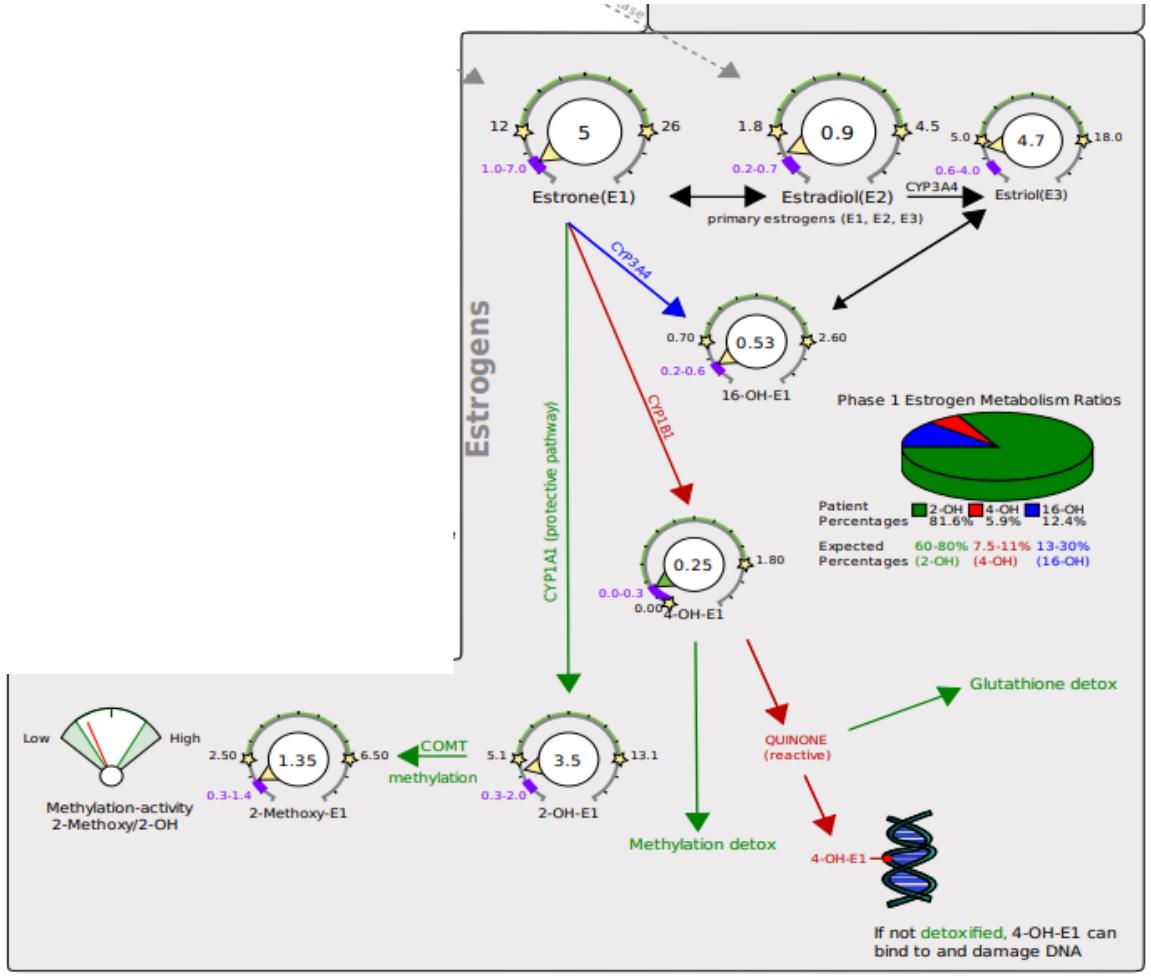
Estrogen Detoxification

Estrogen & its Detoxification

- 3 key phases of detoxification
- Involves proper functioning of ovaries, liver, stomach, gall bladder, intestines, kidneys and more!

