

Estrogen Metabolism & Dietary Influences



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Remember

1. The information in this presentation is provided for informational and educational purposes only and is not medical or treatment advice.
2. Any information and statements regarding dietary or herbal supplements have not been evaluated by the Food and Drug Administration and are not intended to diagnose, treat, cure, or prevent any disease.
3. The use of any information provided in this presentation is solely at your own risk.



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Objectives

- 1. Understand the 3 phases of estrogen detoxification and why estrogen metabolism is important.**
- 2. Review dietary influences on detox pathways.** What may positively or negatively impact these pathways.
- 3. Put it all together:** How can we use this information in a treatment plan? Case Studies
- 4. Q & A** What do you want to know?

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Estrogen Metabolism

Phase 1, Phase 2 and Phase 3



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Estrogen detoxification for hormonal balance and overall health

- Why is estrogen metabolism important?
 - Good detox can support both short term and long term health
 - Reduce symptoms including heavy bleeding, pain, moodiness, breast tenderness etc
 - Better manage proliferative diseases-fibroids, endometriosis
 - Reduce oxidative stress
 - Cancer prevention
- Why through diet?
 - May be more sustainable long term than supplementation
 - May be more cost effective
 - Empowers and educates patients to participate in making healthy choices for themselves and their family
 - Gentle, potentially less risk than high dose supplementation
 - Whole food has potential for more benefit than extracted constituents

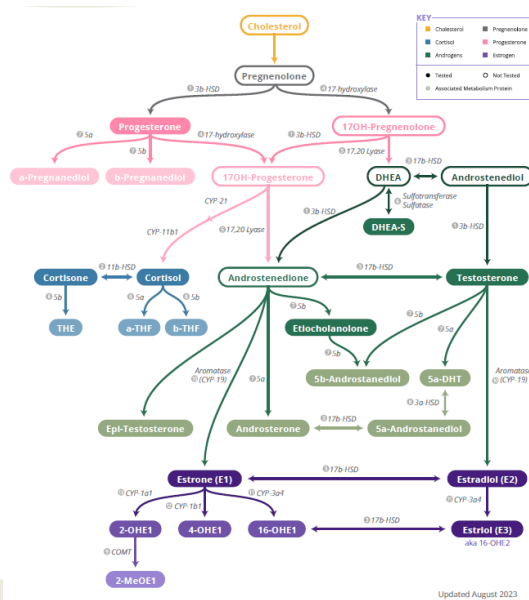
Afrin S, AlAshqar A, El Sabeh M, et al. Diet and Nutrition in Gynecological Disorders: A Focus on Clinical Studies. *Nutrients*. 2021;13(6):1747. Published 2021 May 21. doi:10.3390/nu13061747

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Steroid Pathways

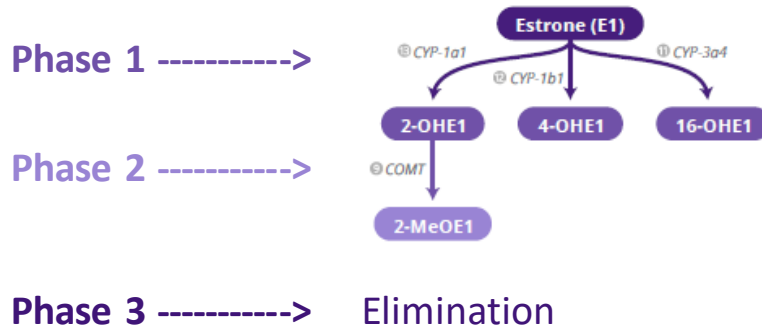


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Estrogen Metabolism



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Phase 1

Happening in the liver through the cytochrome P450 enzymes

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Phase 1

- Primarily in the LIVER, but also happening in other tissues
- Cytochrome P450 enzymes:
 - Take lipid molecules and make them water soluble. Main actions are hydroxylation, oxidation and reduction. For estrogen it is primarily hydroxylation. The main enzymes involved are CYP1A1, CYP1B1, and CYP3A4.
- Phase 1 metabolites are all still somewhat estrogenic and active
 - In some cases more problematic than their parent hormones

