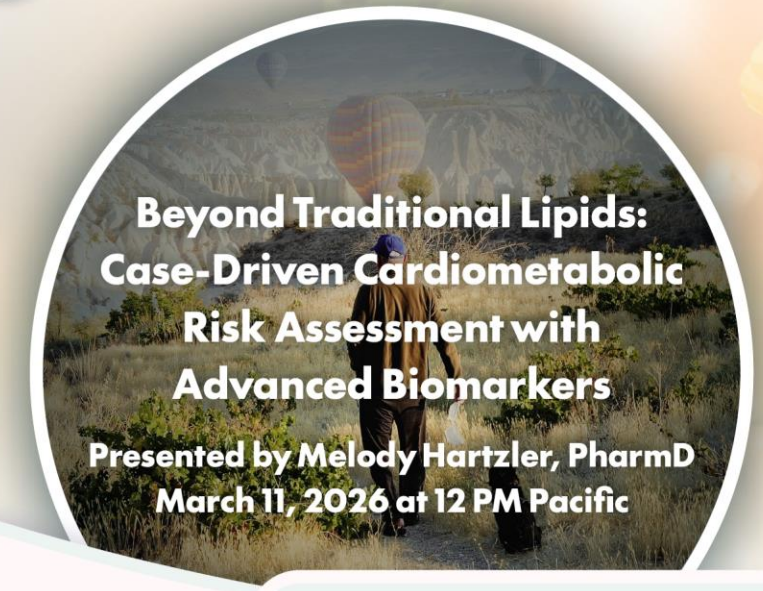
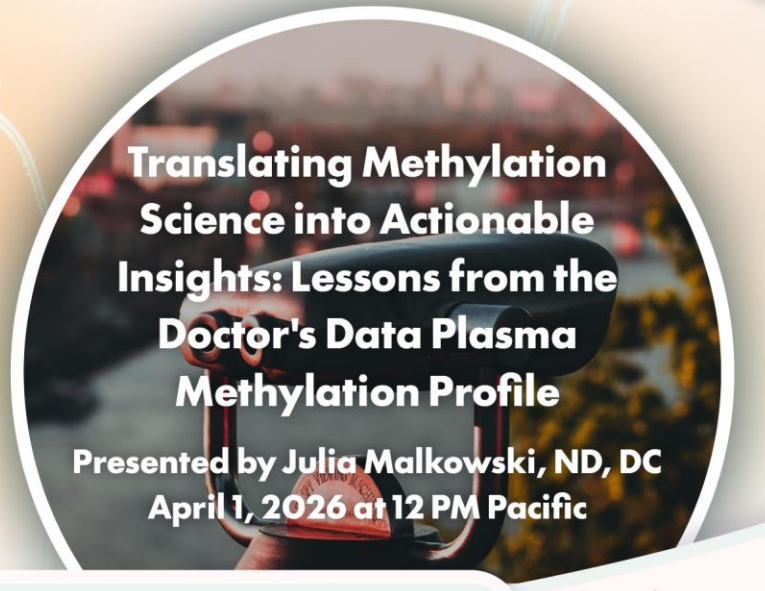
UPCOMING EVENTS





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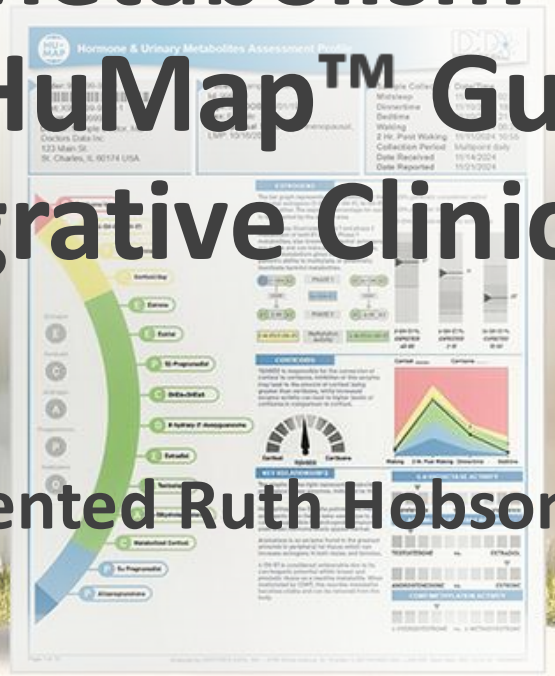
WILL BEGIN SHORTLY

Hormone Metabolism Simplified: A Practical HuMap™ Guide for Busy Integrative Clinicians



Presented Ruth Hobson, ND

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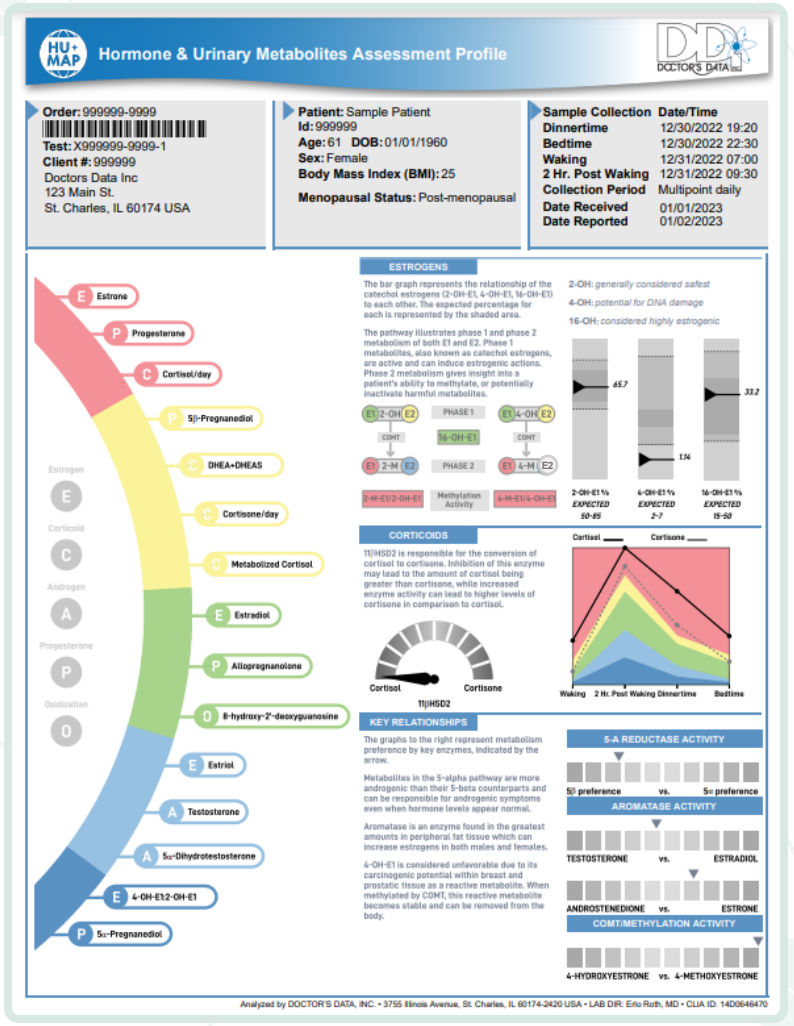
The Hormone and Urinary Metabolites Assessment Profile (HuMap™)

- Provides a comprehensive overview of steroid hormones, their metabolites, and the efficiency of the enzymes that metabolize these hormones.
- This non-invasive test requires only 4 or 5 separate liquid urine collections.
- As the liver and digestive organs play a role in hormone breakdown and elimination, urinary testing of hormones and metabolites may elucidate a need to address other areas of health.
- Additionally, testing urinary hormone metabolites can contribute to further understanding of endogenous hormone secretion, supplemental hormone utilization, enzyme activity, oxidative stress, and insight into how the body metabolizes hormones.