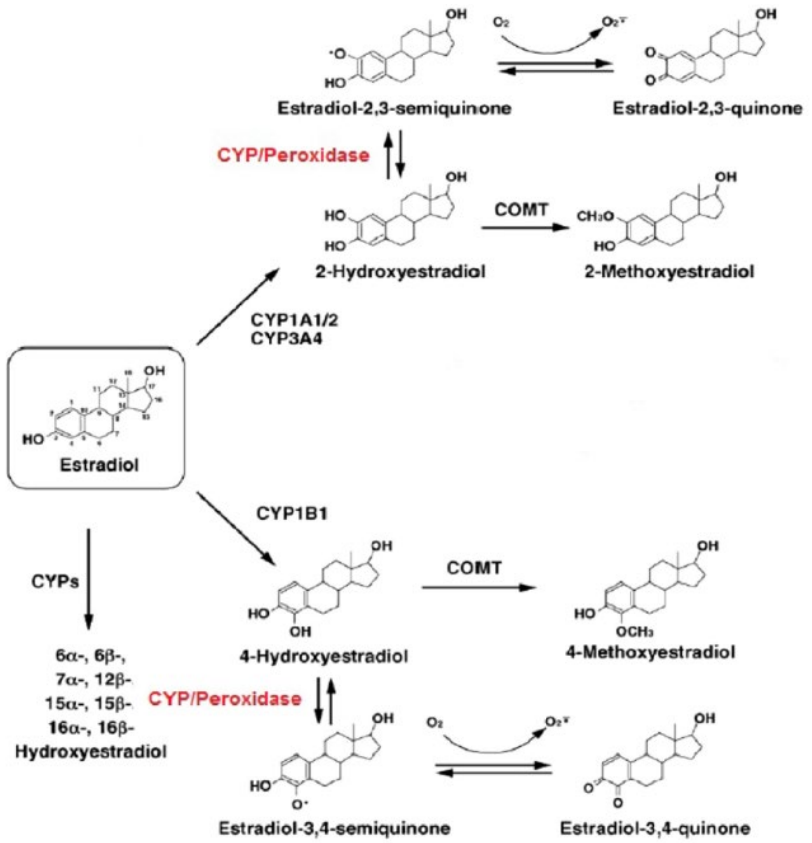


Phase 1 Detoxification

- Recall, all sex hormones are steroid-based hormones (meaning they are built from cholesterol).
- For a steroid hormone to become inert, it must bio-transform through a multi-step process, the first two steps capture urine excreted metabolites (phase 1 and phase 2 detoxification).
- Phase 1 detoxification uses the CYP450 enzyme family to convert estradiol from a fat-based hormone, to a water-soluble hormone.

Phase 1 detoxification: Cytochrome Enzyme Systems

- Occurs mostly in the liver, but also in peripheral tissues
- Estradiol is metabolized using CYP 1A1, 1A2, 1B1, and 3A4 enzymes, dependent on which is most available
- Estrogen undergoes the addition of a hydroxyl group (-OH)
- Highly reactive oxidative intermediates which need further transformation to be excreted
- Metabolites can still act on E receptors (weakly)
- Requires iron, good liver function, alcohol/meds can impede