Main pathways

- **CYP1A1**
 - 1A1 makes the least problematic metabolite 2OH
- **CYP1B1**
 - 1B1 makes the most reactive metabolite 4OH
- **CYP3A4**
 - 3A4 makes the most estrogenic metabolite 16OH

CYP1A1

Preferred pathway

Flax

Contributes to healthy estrogen in numerous ways

- Increases action of CYP1A1, increasing 2OH and 2Methoxy
- High antioxidant properties
- Anti-inflammatory
- Hepatoprotective
- Lignans
 - Phytoestrogen
- Fat
 - alpha-Linolenic acid (ALA), Omega-3
- Fiber
 - Both soluble and insoluble
- Protein
- May improve blood sugar regulation

***To get the most benefit seeds should be ground, either fresh or kept refrigerated



Kajla P, Sharma A, Sood DR. Flaxseed-a potential functional food source. *J Food Sci Technol.* 2015;52(4):1857-1871. doi:10.1007/s13197-014-1293-y

Sirotkin AV. Influence of Flaxseed (*Linum usitatissimum*) on Female Reproduction. *Planta Med.* 2023;89(6):608-615. doi:10.1055/a-2013-2966

Soy

- Improves 1A1 activity
- Phytoestrogen
 - Isoflavones
 - Genistein
 - Daidzein
- Anti-inflammatory
- Antioxidant
- Fiber
- Protein
- Fats
 - a-linolenic acid (ALA)
 - But also high in Omega 6s (inflammatory)

One additional consideration – include non-GMO and/or organic soy whenever possible



Lu LJ, Cree M, Josyula S, Nagamani M, Grady JJ, Anderson KE. Increased urinary excretion of 2-hydroxyestrone but not 16alpha-hydroxyestrone in premenopausal women during a soya diet containing isoflavones. *Cancer Res.* 2000;60(5):1299-1305.

Messina M, Duncan A, Messina V, Lynch H, Kiel J, Erdman JW Jr. The health effects of soy: A reference guide for health professionals. *Front Nutr.* 2022;9:970364. Published 2022 Aug 11. doi:10.3389/fnut.2022.970364

Cruciferous Vegetables: Broccoli, Cauliflower, Kale, Cabbage, Brussel Sprouts, Bok choi etc

- Upreulates 1A1
 - Some research indicates they may increase 1B1 activity in animal models, but most research points to them as a stronger inducer of 1A1
- Contain precursors for Indole-3-carbinol(I3C) and diindolylmethane (DIM)
 - Must be chopped/crushed/chewed
- High sulfur food
- Sulforaphane
 - Induces phase 2 enzymes
 - Increases glutathione – important antioxidant
- Anti-inflammatory
- Fiber



Hodges RE, Minich DM. Modulation of Metabolic Detoxification Pathways Using Foods and Food-Derived Components: A Scientific Review with Clinical Application. *J Nutr Metab.* 2015;2015:760689. doi: 10.1155/2015/760689. Epub 2015 Jun 16. PMID: 26167297; PMCID: PMC4488002.

Omega 3 Fatty Acids Fatty Fish, Fish Oil/Algal Oil, Chia, Avocado

- Increases 1A1 activity
- Anti-inflammatory
- Reduce prostaglandin activity
- Work synergistically with other nutrients including phytochemicals and antioxidants



Chen HW, Tsai CW, Yang JJ, Liu CT, Kuo WW, Lii CK. The combined effects of garlic oil and fish oil on the hepatic antioxidant and drug-metabolizing enzymes of rats. *Br J Nutr.* 2003;89(2):189-200. doi:10.1079/BJN2002766

Alcohol

Has an impact on all the pathways, hepatotoxic

- Decreases 1A1 activity
 - Even moderate amounts-30mL daily
- Increases 3A4 activity
- Inflammatory
- Produces reactive oxygen species and free radicals in the liver
- Disrupt metabolism of fat in the liver
- Can stimulate ovarian estrogen production
- Associated with increased risk of estrogen sensitive conditions
 - Breast cancer
 - Endometriosis
- Lack of nutrients – even nutrient depleting