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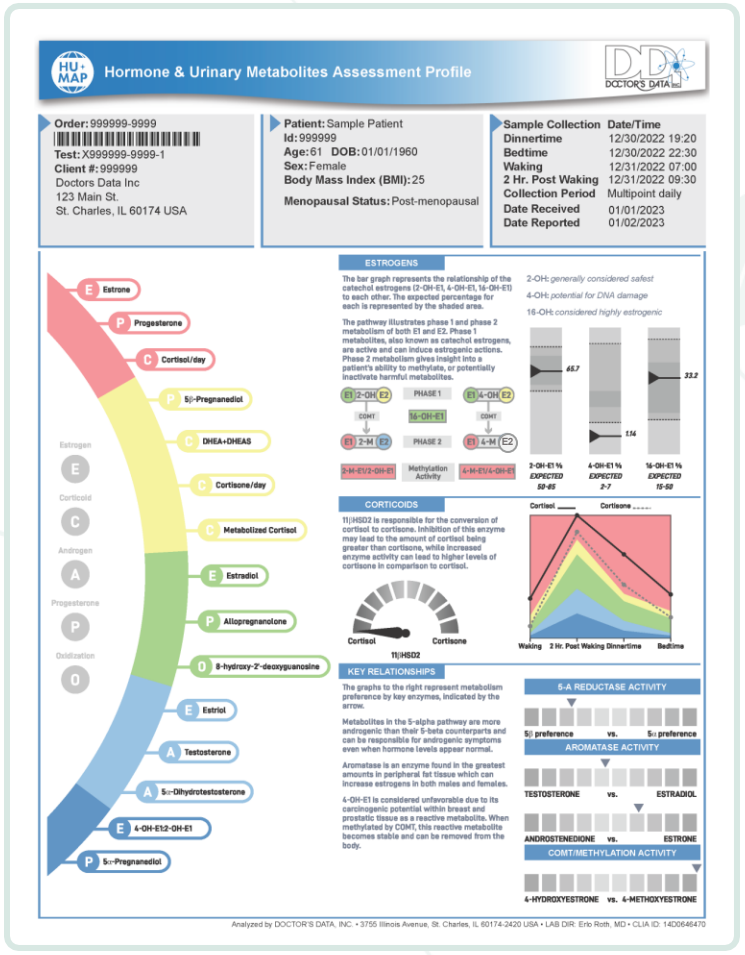
How are urinary hormones measured? LC/MS/MS

- LC separates hormones in a liquid urine sample, which are then injected at various times for MS analysis.
- MS technology monitors the injected sample for specific hormones based on their molecular weights and expected injection times (commonly called retention times).
- Tandem MS verifies each hormone identity based on fragmentation and determines its amount.
- The combination of LC and tandem MS allows for extremely sensitive and specific hormone measurements, even in samples containing similar substances that would interfere with other methods.



What is measured in urinary hormone testing?

- ***Unconjugated hormones*:**

  Sex hormones like progesterone, testosterone, estradiol, etc.

- ***Conjugated metabolites:***

  Consist of hormones that the body has modified by adding a water-soluble side arm - usually glucuronide or sulphate molecules - to facilitate their elimination in urine or stool.

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What are the benefits of looking at hormone urine metabolites over salivary hormones?

Which has been said to be more accurate?

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When to consider using HuMap™

General

- Metabolic syndrome
- Thyroid pathologies
- Inflammation
- Oxidative Stress
- Fatigue/insomnia
- Low libido
- Mood or cognitive concerns
- Family/personal history of hormone-driven cancers
- HRT/BHRT utilization
- Weight gain
- Alopecia

Female

- Menopausal symptoms
- Breast Health
- Endometriosis
- PCOS
- PMS/PMDD

Male

- Erectile dysfunction
- Prostate health
- Lower urinary tract symptoms
- Loss of muscle mass
- Breast health

Common actionable findings on HuMap reports

Androgens

- Excess aromatase or 5 alpha reductase activity depleting testosterone in males
- Excess 5 alpha reduced androgens in females causing symptoms

Progesterones

- Lack of abundance of progesterones in premenopausal females suggesting anovulation (or in males, impacting prostate health)

Oxidative Stress

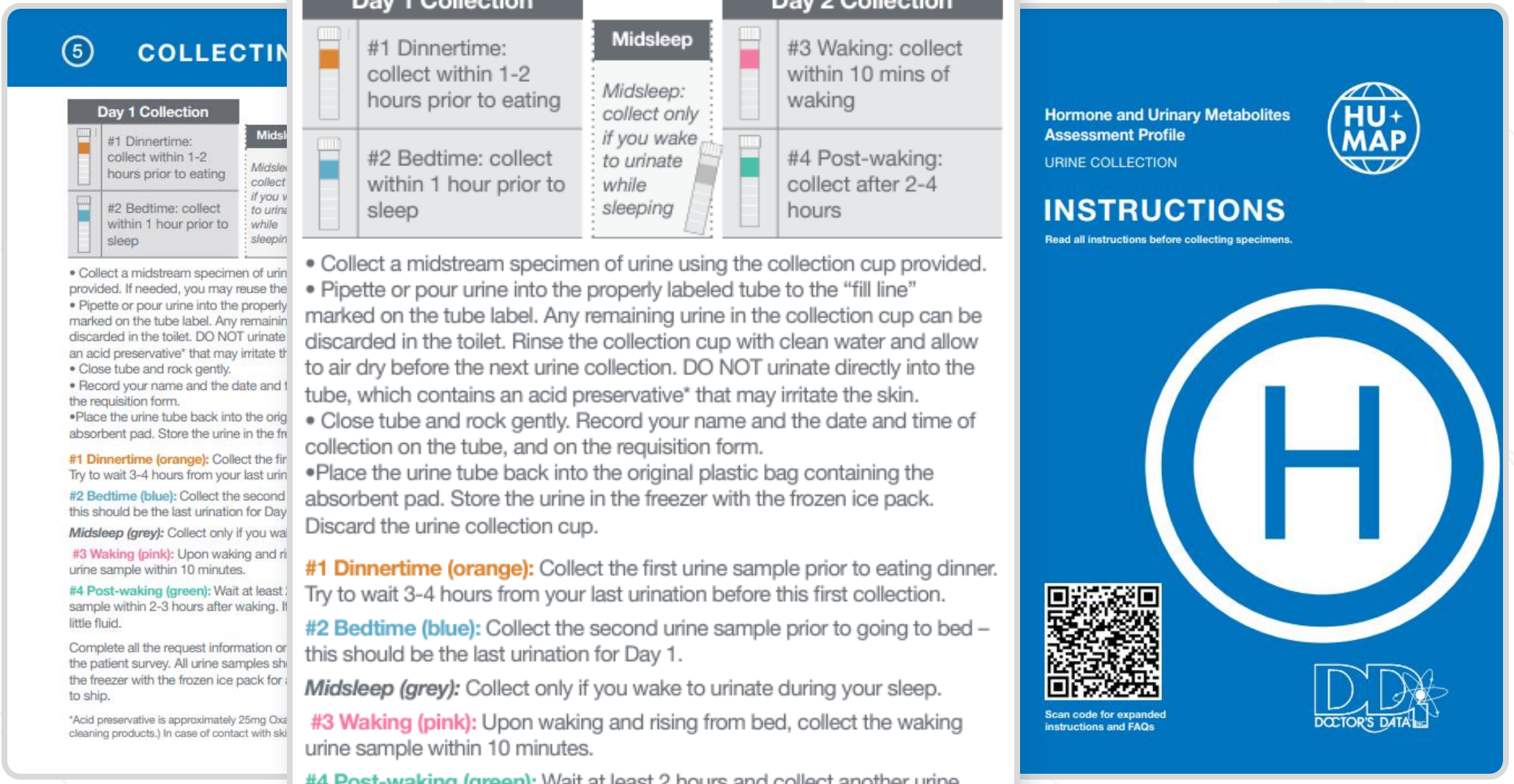
- Elevated 8-OHdG

Estrogens

- Imbalance between 2-, 4-, and 16-hydroxy estrone (Phase I)
- Impaired methylation
- Insufficient phase III detoxification (constipation/dysbiosis) leading to hormone recirculation and excess levels

Corticoids

- Elevations at waking suggestive of excess cortisol excretion while sleeping
- Imbalance between cortisol and cortisone
- Increased or decreased excretion of corticoids



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How does a 4-point liquid urine collection method compare to 24-hour collection?