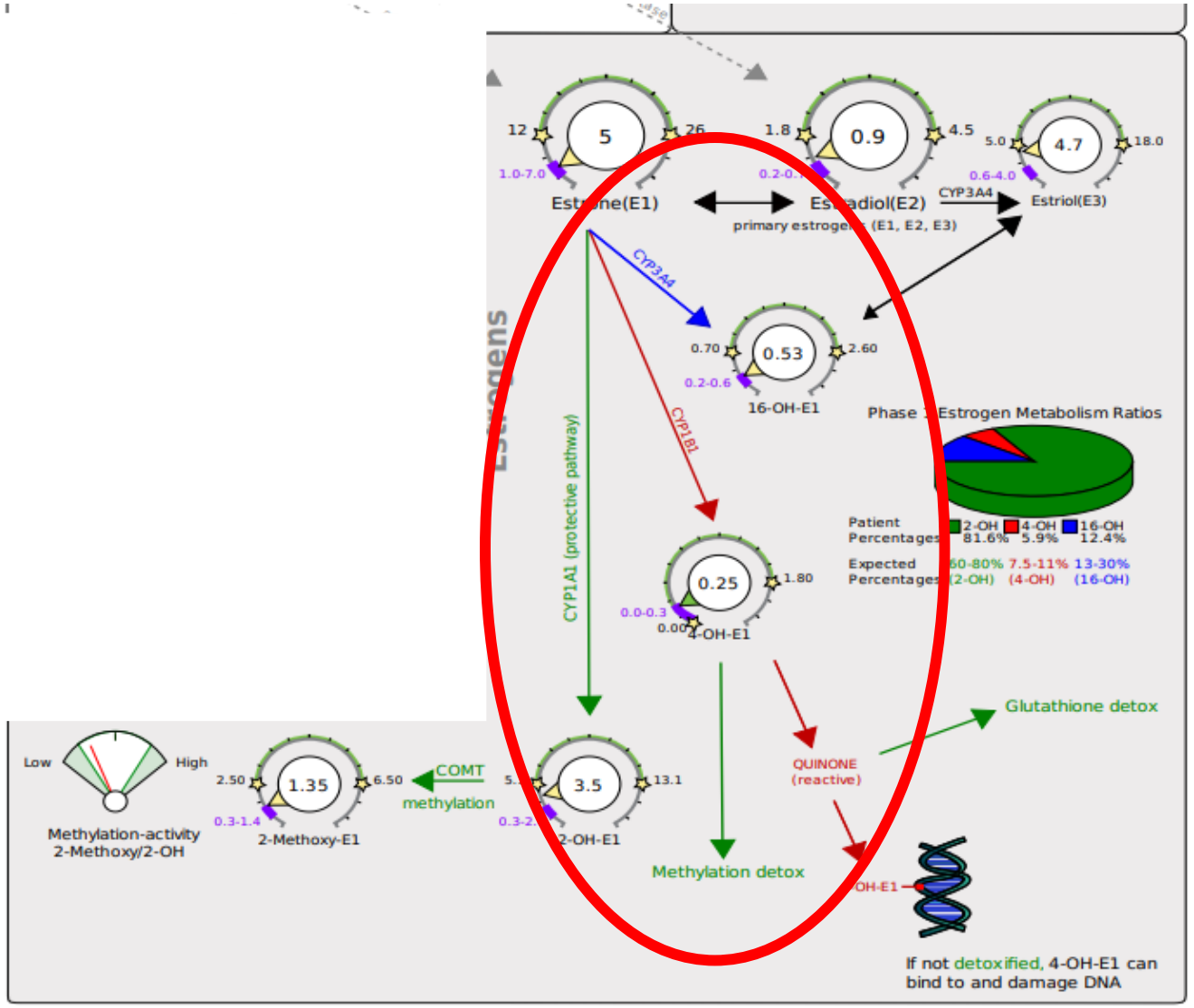


Samavat, H., & Kurzer, M. S. (2015). Estrogen metabolism and breast cancer. *Cancer letters*.

Phase 1 Detoxification: Cytochrome Enzyme Systems

"2-OH" 2-hydroxyestrone & 2-hydroxyestradiol	"4-OH" 4-hydroxyestrone & 4-hydroxyestradiol	"16-OH" 16-hydroxyestrone
CYP1A1 & CYP1A2	CYP1B1	CYP3A4
Most stable and generally "preferred"	Potentially genotoxic	Proliferative Can be good for bones, but not so good with breast/fibroids/endo
Weakest binding potential to E receptor Anti-proliferative effects on cancer cell lines	If not properly metabolized, it can turn down a different pathway to become the free radical 3,4-quinone which can cause DNA damage	Binds most strongly to estrogen receptor, though still weakly
All of these metabolites are reactive oxidative intermediates- they require further biotransformation!		