Mahabir S, Pfeiffer R, Xu X, Baer DJ, Taylor PR. Effects of low-to-moderate alcohol supplementation on urinary estrogen metabolites in postmenopausal women in a controlled feeding study. *Cancer Med.* 2017;6(10):2419-2423. doi:10.1002/cam4.1153

High Sugar Diet

Many of the same factors as alcohol

- Decreases 1A1 activity
- Inflammatory
 - Liver and whole body
- Weight gain
- Insulin resistance
- Affects liver
- Lack of nutrients



Peters LP, Teel RW. Effect of high sucrose diet on cytochrome P450 1A and heterocyclic amine mutagenesis. *Anticancer Res.* 2003;23(1A):399-403.

CYP1B1

Problematic, genotoxic pathway

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Quercetin

Inhibits 1B1

- Flavonoid and antioxidant
- Capers are the food with the highest levels of quercetin
- Also found in red and yellow onions, apples
 - Both have majority in the peels
- Grapes, Blueberries, Cranberries
- Citrus fruits
- Another flavonoid Myricetin
 - Also inhibits 1B1
 - Also founds in berries, fruits, tea
- Many bioflavonoids appear to inhibit 1B1
 - acacetin, diosmetin, eriodictyol, hesperetin, homeroiodictyol, and naringenin



Doostdar H, Burke MD, Mayer RT. Bioflavonoids: selective substrates and inhibitors for cytochrome P450 CYP1A and CYP1B1. *Toxicology*. 2000;144(1-3):31-38. doi:10.1016/s0300-483x(99)00215-2

Androutsopoulos VP, Papakyriakou A, Vourloumis D, Spandidos DA. Comparative CYP1A1 and CYP1B1 substrate and inhibitor profile of dietary flavonoids. *Bioorg Med Chem*. 2011;19(9):2842-2849. doi:10.1016/j.bmc.2011.03.042

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Resveratrol

Inhibits 1B1

- Red Grapes
 - Red Wine
 - Apples
 - Berries
 - Dark Chocolate/Cocoa
 - Pistachios
-
- Also inhibits 3A4
 - May promote 1A1, high doses, mixed research



Chow HH, Garland LL, Hsu CH, et al. Resveratrol modulates drug- and carcinogen-metabolizing enzymes in a healthy volunteer study. *Cancer Prev Res (Phila)*. 2010;3(9):1168-1175. doi:10.1158/1940-6207.CAPR-09-0155

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CYP3A4

Proliferative Pathway

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CYP3A4

- An important note about CYP3A4 activity is that it metabolizes many things, main detox pathway
- Over 50% of pharmaceutical drugs are metabolized down this pathway
 - Some are substrates
 - Some are inducers
 - Some are inhibitors
- Consider this if a patient is on any medications.
- May need to avoid affecting this pathway directly
- Potential for drug interactions
- High levels of expression in the GI, gut health can affect metabolism

Substrates	Inhibitors	Inducers
Benzodiazepines ^a	Amiodarone	Barbiturates (phenobarbital)
Budesonide	Aprepitant	Carbamazepine
Calcium Channel Blockers ^b	Cimetidine	Corticosteroids
Carbamazepine	Ciprofloxacin	Phenytoin
Corticosteroids	Clarithromycin	Rifampicin
Etoposide	Diltiazem	St John's wort
Immunosuppressives ^c	Erythromycin	
Macrolide antibiotics ^d	Fluconazole	
Statins ^e	Grapefruit juice	
Steroids ^f	Itraconazole	
Miscellaneous ^g	Ketoconazole	
	Posaconazole	
	Voriconazole	
	Verapamil	

<https://www.ncbi.nlm.nih.gov/books/NBK553990/table/ch31.Tab1/> doi: 10.1007/978-3-030-0278-5_31



Grapefruit

- Most well know food inhibitor of 3A4
- Prolonged effect - up to 24 hours
- Only need a single glass, 200-250ml
- Affects enzyme in the small intestine, but not necessarily in the liver
- Have not identified active component though several have been proposed
 - Naringin – weak?
 - Naringenin – potent?
- Other citrus juices ie orange juice, do not have the same effect



