Estrogen Metabolism: Are We Assessing It Properly?

Filomena Trindade, MD, MPH

The views and opinions expressed herein are solely those of the presenter and do not necessarily represent those of Genova Diagnostics. Thus, Genova Diagnostics does not accept liability for consequences of any actions taken on the basis of the information provided.
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Technical Issues & Clinical Questions

Please type any technical issue or clinical question into either the “Chat” or “Questions” boxes, making sure to send them to “Organizer” at any time during the webinar.

We will be compiling your clinical questions and answering as many as we can the final 15 minutes of the webinar.

DISCLAIMER: Please note that any and all emails provided may be used for follow up correspondence and/or for further communication.
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Objectives

• Understand the importance of estrogen metabolism with respect to cancer risk
• Be able to devise a treatment plan for a pt with an unfavorable estrogen metabolism profile
• Gain a basic understanding of the importance of methylation in estrogen metabolism, health promotion and cancer prevention
• Learn to apply these principles in the clinical setting in order to assess potential cancer risk in men and women
• Gain knowledge on the relevance of estrogen metabolism and detoxification in hormone related cancers in both men and women
Exposure to genotoxic environmental chemicals is a risk factor for breast cancer.
“There is published evidence to establish a causal relationship between estrogens in the environment and breast cancer.”
...this data supports the role of estradiol metabolism as one of the components in the development of experimental breast cancer.
The 4-hydroxylation pathway of estrogens is the most malign and can increase the risk of breast cancer.
These results provide strong evidence that exposure to 4-OHE1(E2) leads to the formation of DNA adducts. This process is a putative tumor initiating event.

The estrogen metabolites, conjugates and adducts can be used as biomarkers for detecting susceptibility to estrogen-induced cancer.
ESTROGEN METABOLISM

Cholesterol

Pregnenolone → 17-OH-Pregnenolone

Progestrone → 17-OH-Progesterone

Corticosterone

Aldosterone

Cortisol ← Cortisone

DHEA → Androstenediol

Androstenedione ← Testosterone

DHT

 Estrone (E1) ← Estradiol (E2)

2-OHE1 ← 2-MeOE1

16α-OHE1 ← Estriol (E3)

4-OHE1 ← 4-MeOE1

(Androgens)

(Androgens)

(Estrogens)

(Mineralocorticoids)

(Glucocorticoids)
Two Major Pathways of Detoxification

- **Phase I**: Hydroxylation Reactions
  - Cytochrome P450 enzymes

- **Phase II**: Conjugation Reactions

**Activated Intermediate**

- **Fat Soluble Toxin**

- **Water-Soluble Compound**
Single Nucleotide Polymorphism (SNP)
The Metabolism of Estrogen

• Unused Estrogen is primarily metabolized in the liver via Phase I and/or Phase II detoxification:

Phase I
  – Major Pathway
  – Hydroxylation

Phase II
  – Glucuronidation
  – Sulfation
  – Methylation
  – Glutathione conjugation
  – Acetylation
Phase 1 Detoxification
16α-OHE1
2-OHE1
CYP1B1
CYP1A1
CYP3A4
Estrone (E1)
4-OHE1
(pro-carcinogenic)
3,4 Quinones
(carcinogenic)
 Estrone (E1) 

\[ (\text{CYP1A1}) \]

2-OHE1 

\[ \rightarrow \]

2-MeOE1 (protective) 

4-OHE1 (pro-carcinogenic) 

\[ \rightarrow \]

3,4 Quinones (carcinogenic)
2-Hydroxyestrone (2-OHE1)

“2-OHE1 metabolite has very little estrogen receptor binding affinity, and has been shown to decrease cell proliferation by 20 to 30% in cultured breast cancer cell lines.”
Estrone (E1)

- (CYP1B1)
- (CYP1A1)
- 2-OHE1
- 16α-OHE1
- (CYP3A4)

4-OHE1 (pro-carcinogenic)

3,4 Quinones (carcinogenic?)
16α-Hydroxyestrone (16α-OHE1)