Phase 1 Detox On The DUTCH Report

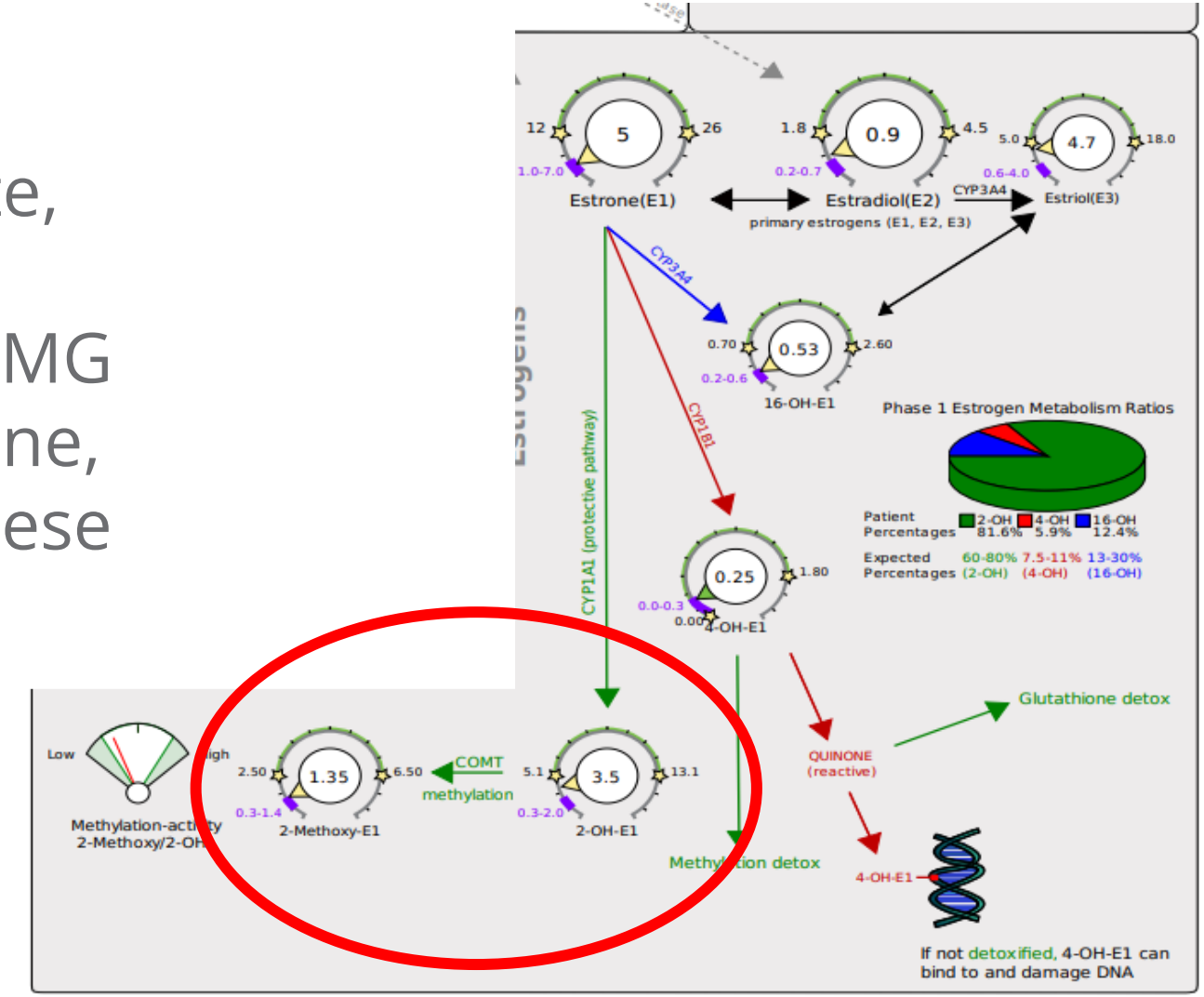


Phase 2 detoxification: Methylation, Sulphation, Glucuronidation

- 2-OH & 4-OH catechol estrogens get a methyl group added by catechol-O-methyltransferase (COMT) and requires SAMe availability
- Leads to production of
  - 2- and 4-methoxyestrone
  - 2- and 4-methoxyestradiol
- Conjugation with glucuronic acid and sulfate in liver → more water soluble
- Sulphation & glucuronidation to support excretion thru bile into gut (like a package now, all tied up!)

Phase 2 Detox on the DUTCH Report

COMT specific methylation support includes B12, folate, B6, B2, magnesium, choline, trimethylglycine (TMG), SAMe, methionine, creatine, vitamin C, lithium, manganese and zinc.