Bailey DG, Malcolm J, Arnold O, Spence JD. Grapefruit juice-drug interactions. *Br J Clin Pharmacol*. 1998;46(2):101-110. doi:10.1046/j.1365-2125.1998.00764.x

Green Tea

- Inhibitory to 3A4
 - Rich in phytochemicals/polyphenols – many are known inhibitors
 - Flavonoids
 - EGCG, ECG (catechins)
 - Phenolic acids
 - Gallic acid
 - May act through several mechanisms
 - Competitive inhibition
 - Directly altering 3A4 enzyme activity
- Catechins may slow COMT activity



Basheer L, Kerem Z. Interactions between CYP3A4 and Dietary Polyphenols. *Oxid Med Cell Longev.* 2015;2015:854015. doi: 10.1155/2015/854015. Epub 2015 Jun 9. PMID: 26180597; PMCID: PMC4477257.

Polyphenols

- Many foods with potential to affect 3A4 activity

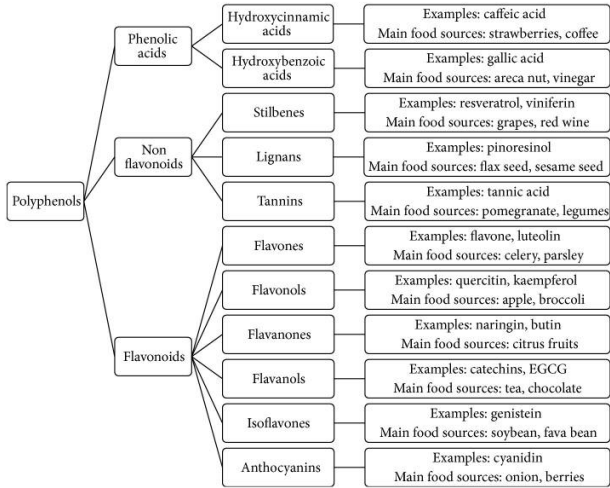
Hodges RE, Minich DM. Modulation of Metabolic Detoxification Pathways Using Foods and Food-Derived Components: A Scientific Review with Clinical Application. *J Nutr Metab.* 2015;2015:760689. doi:10.1155/2015/760689



Category of polyphenols	Subcategory of polyphenols	Polyphenols in category	Interaction with CYP3A4
Flavonoids	Flavonols	Kaempferol, galangin	Inhibition
		Quercetin	Inhibition
	Flavones	Apigenin, chrysin, amentoflavone	Inhibition
		Luteolin, diosmetin	Inhibition
		Flavone, tangeretin	Activation
		α-Naphthoflavone	Activation
	Flavonols	EGCG, ECG	Inhibition
		Naringin, naringenin	Inhibition
	Isoflavones	Genistein	Inhibition
		Anthocyanins	Anthocyanins (and anthocyanin aglycones)
Nonflavonoids	Stilbenes	Resveratrol (and resveratrol derivatives)	Inhibition
		Genistein (B and C)	Inhibition
	Tannins	Silymarin mixture	Inhibition (with slight activation at low concentrations)
		Tannic acid	Inhibition
Phenolic acids	Hydroxycinnamic acid	Caffeic acid	Inhibition
	Hydroxybenzoic acid	Gallic acid	Inhibition

Polyphenols

- Many foods with potential to affect 3A4 activity



Increase 3A4

- Garlic
- Rooibos
- Fish Oil
- Curcumin maybe?
- Caffeine, high consumption

Sowers MR, Crawford S, McConnell DS, et al. Selected diet and lifestyle factors are associated with estrogen metabolites in a multiracial/ethnic population of women. *J Nutr.* 2006;136(6):1588-1595. doi:10.1093/jn/136.6.1588