- Strong estrogenic activity
- Turns on estrogen receptor
- Greater likelihood of estrogen-dependent conditions
16α-Hydroxyestrone (16α-OHE1)

"16α-OHE1 metabolite is a potent estrogenic molecule that activates the ER and induces proliferation of cultured breast cancer cells by 40%."
2:16α-OHE1 Ratio - Historic

• Women with breast CA at all ages show increased 16α-hydroxylation

• Post-menopausal women at baseline who went on to develop breast CA showed 15% lower 2:16-OHE1 ratio than controls

• Association with breast cancer stage: women with lower ratios may have a poorer prognosis
  – (Kabat GC, Cancer Epidemiol Biomarkers Prev 1997;6:505-509)
Estrone (E1)

- (CYP1B1)
- (CYP1A1)
- (CYP3A4)

2-OHE1

16α-OHE1

4-OHE1
(pro-carcinogenic)

3,4 Quinones
(carcinogenic)
In summary, this evidence strongly indicates that estrogens can become endogenous tumor initiators when CE-3,4-Q react with DNA to form specific depurinating adducts.

Initiated cells may be promoted by a number of processes... including hormone receptor stimulated proliferation. These results lay the groundwork for assessing risk and preventing disease.
Cytochrome P450 1B1 (CYP1B1)

- Polymorphism is associated with FASTER enzyme activity
- Increased production of 4-OH-estrogens and other potentially carcinogenic compounds
- Tendency for lower 2:16αOH-estrone
- Increased risk of breast cancer, especially if xenobiotic exposure (e.g., PAHs), high BMI, equine estrogens, coexisting CYP1A1 SNP

Cytochrome P450 1B1 (CYP1B1)

“CYP1B1, which has specific estrogen-4-hydroxylase activity, is present in tissues such as uterus, breast, ovary, and prostate, which often give rise to hormone-responsive cancers”

Short Review of Pathophysiology of Catechol Estrogen. Pak J Physiol 2010;6(2)
4-Hydroxyestrone (4-OHE1)

- Very potent
- If not inactivated by COMT, 4-OHE1 can be oxidized to quinone compounds → DNA adduct formation in tissues such as breast
- Increased 4-hydroxylation of estrogen in uterine fibroids
  - (Reddy VV 1981)
- Link between CYP1B1 SNP (increased 4-OH-estrogen production) and prostate CA
  - (Tang YM 2000)
Estrone (E1)

Conjugated Equine Estrogens

(CYP1B1)

4-OHE1

(pro-carcinogenic)

CEEIs are preferentially 4-hydroxylated

(Chang M 1998)

3,4Quinones

(carcinogenic)
Endocrine Disruptors

- Environmental xenobiotics act as “endocrine disruptors” that modify intercellular communication and function.
- Chemicals commonly detected in people include DDT, Polychlorinated biphenyls (PCB's), Bisphenol A (BPA), Polybrominated diphenyl ethers (PBDE's).
- Perfluorinated chemicals (PFC’s).
- May play role in cancer, obesity.
- Changes in DNA methylation (epigenetic modification) which can ultimately change ER activity.
- Produce a higher ratio of the 4 and 16 hydroxylated estrogen derivatives that are potentially more genotoxic by modifying members of the CYP450 enzyme family.

Latini et al., Mini-Reviews in Medicinal Chemistry, 2010, 10, 846-855
BPA displays weak estrogenic properties and could be a weak carcinogen by a mechanism similar to that of estrone (E(1)), estradiol (E(2)) and the synthetic estrogen diethylstilbestrol, a human carcinogen.... The catechol of BPA may alter expression of estrogen-activating and deactivating enzymes, and/or compete with methoxylation of 4-OHE(1)(E(2)) by catechol-O-methyltransferase, thereby unbalancing the metabolism of estrogens to increase formation of E(1)(E(2))-3,4-Q and the depurinating estrogen-DNA adducts leading to cancer initiation. Thus, exposure to BPA could increase the risk of developing cancer by direct and/or indirect mechanisms.
Xenoestrogens (XEs) are chemicals derived from a variety of natural and anthropogenic sources that can interfere with endogenous estrogens by either mimicking or blocking their responses via non-genomic and/or genomic signaling mechanisms.

