bone Marker (% change)
---|---
| Precision range | | 2 years |
| Active | | 3 months |
| Placebo | | 0 |
Current Diagnostic Markers of Bone Metabolism

**Bone formation**

**Anabolic processes**
- total alkaline phosphatase
- bone alkaline phosphatase (BAP serum)
- Osteocalcin (serum)
- Carboxy-terminal Pro-peptides of type I pro-collagen (PICP, serum) (PINP, serum)

**Bone resorption**

**Anti-resorptive processes**
- tartrate resistant acid phosphatase (TRAP, TRAP5b plasma)
- calcium
- OH-proline
- Bone sialy-protein (BSP)
- Pyridinium Crosslinks (Pyd, Dpd, urine)
- type I collagen telopeptide (CTx, NTx, ICTP urine, serum)

Modified according to Seibel et al. Clin Biochem Rev Vol 26 November 2005
Treatment of Osteoporosis: Teriparatide and Alendronate
Clinical and patient feedback in just 90 days

Treatments for osteoporosis can be either anabolic (such as teriparatide) or anti-catabolic (such as alendronate)

This example shows the effect of teriparatide and alendronate on biochemical markers

Teriparatide therapy is associated with an early and large increase in bone formation markers; the change is so large that most patients can be identified as responders in as early as 1 month

Alendronate therapy is associated with an early and large decrease in bone resorption markers; the change is so large that most patients can be identified as responders in as early as 3 months
• Suppression of biochemical markers of bone turnover after 3–6 months of specific anti-resorptive osteoporosis therapies, and biochemical marker increases after 1–3 months of specific anabolic therapies, have been predictive of greater BMD responses in studies evaluating large groups of patients.

• Because of the high degree of biological and analytical variability in measurement of biochemical markers, changes in individuals must be large in order to be clinically meaningful.

• Biological variability can be reduced by obtaining samples in the early morning after an overnight fast. Serial measurements should be made at the same time of day and preferably during the same season of the year.
Bone Turnover Marker Utilization
How to use a serum CTx in clinical practice

Non-Responder or Non-Compliant
There is no significant decrease in bone markers. The patient is either non-compliant or non-responsive to therapy.

Non-Compliant
Patient initially takes medication and shows an appropriate reduction in bone marker levels. The increase later indicates non-compliant behavior with medication.

Responder
Patient successfully responds to therapy. The bone marker level remains reduced throughout therapy.

Osteoporos Int. 2000;11(Suppl 6):S66-S76.
Individual Treatment Responses

Case scenarios with S-CTx and Alendronate

* B CTX ug/L x100

Slide and case scenarios courtesy of Fraser, W. 2013. Data on file UEA
Summary

• Over 200 million people are affected by Osteoporosis worldwide, 80% of them are women
• In the US about 2 million fractures related to Osteoporosis occur each year, resulting in about half a million hospitalizations
• The burden of osteoporotic fractures is not perceived as an important health risk by many women and risk factors are not taken seriously, compared to risks factors for cardiovascular disease or breast cancer
• Adherence to Osteoporosis treatment is poor, less than 50% of patients persist with their prescribed therapy for more than one year
• Patient information and communication can help improve adherence to therapy
• Bone turnover markers can provide information on therapy effectiveness within 1-3 months and when this information is shared with the patient may improve adherence to therapy
Agenda

- Oncology – Breast and Ovarian Cancer
- Bone Health - Osteoporosis
- Pregnancy Complications - Preeclampsia
The ACOG Task Force on Hypertension in Pregnancy published a revised definition of Preeclampsia in their report in November 2013.

- **Blood Pressure**
  - A new-onset hypertension
    - with blood pressure $\geq 140 / 90$ mmHg measured twice at least 4h apart
    - with blood pressure $\geq 160 / 110$ mmHg which can be confirmed by a second measurement within minutes

- **Proteinuria**
  - $\geq 300$ mg / 24 h
    - OR
  - Protein/Creatinine ratio $\geq 0.3$ (both in mg/dL)
    - Dipstick reading of 1+ if quantitative methods are not available

- OR in the absence of Proteinuria, new onset hypertension with any of the following:
  - Thrombocytopenia
  - Renal Insufficiency
  - Impaired Liver Function
  - Pulmonary Edema
  - Cerebral or Visual Symptoms

ACOG Task Force on Hypertension in Pregnancy © 2013 ACOG
Preeclampsia Prevalence and Risk Factors

- Incidence rates for Preeclampsia in the US range from 2-5%. With ~4 million births in 2013, about 80,000 to 200,000 pregnancies were affected by the disease.