- ALCOHOL, even moderate consumption



Phase 2: Methylation/COMT

Happening in the Liver through conjugation

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Phase 2

- Primarily in the LIVER, but also happening in other tissues
- Conjugation:
 - Makes Phase 1 metabolites more water soluble and inactive
 - Packages them up to be excreted from the body
- Main Enzyme: COMT
 - Involved in estrogen detox
 - Also involved in detox of many other substances, any catechol in the body endogenous or exogenous
 - Action is Methylation
 - Adding a methyl group
 - Essential nutrient cofactors
 - B6
 - Magnesium

Methylation

- SAmE is the direct methyl donor utilized
 - S-adenosyl methionine
 - Made in the body
 - No food sources
- Support SAmE production
 - Nutrients and foods
- Why not supplement SAmE directly?
 - Not well absorbed
 - Not always sure where/how body will utilize
 - Expensive
 - Some patients have negative side effects

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Phase 2 – COMT supports

- Sources of B6
 - Salmon & Tuna
 - Animal proteins
 - Turkey
 - Chicken
 - Pork
 - Beef
 - Sweet Potato
 - Banana
 - Potato
 - Avocado
 - Pistachio



Phase 2 – COMT supports

- Sources of Magnesium
 - Spinach
 - Pumpkin, Chia and Hemp seeds
 - Almonds, Cashews
 - Lima beans, Black beans
 - Tuna
 - Brown Rice
 - Quinoa
 - Dark Chocolate
 - Avocado
 - Banana



Phase 2 – Support SAME

Support methylation cycle and SAME production:

- Primary supports
 - Folate
 - Chickpeas, Legumes, Liver
 - Probiotic *Lactobacillus plantarum*
 - Probiotic *Bifidobacterium*
 - B12
 - Clams/shellfish, Liver, Fish
 - Betaine
 - Beets, Spinach, Quinoa, Egg yolk, Liver, Sunflower seeds
 - Choline
 - Precursor to Betaine
 - Egg yolks, Liver, Lentils



Rossi M, Amaretti A, Raimondi S. Folate production by probiotic bacteria. *Nutrients*. 2011;3(1):118-134. doi:10.3390/nu3010118

Phase 2 – Support SAME

Support methylation cycle and SAME production:

- Secondary supports
 - Methionine
 - Nuts, Beef, Lamb, Eggs, Beans
 - Other B vitamins
 - B6 – pyridoxine
 - Pork, Poultry, Soy, Chickpeas, Oats, Banana, Dark leafy greens
 - B2 – riboflavin
 - Eggs, Mushrooms, Dairy, Almonds
 - B3 – niacin
 - Wheat, Meat, Fish, Eggs, Brown Rice
 - Magnesium
 - Vitamin K
 - Leafy greens, Fermented soy (Natto), Meat
 - Zinc
 - Shellfish, Meats, Legumes, Nuts and seeds
- Other nutrient supports
 - Sulfur
 - Meat and vegetable proteins
 - Allium vegetables
 - Cruciferous vegetables
 - Cysteine
 - Includes sulfur
 - Meat and animal proteins
 - Taurine
 - Shellfish
 - Poultry
 - Eggs
 - Seaweeds
 - Biotin
 - Meat
 - Nuts and seeds
 - Sweet potato
 - DHA (Docosahexaenoic acid)
 - Fatty fish, shellfish, some algae

Phase 2 – Other Pathways

Sulfation:

Primary phase 2 pathway for 16OH
Attach to sulfate group

- Sulfur donors
 - Taurine, NAC, MSM, Methionine, Glutathione
 - Asparagus, Broccoli, Cauliflower, Cabbage, Onion, Leeks, Garlic, Eggs, Chicken, Crab and Lobster
- Cofactor – Molybdenum
 - Black eyed peas, Lima beans, Legumes



- Support glutathione and antioxidants
- Gallbladder supports –Bile Acid
- Control/Reduce inflammation
- General liver support
 - Artichoke, Milk thistle, Beets
- Ensure adequate protein intake



Glucuronidation:

Attach to glucuronic acid

- Derived from glucose
 - Support glucose metabolism
 - B-vitamins, magnesium, manganese, and chromium
 - Cofactor – NAD+
 - Niacin, Tryptophan