Xenoestrogens can alter endogenous estrogens' signaling and thereby disrupt normal signaling pathways, leading to malfunctions in many tissue types.
Finally, folliculogenesis was severely impaired in BPA and DEHP exposed ovaries after transplantation into the kidney capsules of immunodeficient mice.

In conclusion, BPA and DEHP exposures impair mouse primordial follicle assembly in vitro.
Many xenoestrogens originally deemed “weak” appear to be potent via some nongenomic signaling pathways, and could contribute to these compounds’ ability to disrupt endocrine functions.
Xenoestrogens are both imperfect potent estrogens and endocrine disruptors; the more efficacious a XE, the more it disrupts actions of physiologic estrogens.
These data demonstrate that ERα intracellular concentration is an important target through which EDs hamper the hormonal milieu of E2 target cells driving cells to different outcomes or mimicking E2 even in the absence of the hormone.
If ER alpha is over stimulated by an excess of E2 or the action of an environmental estrogen such as BPA, it will produce an excessive insulin signaling.
Modulators of CYP450 enzymes

• CYP1A1 and/or CYP1A2:
  – Resveratrol (purple grapes) (blocks dioxin induction via aryl hydrocarbon receptor)
  – Ellagic acid (berries)
  – Green tea catechins (EGCG)
  – Kava
  – DHEA

• CYP1B1:
  – Green tea catechins (EGCG)
  – DHEA
  – Di-indolylmethane
  – I3C
  – Red Clover extracts
Phase 2 Detoxification
Two Major Pathways of Detoxification

**Phase I**
- Hydroxylation Reactions
- Cytochrome P450 enzymes

**Activated Intermediate**

**Phase II**
- Conjugation Reactions

- Fat Soluble Toxin
- Water-Soluble Compound
Phase II Substrate Classes

• Sulfation & Glucuronidation
  – Many drugs and xenobiotics (esp. phenolic compounds)
  – Many steroid hormones and the fat-soluble vitamins
  – Bile acids, bilirubin, some neurotransmitters

• Acetylation & Methylation
  – Many drugs and some xenobiotics (esp. metals/minerals)
  – Many neurotransmitters

• Amino Acid Conjugation
  – Some drugs and xenobiotics (esp. aliphatic compounds)
  – Fatty acids and bile acids

• Glutathione Conjugation
  – Few drugs but many xenobiotics (esp. toxic metals)
  – Small carbon molecules, prostaglandins, and lipid peroxides
Estrone (E1)

- 2-OHE1
  - 16α-OHE1
  - 4-OHE1
    - 3,4 Quinones
      - (carcinogenic)
  - (pro-carcinogenic)

- 2-MeOE1
  - (neutralized)
  - (protective)

- 4-MeOE1
  - (neutralized)

- (Neutralized mercapturate)

(COMT)

(GST)
Role of Methylation

• 2-OHE1 is only protective against cancer when methylated by catechol-O-methyltransferase (COMT)
  – 2-methoxy-estrogens are being researched for therapeutic use in breast cancer and CV disease

• 4-OHE1 is less likely to oxidize to carcinogenic compounds if neutralized by COMT

• 2-MeOE1:2-OHE1 and 4-MeOE1:4-OE1 ratios in urine provide a gauge of methylation capacity in a given patient
COMT (catechol-o-methyltransferase)

Catalyses the shift of a methyl group from the co-enzyme S-adenosyl-L-methionine (SAMe) to one hydroxyl group of the catechols with Mg2+ acting as a co-factor

— (Guldberg and Marsden, 1975)
Catechol-O-methyltransferase (COMT)

- Polymorphism associated with reduced enzyme activity
- Less production of protective 2-methoxy-estrogens, less neutralization of pro-carcinogenic 4-OH-estrogens
- Higher serum levels of E2 in women using E2 HRT
- Impaired clearance of catecholamines → nervousness, anxiety, increased sensitivity to pain
COMT

• Increasing breast CA risk with decreasing COMT activity

• Risk higher in women...
  – With prolonged estrogen exposure
    • (HRT, early menarche, or high BMI) (Huang CS 1999)
  – Low folate or high homocysteine
    • (Goodman JE 2001)
  – Co-existing GST polymorphisms
    • especially if on HRT (Mitrunen K 2002)
Several epidemiological studies have shown that individuals with low activity form of COMT may have a greater risk for breast cancer.