4 (or 5) - point urine collection throughout a 24-hour period offers a few advantages over 24-hour collection.

Collection of 4 urine samples is easier than collecting all urine in a 24-hour period as up to 40% of patients who attempt 24-hour urine collection do not collect properly.

4-point collection allows measurement of the diurnal cortisol rhythm whereas 24-hour collection can only provide a measure of overall cortisol production.

Hormone values measured from a pool of the 4 collections correspond well with 24-hour hormone values.

What are the advantages of a liquid sample?

- The main advantage of liquid urine collection is enhanced sensitivity, especially for low concentration metabolites. Dried urine must be reconstituted from the filter paper once the sample arrives. This reconstitution can lead to loss of polar steroid metabolites or creatinine for some patient samples.
- With liquid urine, samples can be shipped after being frozen for 4-6 hours, can be processed faster, and concentrated further to enhance the detection of low-level analytes. Steroid hormones and metabolites are also quite stable in liquid urine if the correct preservative is used.
- Ability to add on other urinary tests (NTs or Amino Acids)

BEST PRACTICES FOR SPECIMEN COLLECTION

HORMONE AND URINARY METABOLITES ASSESSMENT PROFILE

The following collection recommendations are specific to Doctor's Data. Adhering to these recommendations ensures test results correlate with established reference ranges. *Never discontinue prescription medications without first consulting your provider.*

version 4.22

Hormone Supplementation	Timing of Last Supplementation
Topical, IM/SQ Injections, subcutaneous pellets, transdermal patches	Continue hormones based on your regular schedule
Vaginal	Discontinue 72 hours prior and during sample collection as this may directly contaminate the urine
Sublingual (dissolved under the tongue), Oral	Discontinue 72 hours prior and during sample collection
Cortisol/Hydrocortisone	Discontinue 4-5 days prior to sample collection to test endogenous secretion
Additional Considerations	
Glucocorticoid supplementation: Consult with your health care provider if you are taking glucocorticoids. Certain medications such as asthma inhalers and anti-itch creams contain cortisol and can impact cortisol/cortisone levels.	
24 hours prior and during collection: avoid alcohol, caffeine, tobacco or nicotine-containing products and strenuous exercise.	
On day 1 of collection, do not drink more than 4 liters of fluids.	
If you are also testing Neurotransmitters from the same urine samples	
24 hours prior and during collection: avoid avocados, eggplant, tomatoes, bananas, melons, pineapple, grapefruit, plums, fruit juice, nuts, nut butters, wine, cheese, rice, and chocolate.	
Day of both collections: it is recommended to avoid all supplements and medications until after all samples have been collected (including those that regulate allergy, mood, sleep, pain and inflammation)	

Collection Schedule

Menopausal Status	When to Collect Samples
Premenopausal, regular cycles (28 days)	Days 19-23 (Mid luteal phase)
Premenopausal, regular cycles longer than 28 days	Count back 7-9 days from usual end of cycle, at a minimum of day 19 (Luteal phase is almost always 14-16 days long)
Perimenopausal, irregular cycles with ovulation pains	7 days after ovulation
Perimenopausal, irregular cycles, no ovulation pains	Test after day 14, and before day 1 of next cycle
Premenopausal, irregular cycle shorter than 14 days	Days 7-9
When there is no point of reference, e.g. 60 days	Collect samples; freeze; if no period within 2 days then mail the sample
Men and postmenopausal women	Anytime

Schedule	When to Collect Sample
Night shift workers	Shift workers should adapt the collection times in accordance with their own sleep / wake schedule.
Frequent travelers (especially across multiple time zones)	If possible, collect samples after 2 weeks at home on regular schedule.

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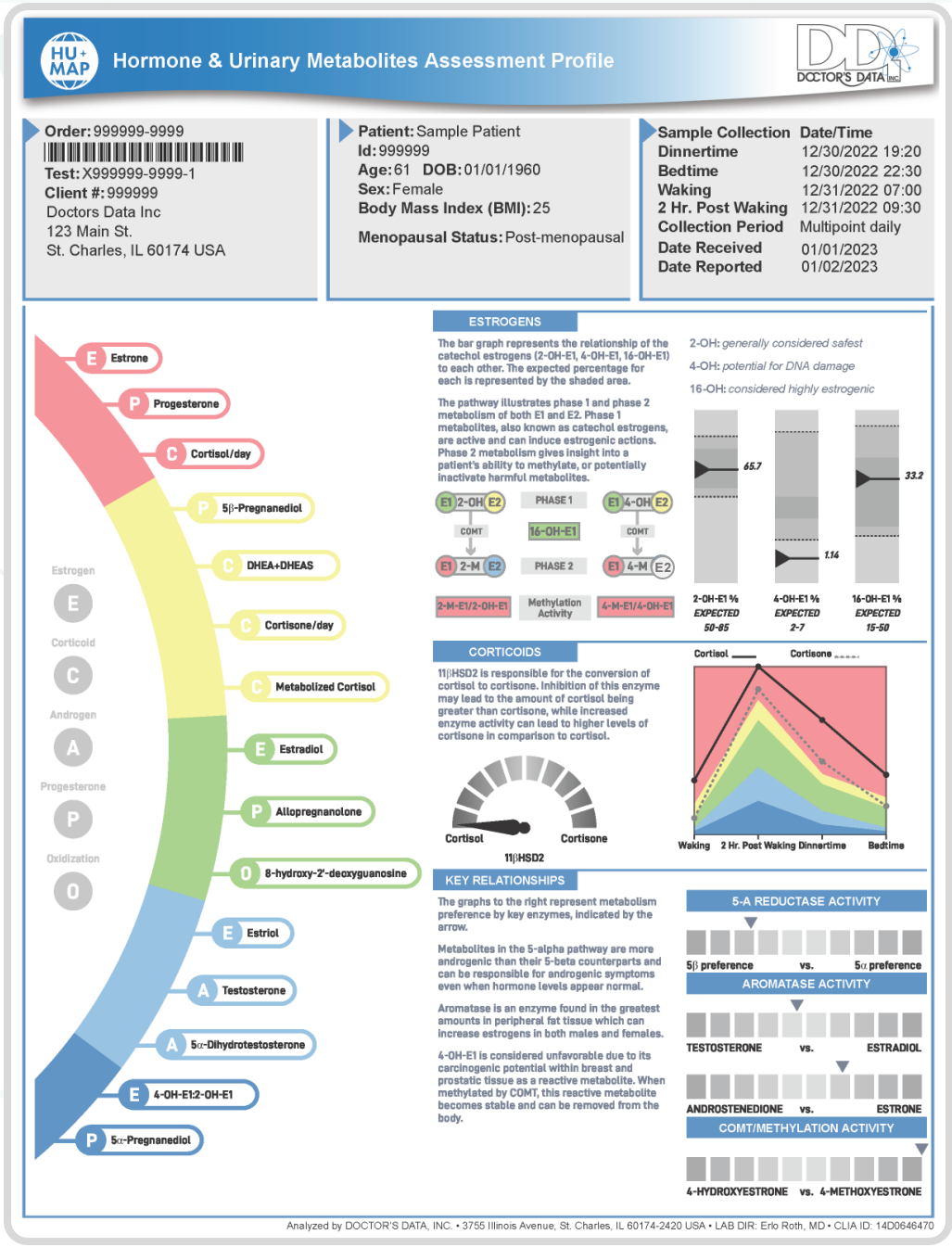