Phase 3: Elimination

Primarily Kidneys and Intestines

Elimination

- Actual removal of toxins. The water soluble substances are now excreted from the body
- Performed by transport proteins
- GI tract through bile then feces
- Urinary Tract/Kidneys through urine
- There are other organs of elimination, less of a factor in estrogen detox, ie skin through sweat, lungs through breath etc



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Phase 3: Elimination

- Support the gut
 - Bile
 - Bitter foods: Artichoke, dandelion
 - Spices: Cumin, Coriander, Fennel, Ajowan, Mint
 - Platel K, Srinivasan K. Stimulatory influence of select spices on bile secretion in rats. *Nutrition Research*. 2000;20(10):1493-1503.
 - Fiber: aim for more than 25g a day
 - Vegetables: peas, broccoli, potato with skin
 - Whole grains
 - Legumes
 - Chia seeds
 - Best to have a mix of soluble and insoluble fiber
 - Regular, 1-2 daily bowel movements
 - Formed
 - Complete
- Gut microbiome
 - Fermented foods
 - Probiotics
- Support the kidneys
 - Hydration: 60-80+ oz a day
 - Water!
- Other potential supports
 - Movement
 - Gentle movement
 - Aerobic exercise
 - Sauna
 - Deep breathing

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Estrogen Metabolism

What that looks like on DUTCH testing

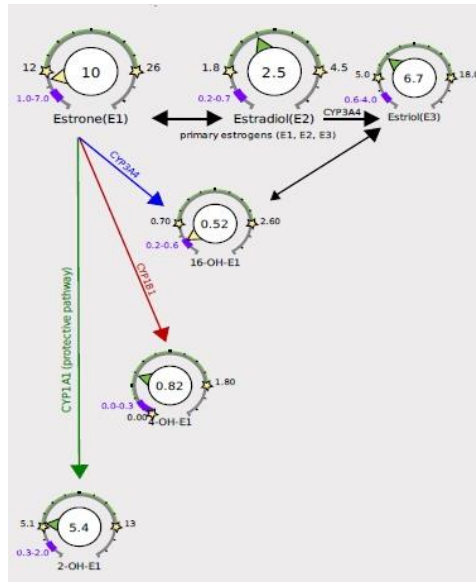


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Phase 1 pathways on DUTCH

Illustrated using Estrone (E1) as the example as it is the more prevalent estrogen

Estradiol (E2) goes through the same phase 1 detox pathways



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Cytochrome P450 Enzymes are listed above their pathways