Catechol Estrogens and the Uterus

“Catechol estrogens can also stimulate prostaglandin synthesis (Kelly and Abel, 1981) in the uterus, which can influence uterine function such as implantation... But the 2-OH estrogens have no effect on the uterus.”

Estrogen Metabolism and Ovarian Cancer

“These findings indicate that estrogen metabolism is unbalanced in ovarian cancer and suggest that formation of estrogen-DNA adducts plays a critical role in the initiation of ovarian cancer.”

Polymorphisms in genes encoding enzymes of folate metabolism are a focus of breast cancer risk studies due to the role of these enzymes in DNA methylation, synthesis, and repair. Results have been controversial. This case control study showed MTHFR polymorphisms are associated with breast cancer risk when co-existent with methionine synthase (MTR) polymorphisms in the heterozygous state.
Are Urinary Metabolites Representative of Tissue Levels?

“The urinary 2/16 ratio seems a good approximation of the ratio observed in breast tissue.”

Taioli et al. Reproductive Biology and Endocrinology 2010, 8:93
Aberrant DNA methylation in serum/plasma or vaginal fluid will enable early identification of individuals before the cancer becomes symptomatic and poses serious risk to well-being; and monitoring and personalization of cancer treatment.
## Estrogen Metabolites

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<tr>
<th>Metabolite</th>
<th>Value</th>
<th>Range</th>
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<tr>
<td>2-Hydroxyestrone (24hr urine)</td>
<td>6.46</td>
<td>0.26-13.68 mcg/24 hr</td>
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<tr>
<td>2-Methoxyestrone (24hr urine)</td>
<td>0.60</td>
<td>0.34-9.03 mcg/24 hr</td>
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<tr>
<td>16α-Hydroxyestrone (24hr urine)</td>
<td>6.63</td>
<td>0.25-7.89 mcg/24 hr</td>
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<td>4-Hydroxyestrone (24hr urine)</td>
<td>2.92</td>
<td>0.33-1.98 mcg/24 hr</td>
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<tr>
<td>4-Methoxyestrone (24hr urine)</td>
<td>&lt;0.38</td>
<td>0.20-1.60 mcg/24 hr</td>
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<td>2-Hydroxyestrone/16α-Hydroxyestrone</td>
<td>0.97</td>
<td>0.94-1.56</td>
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<td>4-Methoxyestrone/4-Hydroxyestrone</td>
<td>&lt;0.13</td>
<td>0.18-3.60</td>
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"The depurinating adducts that migrate from cells and can be found in body fluids can also serve as biomarkers of cancer risk.

In fact, a higher level of estrogen-DNA adducts has been found in the urine of men with prostate cancer and in women with breast cancer compared to healthy controls.

This unifying mechanism of the origin of cancer and other diseases suggests preventive strategies based on the level of depurinating DNA adducts that generate the first critical step in the initiation of diseases."
Estrone (E1)

- 2-OHE1 (CYP1A1)
- 16α-OHE1 (CYP3A4, CYP1B1)
- 4-OHE1 (pro-carcinogenic)
- 3,4 Quinones (carcinogenic?)

Estradiol (E2)

- 2-OHE1 (COMT)
- 2-MeOE1 (neutralized, protective)

Estriol (E3)

- 4-OHE1 (COMT)
- 4-MeOE1 (neutralized)

Carcinogenic?

Neutralized mercapturate

Neutralized (GST)
"The most common pathway of conjugation of 4-OHE1(E2) in extrahepatic tissues occurs by O-methylation, which is catalyzed by the ubiquitous catechol-O-methyltransferase (COMT).