- Worldwide about 76,000 pregnant women die each year from preeclampsia and related hypertensive disorders.

- About 80% of women that show suspicion of preeclampsia never develop the disease and might be unnecessarily hospitalized.

- Most important risk factors include: history of preeclampsia, first pregnancy, a pregnancy in early teens or over the age of 40, kidney disease, obesity, multiple pregnancies, and intervals between pregnancies of less the 2 or more than 10 years apart.

- Delivery of the baby is the only cure for preeclampsia.

Pathogenesis of Preeclampsia

The exact pathogenesis of preeclampsia is poorly understood, but an imbalance of placental angiogenic and anti-angiogenic factors are thought to play an important role.

Increased concentrations of the anti-angiogenic enzyme sFlt-1 disable proteins needed for blood vessel growth. The increase in maternal blood pressure seems to be a compensatory response to the resulting insufficient blood supply to the uterus and placenta.

Diagnosing preeclampsia

“Gold standard” tests have a low sensitivity and specificity for disease progression

New-onset hypertension and proteinuria after 20 weeks of gestation or other clinical symptoms

Definition of PE:

• Clinical presentation and the clinical disease course can be highly variable
• Blood pressure and urine protein level measurements lack sensitivity and specificity for assessing disease severity or predicting the course of the disease
• Autoimmune disorders and renal diseases can mimic preeclampsia

However, diagnosis of PE is not straightforward

Biomarkers in preeclampsia

Placental dysfunction

The angiogenic **placental growth factor (PIGF)** and anti-angiogenic **soluble fms-like tyrosine kinase-1 (sFlt-1)** are biomarkers closely related to placental dysfunction.

No current FDA cleared tests available with referenced biomarkers.

Biomarkers as an Aid in the Diagnosis of Preeclampsia

sFlt-1 concentrations increase app. 5 weeks before the onset of preeclampsia

PIGF concentrations decrease 11 to 9 weeks prior to onset, with a substantial decrease 5 weeks before onset of preeclampsia

N Engl J Med 2004;350:672-83
The differences between PE and control groups are highly significant. The sFlt-1/PIGF ratio clearly separated PE and control groups. The PE group had a mean sFlt-1/PIGF ratio of 354.5±44.84 compared to 19.43 ± 1.620 in the control group (P < .0001).

Calculated sFlt-1/PIGF ratios of PE patients

Calculated sFlt-1/PIGF ratios of control patients

Week of gestation

Am J Obstes Gynecol 2010;202:161.e1-11
Prediction of Short-Term Outcome in Pregnant Women with Suspected Preeclampsia - PROGNOSIS

1273 women enrolled, 1050 met criteria

199 women developed Preeclampsia
851 women did not develop Preeclampsia

Large prospective blinded study at 30 study sites in 14 countries.

Final results were published in January 2016 in „The New England Journal of Medicine“

Results:

• A low ratio of sFlt-1/PIGF ≤38, predicted the absence of preeclampsia / eclampsia / HELLP syndrome within one week of baseline visit (rule out) with a NPP of 99.3% with 80% sensitivity and 78.3% specificity

• The authors concluded that „...the ability to accurately rule-out Preeclampsia within 1 week ... is likely to improve clinical decisions with regard to hospitalization...“ „Data from randomized trials are needed to establish whether use of this ratio in clinical practice, as compared to the current standard of care, could reduce unnecessary hospitalizations and costs, with improved of similar results with respect to fetal and maternal adverse outcomes.“

NEngJMed Jan 2016, 374 (1);
Summary

• Preeclampsia is a serious multi-system complication of pregnancy, occurring in 2-5% of pregnancies in the US.

• The most important signs and symptoms are hypertension and proteinuria, but clinical presentation can be highly variable.

• Pathogenesis of preeclampsia is poorly understood, although recent studies suggest an involvement of the anti-angiogenic enzyme sFlt-1 which disable proteins needed for blood vessel growth.

• A number of studies conducted outside the US have assessed the use of biomarkers for the diagnosis and prognosis of preeclampsia. Currently, there are no FDA-approved products for the biomarkers used in those studies.
Doing now what patients need next