Phase 1 pathways on DUTCH

CYP1A1---->2OH-E1

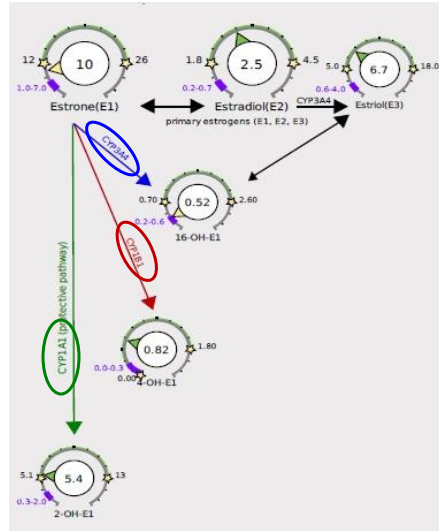
Preferred pathway

CYP1B1---->4OH-E1

Potentially genotoxic

CYP3A4---->16OH-E1

Proliferative



Can also look at the ratios of metabolites to each other

Phase 1 pathways on DUTCH

CYP1A1---->2OH-E1

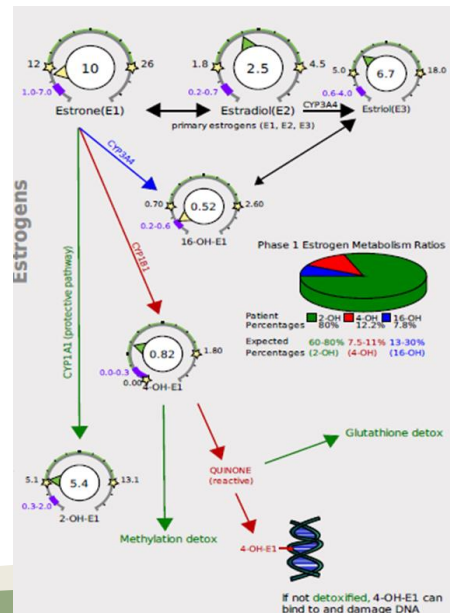
Preferred pathway

CYP1B1---->4OH-E1

Potentially genotoxic

CYP3A4---->16OH-E1

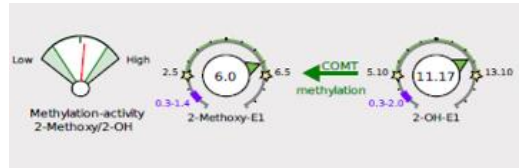
Proliferative



Phase 2 on DUTCH

Methylation primarily supports 2OH and 4OH metabolites

Fan gauge is a functional assessment (a ratio) of estrogen metabolite methylation, want to see in the middle or towards high

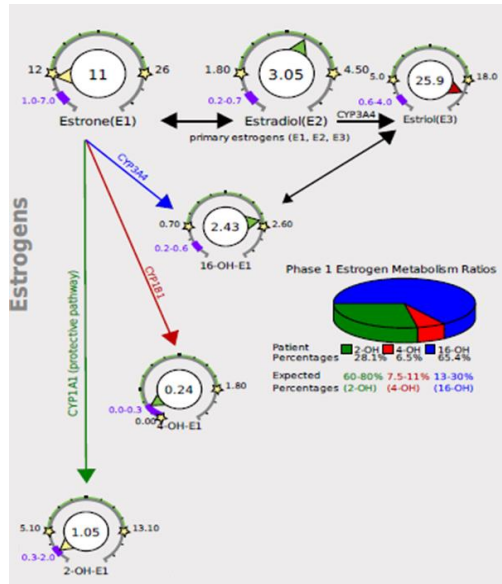


Case studies

What would you do?

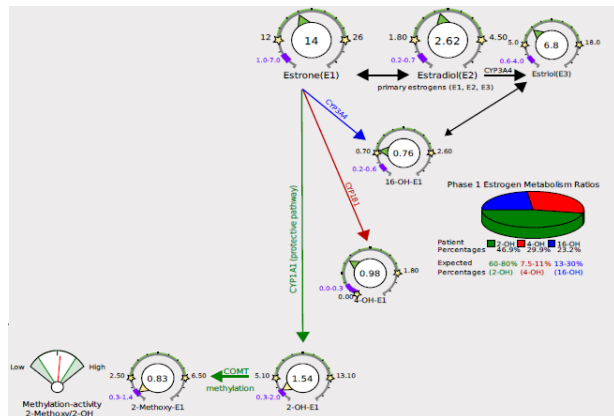
High 16OH-E1

- 31 yo F
 - Complaints of heavy bleeding and PMS
- Occasionally consuming alcohol
 - Social drinker 4-5 drinks, 2-3 times a week
- High carb diet
 - Gets take out often
 - Loves pasta and potatoes
- Reduce 3A4 and increase 1A1
- Support Phase 2 sulfation



High 4OH-E1

- 38 yo F
 - Working to optimize health
 - No specific complaints
- FHx of Breast Cancer
 - Aunt and Grandmother
- Exercises regularly but doesn't think much about diet. Tends to eat the same thing every day, little variety and most common vegetable included is iceberg lettuce.
 - Says she likes vegetables though!
- Decrease 1B1 while increasing 1A1
- Support Phase 2 methylation



Take Aways

- 1. Healthy estrogen detox is important for both short term symptom management as well as long term health outcomes.**
- 2. Estrogen detox can be influenced by a variety of factors including diet.**
These dietary influences can have both positive or negative implications
- 3. Variety is important!** Eating a rich and varied diet supports us all. Tailoring diet to improve estrogen detox works best when there is a healthy diet already in place.

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Thank You!



For questions, contact:

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