This inactivating pathway is in competition with the activation of CE to semiquinones and quinones.... The quinones can be inactivated by formation of glutathione (GSH) conjugates and/or by reduction to CE by quinone reductase.

If, however, these two processes are insufficient, the CE-3,4-quinones can react with DNA to form depurinating adducts (4-OHE1(E2)-1-N3Ade and 4-OHE1(E2)-1-N7Gua)."
Phase I

Cytochrome P-450

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Phase II
### Methylation

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### Acetylation (N-acetyl transferase)

#### SLOW METABOLIZER POLYMORPHISM

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#### FAST METABOLIZER POLYMORPHISM

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### Glutathione Conjugation (Glutathione s-transferase)

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### Oxidative Protection

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Estrone (E1)

2-OHE1 → 2-MeOE1 (protective)

4-OHE1 → 4-MeOE1 (neutralized)

3,4 Quinones → (Neutralized mercapturate)

4-OHE1 (pro-carcinogenic)

3,4 Quinones (carcinogenic)

(CYP1B1)

(COMT)

(GST)
Treatment
Postmenopausal breast cancer risk associated with hormone therapy may be modified by genetically determined variations in phase I and II enzymes involved in steroid hormone metabolism.
How Do We Decrease Our Risk?

- Proper Risk Assessment
  - Connect the dots
- Decrease exposure
- Promote detoxification
- Enhance Elimination
- Awareness
These findings suggest opportunities for breast cancer prevention by modifying individual estrogen metabolism profiles through either lifestyle or chemopreventive strategies.
Overview of My Protocol

• Decrease Exposures
• Nutritional Support with wholesome food
  – (fresh, whole, unprocessed, organic, colorful, high fiber, with nuts, seeds and omega 3’s) herbs, spices, fermented products, soluble fiber and low glycemic load
• Decrease Insulin Stimulation
• Elimination Diet
  – 21-day or longer, personalize
• Targeted Supplementation
  – Food is the foundation
• Lifestyle Modification
• Address digestion
• Exercise/Movement
• Sleep
• Mind-body-spirit connection
• Support
Scents and Perfumes

• Air Fresheners/Deodorizers
• Fabric Softeners
• Scented Candles
• Body Perfumes
Cosmetic & Personal Care Products

Organic Plant Sources - Toxin Free
Avoid Glandulars
Free of Chemical Colorings
Free of Chemical Preservatives
Free of TALC
Free of Organochlorines
Safe Packaging
Safe Processing Methods
Toxic Ingredients to Avoid

• DEA (DIETHANOLAMINE), MEA (MONOETHANOLAMINE), TEA (TRIETHANOLAMINE)
• PARABENS PRESERVATIVES (METHYL, PROPYL, BUTYL, ISOBUTYL, and ETHYL)
• MINERAL OIL: PETROLATUM, PETROLEUM JELLY (LIQUID PARAFFINUM, PARAFFIN OIL, PARAFFIN WAX, POSH MINERAL OIL)
• PROPYLENE GLYCOL/BUTYLENE GLYCOL
• SILICONE DERIVED EMOLLIENTS (DIMETHICONE, DIMETHICONE COPOLYL, CYCLOMETHICONE)
• TALC
• DIBUTYL PHTHALATE
• 1.4–DIOXANE
• BHT (BUTILATED HYDROXYTOLUENE)/BHA(BUTILATED HYDROXYANISOLE)
• BENZALKONIUM CHLORIDE and BENZETHONIUM CHLORIDE
• TRICLOSAN AND TRICLOCARBAN
• PARFUM
Common Personal Care Products

- Fabric detergents
- Dishwashing detergents
- Clothing softeners
  - Rinse cycle
  - Dryer
- Clothing
  - Choose natural fibers
Cosmetic & Personal Care Products

- Lotions/Creams
- Cleansers
- Toners
- Make-up
- Gels
- Hair Spray
- Hair Dyes
- Nail Polish
Lowest in pesticides – *OK to eat conventionally grown*...