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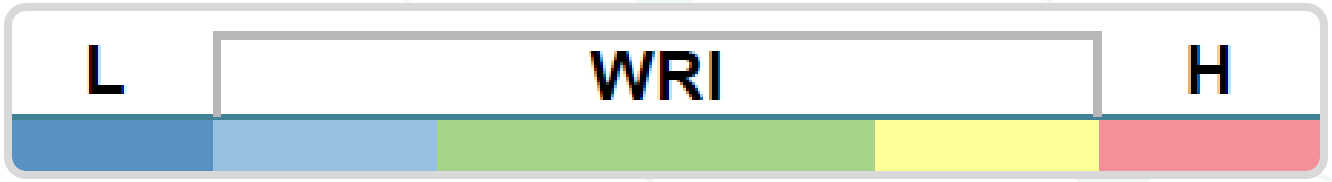
HuMap Colors

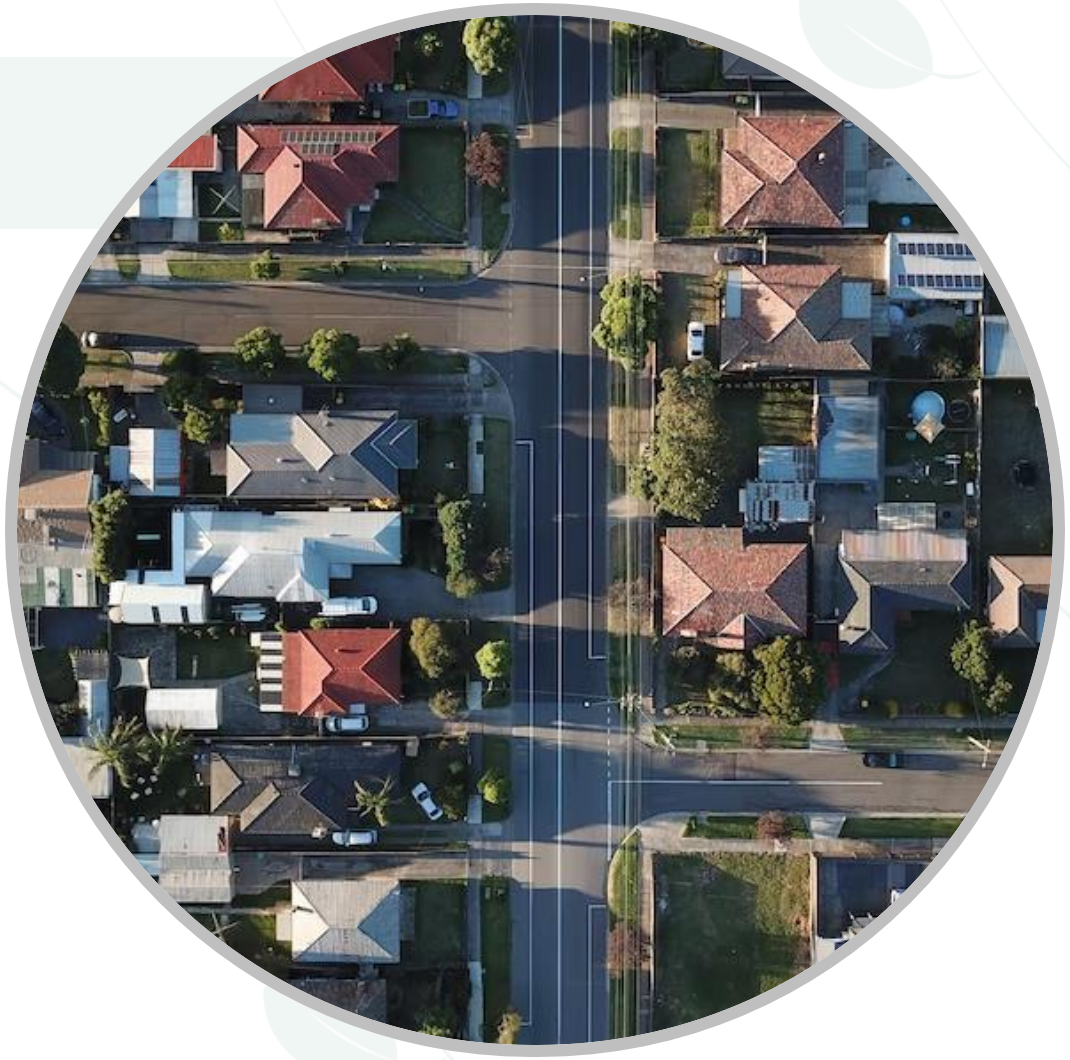


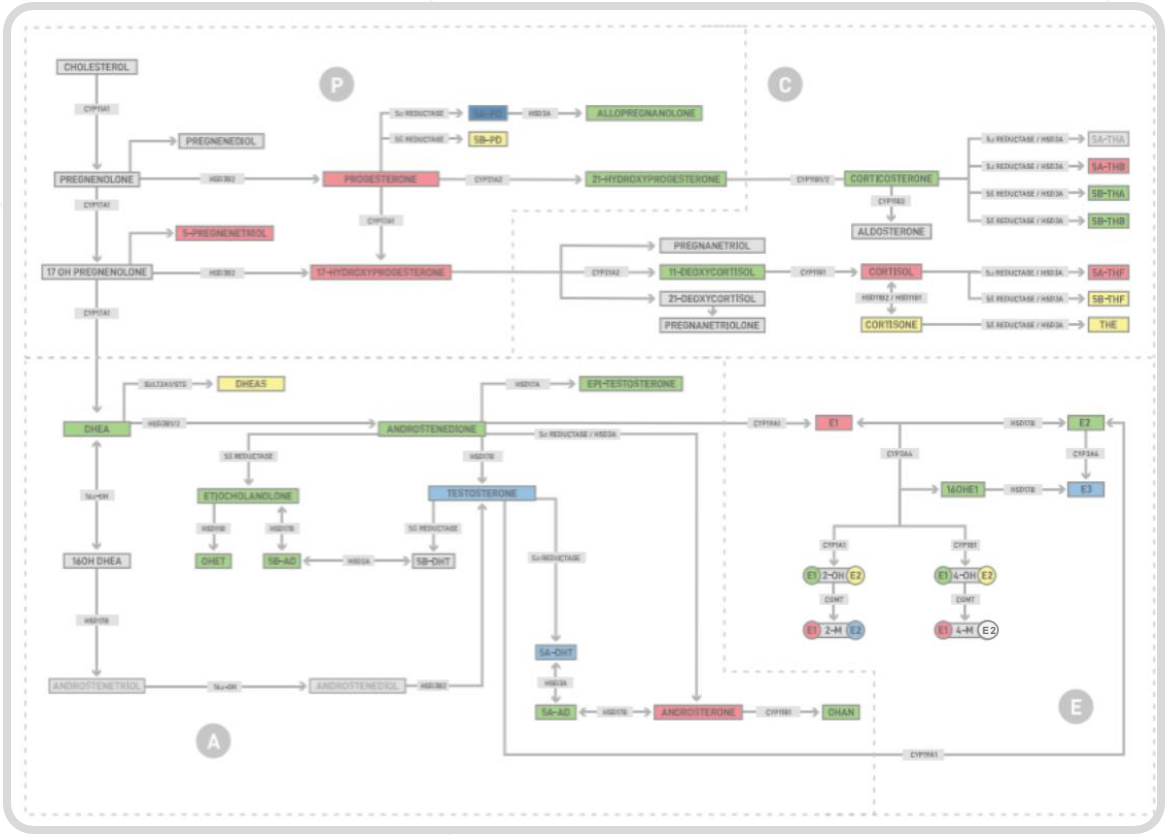
- WRI – Within Reference Interval - represented by bracket and stated ranges on report

- Dark Blue = Below RI
- Light Blue = WRI low
- Green = Optimal
- Yellow = WRI high
- Red = Above RI

Neighborhoods

- The HuMap™ test can be divided into 4 neighborhoods
  - Progesterones
  - Corticoids
  - Androgens
  - Estrogens