Phase 3 detoxification: Out of cells & into (& out of) gut

- Estrogen metabolites leave the liver thru bile and are excreted through feces or urine
- B-glucuronidase
  - Found in tissues (ie breast) but also made in the gut by microbiome
  - When made in gut, estrogens can be recirculated rather than excreted, increasing estrogen load
- Indican can be a marker for gut dysbiosis, and we have seen (in our data) that higher indican correlates with higher estrogen levels

Phase 3 Detox on the DUTCH Report

Tough to exactly measure, as it's not a urine metabolite

We added indican to our report in 2022 to give insight into gut health.

Data from Precision Analytical samples in postmenopausal women and in men have shown a small, but statistically significant association between elevated urinary indican levels (suggesting dysbiosis) and estradiol levels, reinforcing the assertion that GI dysbiosis is an important factor in circulating estrogen levels.

Category	Test		Result	Units	Normal Range
Nutritional Organic Acids					
Vitamin B12 Marker (may be deficient if high) - (Urine)					
	Methylmalonate (MMA)	Above range	4.89	ug/mg	0 - 2.5
Vitamin B6 Markers (may be deficient if high) - (Urine)					
	Xanthurenate	Above range	1.23	ug/mg	0.12 - 1.2
	Kynurenate	Above range	5.35	ug/mg	0.8 - 4.5
Biotin Marker (may be deficient if high) - (Urine)					
	b-Hydroxyisovalerate	Within range	7.9	ug/mg	0 - 12.5
Glutathione Marker (may be deficient if low or high) - (Urine)					
	Pyroglutamate	Below Limit of Detection	0.0	ug/mg	28 - 58
Gut Marker (potential gut putrefaction or dysbiosis if high) - (Urine)					
	Indican	High end of range	90.4	ug/mg	0 - 100
Neuro-related Markers					
Dopamine Metabolite - (Urine)					
	Homovanillate (HVA)	Low end of range	4.4	ug/mg	3 - 11
Norepinephrine/Epinephrine Metabolite - (Urine)					
	Vanilmandelate (VMA)	Above range	7.3	ug/mg	2.2 - 5.5
Neuroinflammation Marker - (Urine)					
	Quinolinate	Above range	13.2	ug/mg	0 - 9.6
Additional Markers					
Melatonin (*measured as 6-OH-Melatonin-Sulfate) - (Urine)					
	Melatonin* (Waking)	Below range	1.3	ng/mg	10 - 85
Oxidative Stress / DNA Damage, measured as 8-Hydroxy-2-deoxyguanosine (8-OHdG) - (Urine)					
	8-OHdG (Waking)	Within range	3.8	ng/mg	0 - 5.2

Summary

	Phase 1: CYP Enzyme detox	Phase 2: Neutralization & water solubility	Phase 3: Excretion
Key steps	CYP enzymes convert estradiol into 3 main metabolites, 2-OH, 4-OH, 16-OH (which are oxidative!)	Neutralization of metabolites to avoid DNA damage and make more water soluble	Excretion out of liver cells and into bile to feces/urine (hopefully no excess B-glucuronidase and no excess reabsorption!)
Potential signs of a problem	Excess relative production of 4-OH or 16-OH metabolites	Poor methylation – see lower 2-Methoxy than 2-OH-E1 Anxiety (can also be linked to slow COMT)	BM infrequent Signs of estrogen dominance
How to help	Ensure liver function **Requires** Iron +DIM, I3C, quercetin, sulforaphane	+sulforaphane (if from food, requires stomach acid!) **Requires** SAMe, choline, Mg, TMG/betaine, methyl B12/folate/Bs, methionine, Zinc **INHIBITED BY:** E dominance, gut infxn, quercetin, green tea, PCBs, BPA, heavy metals, nutr deficiency	Improve the microbiome BM daily Ensure stomach acid Increase water, fiber + Prebiotics, Calcium D glucarate Unpeeled, raw carrots **AVOID:** antibiotics, junk food, alcohol

Thank You!

If you are interested in learning more about hormones, each week we hold one-hour long mentorship sessions! Once you are a registered DUTCH provider, you can book these through our online scheduling link. Please call to get registered today.

For questions, contact:

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