- Onions
- Avocado
- Sweet Corn
- Pineapple
- Mangos
- Sweet Peas
- Asparagus
- Kiwi
- Cabbage
- Eggplant
- Cantaloupe
- Watermelon
- Grapefruit
- Sweet Potato
- Honeydew & Melon
higher fish consumption was inversely associated with risk.
Quantification and Speciation of Mercury and Selenium in Fish Samples of High Consumption in Spain and Portugal

Ana I. Cabañero,1 Cristina Carvalho,2 Yolanda Madrid,1 Camila Batoreu,2 and Carmen Cámara1,∗

Sardines have the best ratio of Selenium/Mercury

ABSTRACT

Mercury (Hg) and selenium (Se) determinations were carried out to evaluate human exposure to those elements through fish consumption in Spain and Portugal. Atomic fluorescence spectroscopy (AFS) was applied in a cold vapor mode for total mercury quantification and was also hyphenated to gas chromatography (GC) to achieve the speciation of organomercurial species in fish samples. The results obtained show the highest concentration of Hg in swordfish and tuna (0.47 ± 0.02 and 0.51 ± 0.01 μg g⁻¹, respectively) and a much lower concentration in sardine, mackerel, shad, and octopus (0.048 ± 0.002, 0.033 ± 0.001, and 0.024 ± 0.001 μg g⁻¹, respectively). The determination of alkyl mercury compounds revealed that 93–98% of mercury in the fish samples was in the organic form. Methylmercury (MeHg) was the only species found in the three fish species with higher mercury content.

Total selenium concentration was high in sardine, swordfish, and tuna (0.43 ± 0.02, 0.47 ± 0.02, and 0.92 ± 0.01 μg g⁻¹, respectively), but low in mackerel, shad, and octopus (0.26 ± 0.01 and 0.13 ± 0.01 μg g⁻¹, respectively). Speciation of selenium compounds was done by high-performance liquid
Diets rich in dietary fiber and, particularly, fiber from vegetables may be associated with a small reduction in risk of BC, independently of menopausal status.
Dietary fiber intake and risk of breast cancer: a meta-analysis of prospective cohort studies.

Dong JY¹, He K, Wang P, Qin LQ.

Abstract

BACKGROUND: Observational results are inconclusive regarding the association between dietary fiber and breast cancer (BC) risk.

OBJECTIVE: We aimed to conduct a meta-analysis of prospective studies to evaluate this association.

DESIGN: Relevant studies were identified through a systematic search strategy. Dietary fiber intake and breast cancer risk were analyzed.

RESULTS: We identified 10 studies involving 712,196 participants. The combined relative risk (RR) of breast cancer for the highest compared with the lowest dietary fiber intake was 0.89 (95% CI: 0.83, 0.96), and little evidence of heterogeneity was observed. The association between dietary fiber intake and risk of breast cancer did not significantly differ by geographic region, length of follow-up, or menopausal status of the participants. Omission of any single study had little effect on the combined risk estimate. Dose-response analysis showed that every 10-g/d increment in dietary fiber intake was associated with a significant 7% reduction in breast cancer risk. Little evidence of publication bias was found.

CONCLUSION: This meta-analysis provides evidence of a significant inverse dose-response association between dietary fiber intake and breast cancer risk.
• COMT uses SAMe as its methyl donor; therefore, maintaining SAMe availability will encourage COMT activity
  – Methionine-esp important if low homocysteine
  – Magnesium
  – B2, B6, B12
  – Folic acid (also as folinic acid, 5-formyl THF, or 5-methyl THF)
  – TMG (betaine)
Dietary Supplements to Optimize Reduced Glutathione Levels

- **Reduced glutathione**  1-3 g/day
- **N-acetyl-cysteine**  600-3,000 mg/day
- **Lipoic acid**  200-1,000 mg/day
- **Whey protein concentrates**  2-3 servings/day
- **Magnesium**  400 + mg
- **Vitamin C**  500+mg
- **Vitamin E**  400 IU
- **Silymarin**  400-1,200 mg/day
- **Pantothenic acid**  500-1,000 mg/day
- **SAMe**  400-800 mg/day
Dietary Supplements to Optimize Reduced Glutathione Levels Continued...