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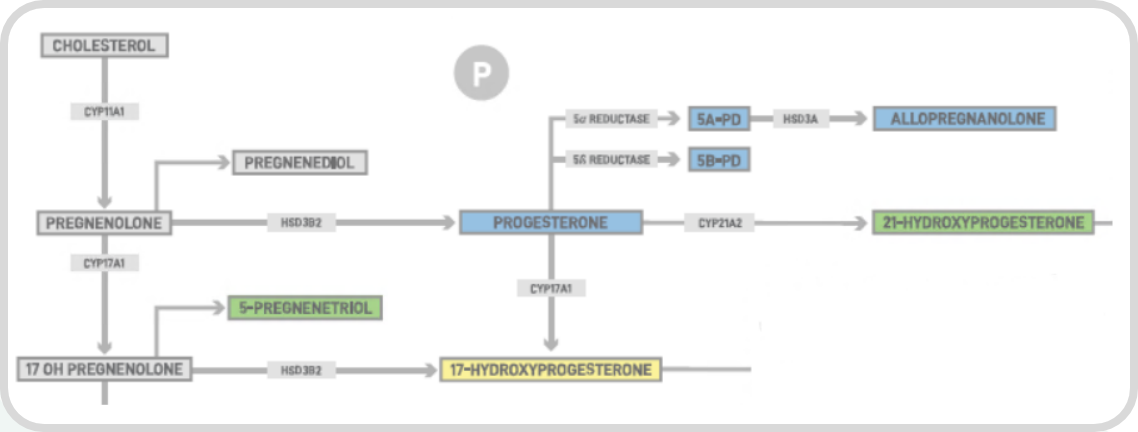
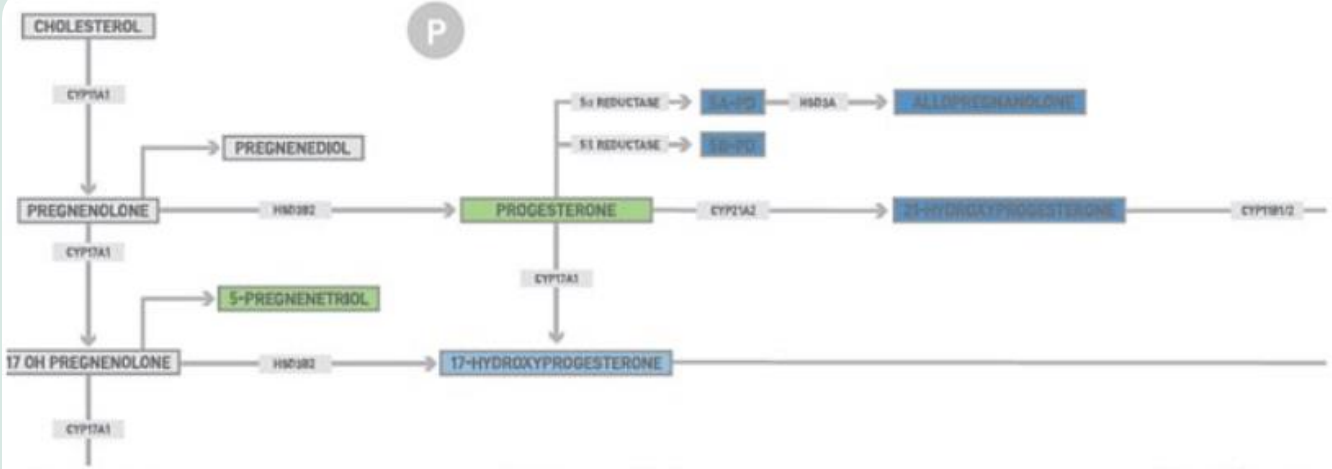


Progesterone Neighborhood

- Progesterone
- 5-alpha pregnanediol
- 5-beta pregnanediol
  - Dominant metabolite
  - Can correlate with ovulation
- Allopregnanolone
- 5-pregnenetriol
  - Elevations seen in PCOS, CAH, Cushing's
- 17-hydroxyprogesterone
  - Elevations seen in PCOS, idiopathic hirsutism, CAH, and NCCAH, hyperinsulinemia, stress, and alcohol use
- 21-hydroxyprogesterone
  - Elevations seen in Cushing's, DMII, CAH

Allopregnanolone

- Crosses the BBB and binds the GABA receptor
- May help evaluate oral progesterone metabolism



Progesterones		Result	Unit	L WRI H	Reference Interval
Progesterone‡	(P4)	0.057	ng/mg Creat/Day		0 – 0.34
5α-Pregnanediol‡	(5A-PD)	5.68	ng/mg Creat/Day		10 – 35
5β-Pregnanediol‡	(5B-PD)	84.8	ng/mg Creat/Day		99 – 290
Allopregnanolone‡	(ALLOP)	0.290	ng/mg Creat/Day		0.8 – 6.4
21-Hydroxyprogesterone‡	(21-OHP)	0.372	ng/mg Creat/Day		0.6 – 3
17-Hydroxyprogesterone‡	(17-OHP)	0.245	ng/mg Creat/Day		0.19 – 0.85
5-pregnenetriol‡	(5-PT)	53.4	ng/mg Creat/Day		35 – 105

Ratios and Calculations		Result	Unit	L WRI H	Reference Interval
5A-PD:5B-PD‡	(alpha vs beta metabolism)	0.067			0.1 – 0.5

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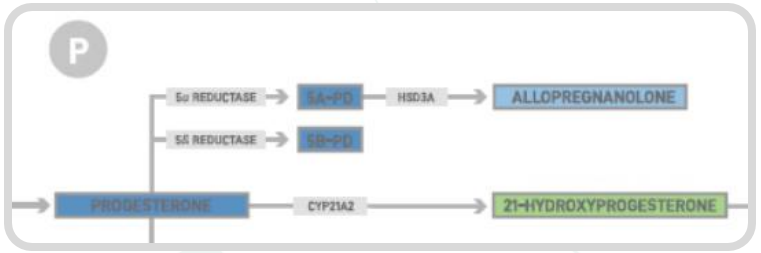
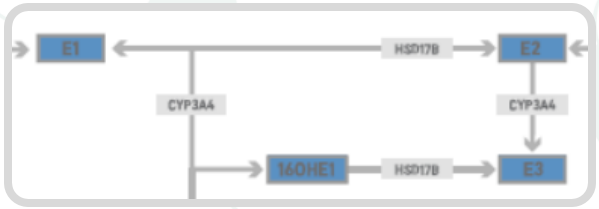
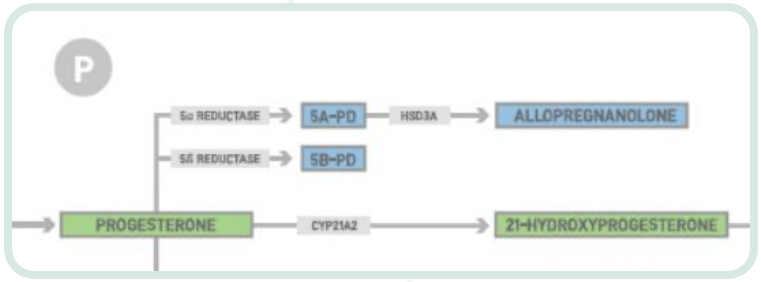
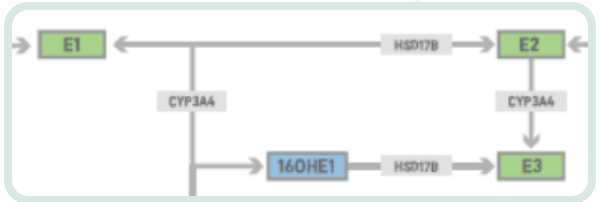
Is there any utility to testing a patient on oral contraceptives?