• Glycine and Glutamine
• B vitamins (B2, B6, B12, 5MTHF)
• Extracts:
  – Turmeric extract, grape seed extract
  – Bilberry, strawberry/black raspberry extracts
• Antioxidants
  – (to discourage formation of quinone compounds)
• Melatonin
• Theanine
• Sulforaphane
Clinical Cases
Case #1:

CS is 51 yo menopausal woman still menstruating but having increasing hot flashes, night sweats, fatigue and insomnia. Low estrogen and low progesterone on testing, low thyroid and stage 1 adrenal fatigue. Started on HRT, thyroid replacement and adaptogens as well as lifestyle modification. Good symptom control. Feeling great on follow-up.
### Estrogen Metabolites

<table>
<thead>
<tr>
<th>Metabolite</th>
<th>Value</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-Hydroxyestrone (24hr urine)</td>
<td>26.7</td>
<td>9.2-76.6 mcg/g Creat.</td>
</tr>
<tr>
<td>16α-Hydroxyestrone (24hr urine)</td>
<td>8.5</td>
<td>2.4-20.3 mcg/g Creat.</td>
</tr>
<tr>
<td>4-Hydroxyestrone (24hr urine)</td>
<td>9.1</td>
<td>&lt;= 5.3 mcg/g Creat.</td>
</tr>
<tr>
<td>2-Methoxyestrone (24hr urine)</td>
<td>3.2</td>
<td>&gt;= 1.7 mcg/g Creat.</td>
</tr>
<tr>
<td>4-Methoxyestrone (24hr urine)</td>
<td>0.7</td>
<td>&gt;= 1.9 mcg/g Creat.</td>
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### Ratios

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<tbody>
<tr>
<td>Anabolic/Catabolic Balance (24hr urine)</td>
<td>0.6</td>
<td>1.0-3.9</td>
</tr>
<tr>
<td>11β-HSD Index (24hr urine)</td>
<td>0.35</td>
<td>0.59-1.42</td>
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<tr>
<td>E/A: 5β/5α Ratio (24hr urine)</td>
<td>0.5</td>
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<td>2-Hydroxyestrone/16α-Hydroxyestrone Ratio</td>
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</tr>
<tr>
<td>2-Methoxyestrone/2-Hydroxyestrone Ratio</td>
<td>0.12</td>
<td>&gt;= 0.09</td>
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Treatment

- Increase cruciferous vegetables
- Methylating factors
- I3C/Dim
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What Would You Do Now?
Case #2

- Pt: 55yo post-menopausal
- History of breast cancer
- Current S/Sx
- Fairly low energy which has improved over last few months
- Some GI complaints, mostly constipation but occasional diarrhea
- Low thyroid function
- High stress levels
- Meds/Supplements
Case #2 Continued

• Since first test: been doing some methylation support and estrogen detox support
  – 5-MTHF
  – P-5-P
  – Methylcobalamin
  – TMG
  – Turmeric
  – Rosemary
  – Broccoli extract, plus some DIM
• Not on any Rx medications
• Follow-up: Labs much improved
  – Improvement in energy, but is a slow process
  – Continuing to work on stress reduction
Follow-Up Test – 8.16.16
Thank You
Questions?

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LIVE GDX – Previous webinar recordings
GI University – Focused learning modules
Conferences – Schedule of events we attend
Test Menu – Detailed test profile information

MY GDX – Order materials and get results

Michael Chapman, ND
Moderator

Filomena Trindade, MD, MPH
Presenter
Additional Questions?

US Client Services: 800-522-4762
UK Client Services: 020-8336-7750

Please schedule a complimentary appointment with one of our Medical Education Specialists for questions related to:

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- How Genova’s profiles might support patients in your clinical practice
- Review a profile that has already been completed on one of your patients

We look forward to hearing from you!
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**GI Effects in Clinical Practice:**
*Focusing on the Gut*

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Estrogen Metabolism: Are We Assessing It Properly?

Filomena Trindade, MD, MPH

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