23yo F, OCP
(E2 + progestin)



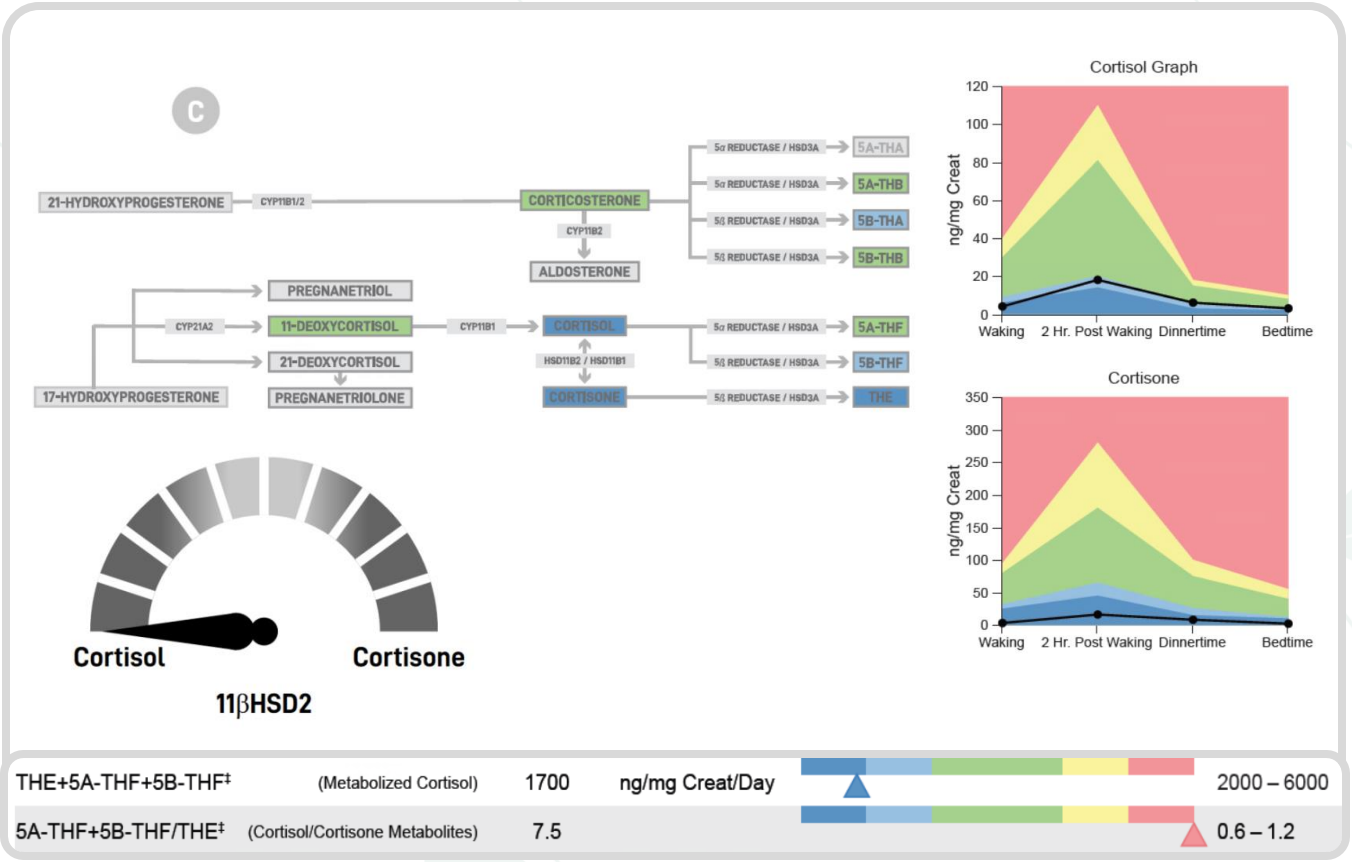


29yo F, progestin IUD

Corticoids

Corticoids Neighborhood

- Graphical representation of each timed collection
- Cortisol vs. Cortisone
- Metabolized cortisol
- Cortisol vs. cortisone metabolites



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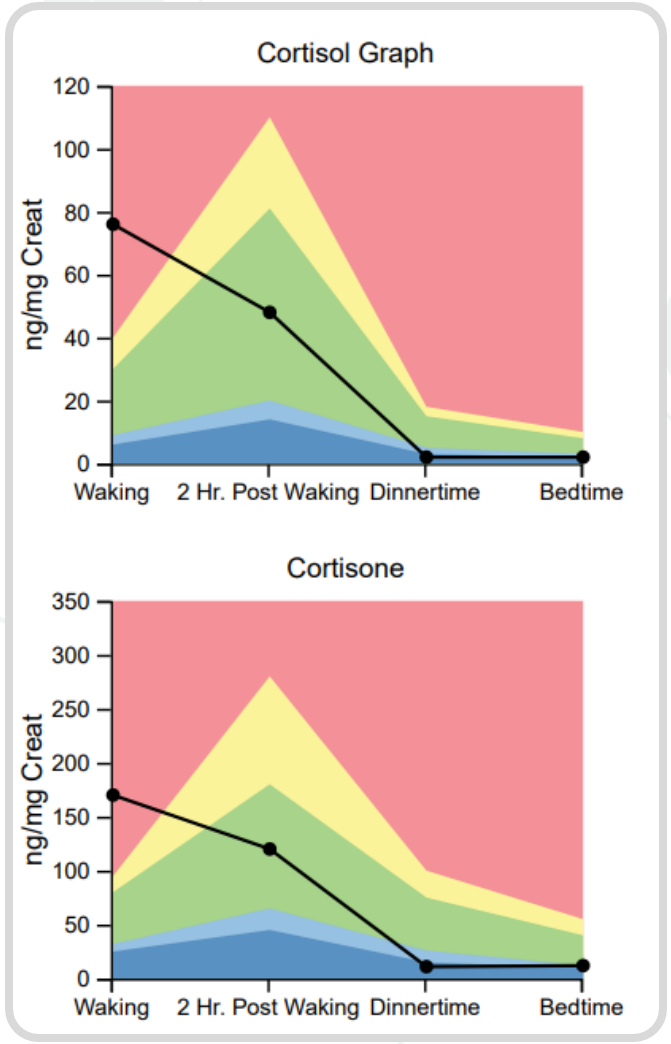
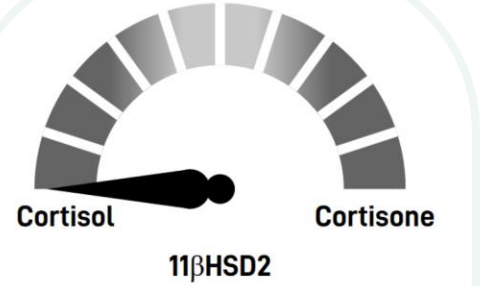


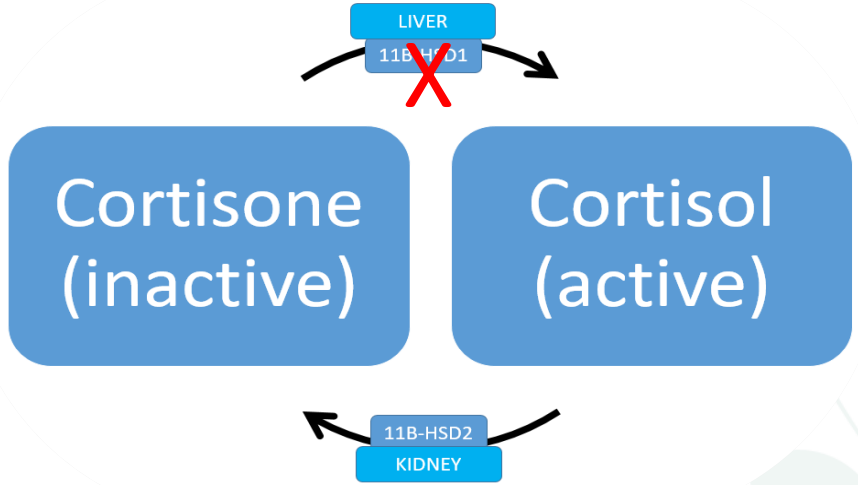
Diurnal Pattern

- Time stamps correspond to time 3-4 hrs before collection
- Gives information on overnight cortisol secretion.
  - Can identify one etiology of insomnia/nighttime wakefulness
  - Often associated with hypoglycemia overnight

Urinary Corticoids = HPA axis + Bodies Response to Stress

- Cortisol (active) vs. Cortisone (storage)
  - 11BHSD enzyme: most active in the kidney
    - 11BHSD1-pulls cortisol out of storage
      - Affected by obesity, metabolic syndrome, inflammation, thyroid function.
    - 11BHSD2- protects the mineralocorticoid receptor from cortisol effects
- Because we are looking at the influence of the kidney, we aren't necessarily seeing the HPA axis activity directly, rather the bodies response to cortisol levels





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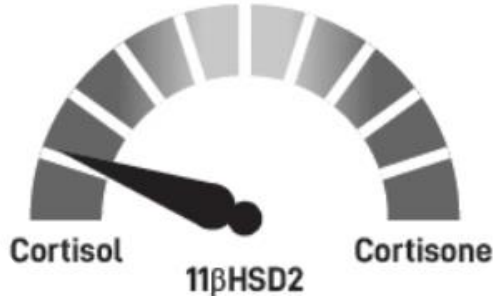
Corticoid Ratios and Calculations

- Metabolized cortisol: (THE + 5αTHF + 5βTHF)
  - Measure of what the body has utilized
  - High: increased cortisol clearance due to over production of cortisol, also influenced by; obesity, IR, inflammation, hyperthyroidism
  - Low: decreased cortisol clearance which could also be due to obesity, inflammation, IR, hypothyroidism
- Cortisol metabolites/ Cortisone metabolites: (5αTHF + 5βTHF) vs. THE
  - Metabolite ratios can give clinicians a better idea of overall preference within the body

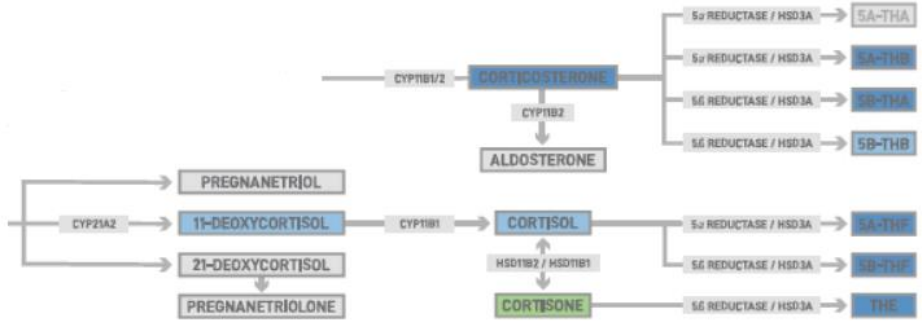
Patterns seen on corticoid reports

Underweight patient may have decreased cortisol metabolites

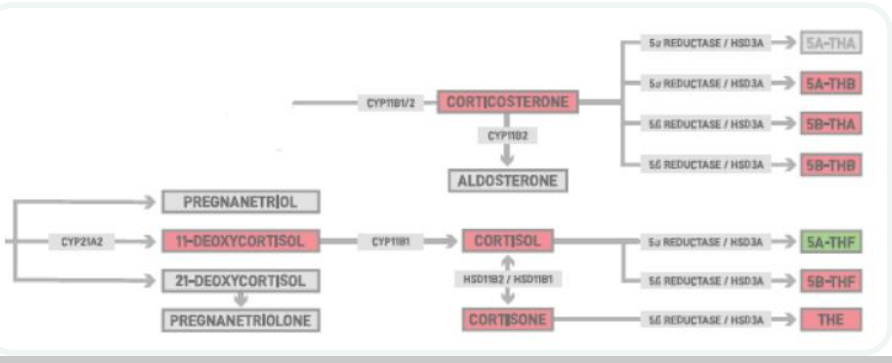
Obesity can increase cortisol clearance and 11BHSD1 activity causing a cortisol preference



Hypothyroidism can slow cortisol clearance and decrease cortisol metabolites

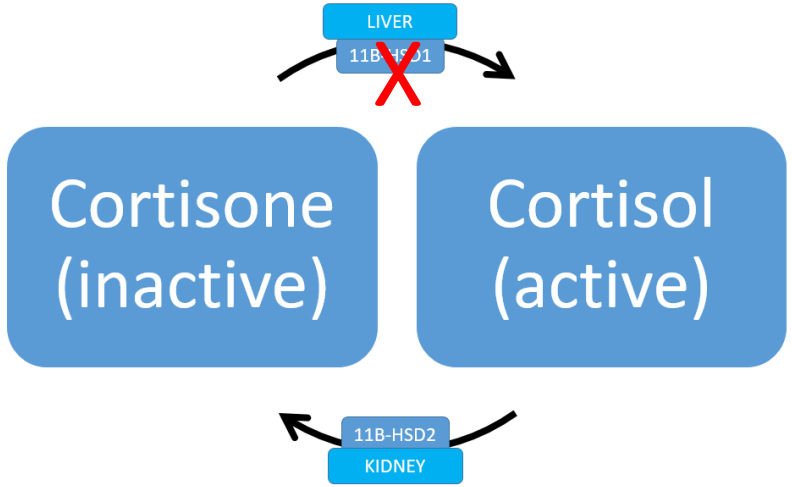


Hyperthyroidism can upregulate liver clearance of cortisol



What downregulates 11B-HSD1 activity?

- Reduce inflammation, insulin resistance/insulin, central adiposity
- Physical activity
- Rooibos
- Holy Basil
- Curcumin
- Bitter melon
- EGCG
- Progesterone
- Coffee



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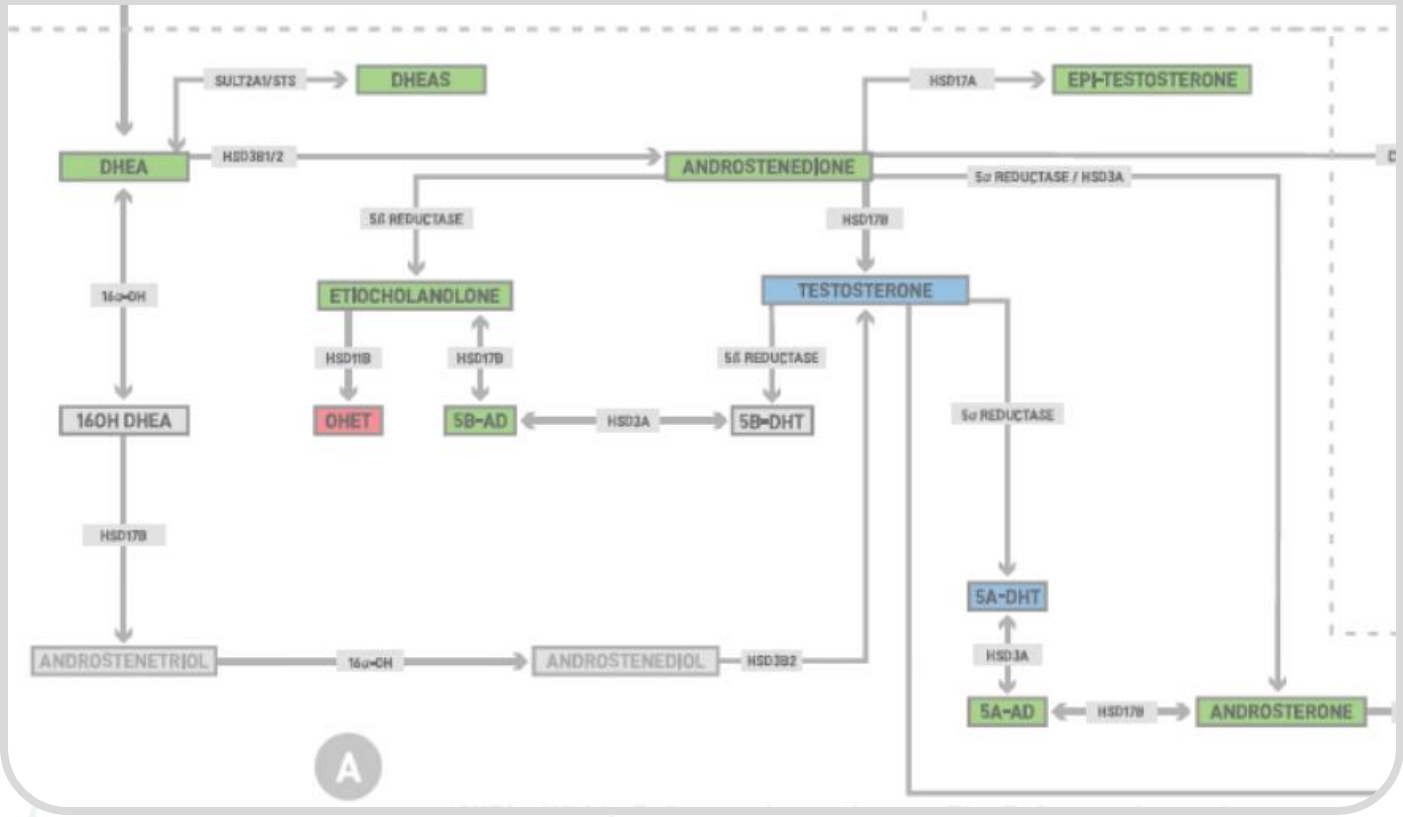
Androgens

Androgen Neighborhood

- Evaluate enzyme activity
  - Aromatase and 5 alpha reductase
  - 5 alpha vs 5 beta metabolism
- Monitor the level of 5A-DHT
- DHEA + DHEAs
- Further evaluation of:
  - PCOS and hyperandrogenism in females (symptoms, pathways, enzymes)
  - Hypogonadism in males
  - Metabolism of supplemented testosterone
  - Testosterone/EPI-Testosterone ratio may reveal undisclosed supplementation (or exposure)

Ratios and Calculations		Result	Unit	L WRI H	Reference Interval
DHEA+DHEAS‡		170	ng/mg Creat/Day		25 – 370
Androsterone (5α) / Etiocholanolone (5β)‡	(5α Reductase Activity)	0.25			0.5 – 1.4
Testosterone / EPI-Testosterone‡		8.5			0.1 – 2.0



Can You Explain Aromatization?

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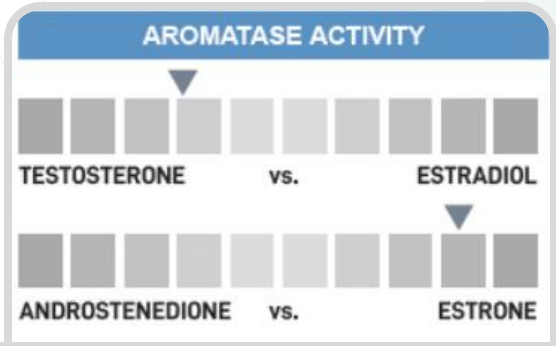
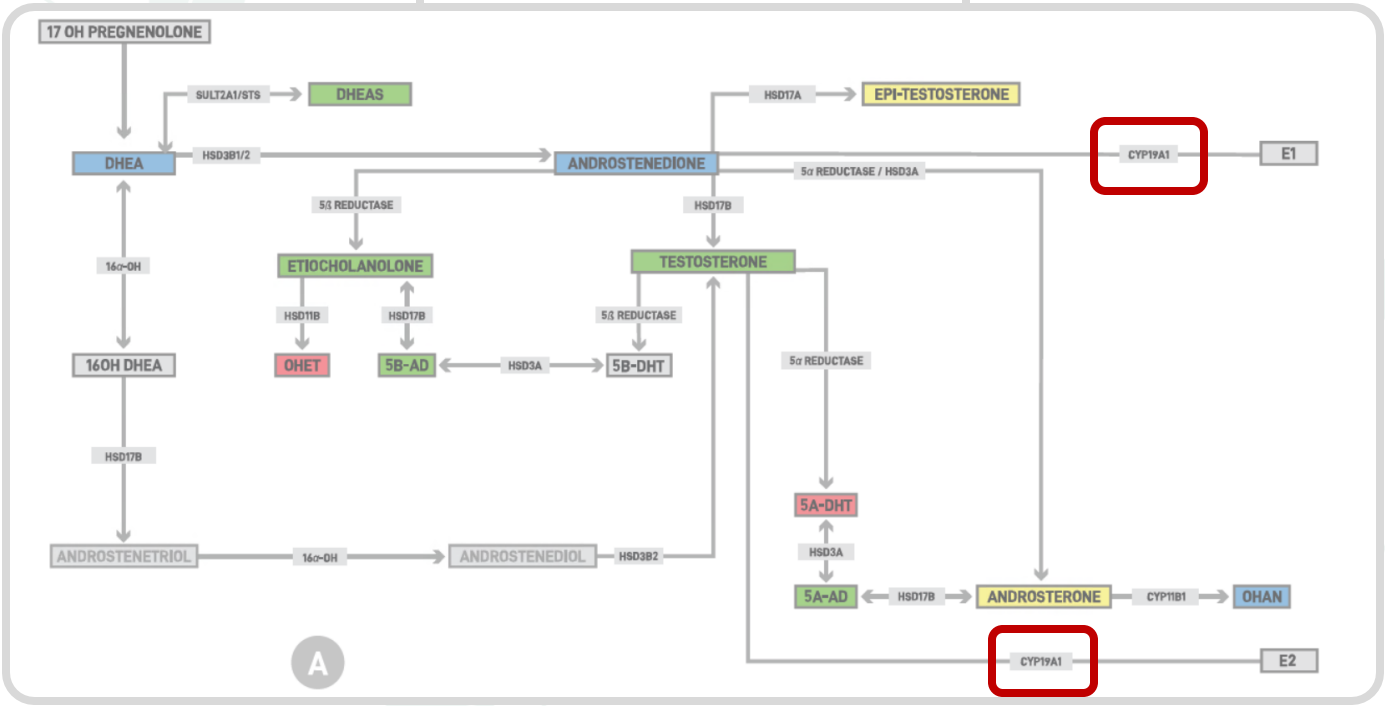
Aromatase (CYP19A1)

- Converts androstenedione to estrone and testosterone to estradiol
- Active in adipose tissue
- Many of these CYP450 genes are subject to genetic polymorphisms
- Well-known for its role in the carcinogenic bioactivation of polycyclic aromatic hydrocarbons (PAHs), heterocyclic aromatic amines/amides, polychlorinated biphenyls (PCBs), and other environmental toxins





Minich, D., and R. Hodges. "Modulation of metabolic detoxification pathways using foods and food-derived components: A scientific review with clinical application." *Journal of Nutrition and Metabolism,* Vol. 2015 (2015): 760689.

Activation of Aromatase (CYP19A1)

- Stress/cortisol: PMID: 21878510 PMID: 23835908 (animal studies, acts in a protective manner for brain health
- Xeno-estrogens/endocrine disruptors/toxins (pesticides, herbicides, benzene, plastic by-products, some pharmaceuticals and cosmetics, petroleum, UV filters) PMID: 2223368
- Estrogen PMID: 2223368
- Poor dietary choices/high glycemic foods PMID: 2223368
- Major illness PMID 16670151
- Brain injury PMID: 16498364 (animal study)
- Alcohol/Red wine PMID: 19268535
- Forskolin (found in coleus plant) PMID: 14709151
- High insulin: PMID: 3322018
- Excess adipose tissue/Obesity/Leptin resistance: PMID: 10349800 PMID: 3226011
- Free-fatty acids (increased in metabolic syndrome): PMID: 2223368
- Inflammatory cytokines: IL-6, TNFalpha, prostaglandin PGE(2) PMID: 10405348

Aromatase activity and its effect on estrogen levels in males

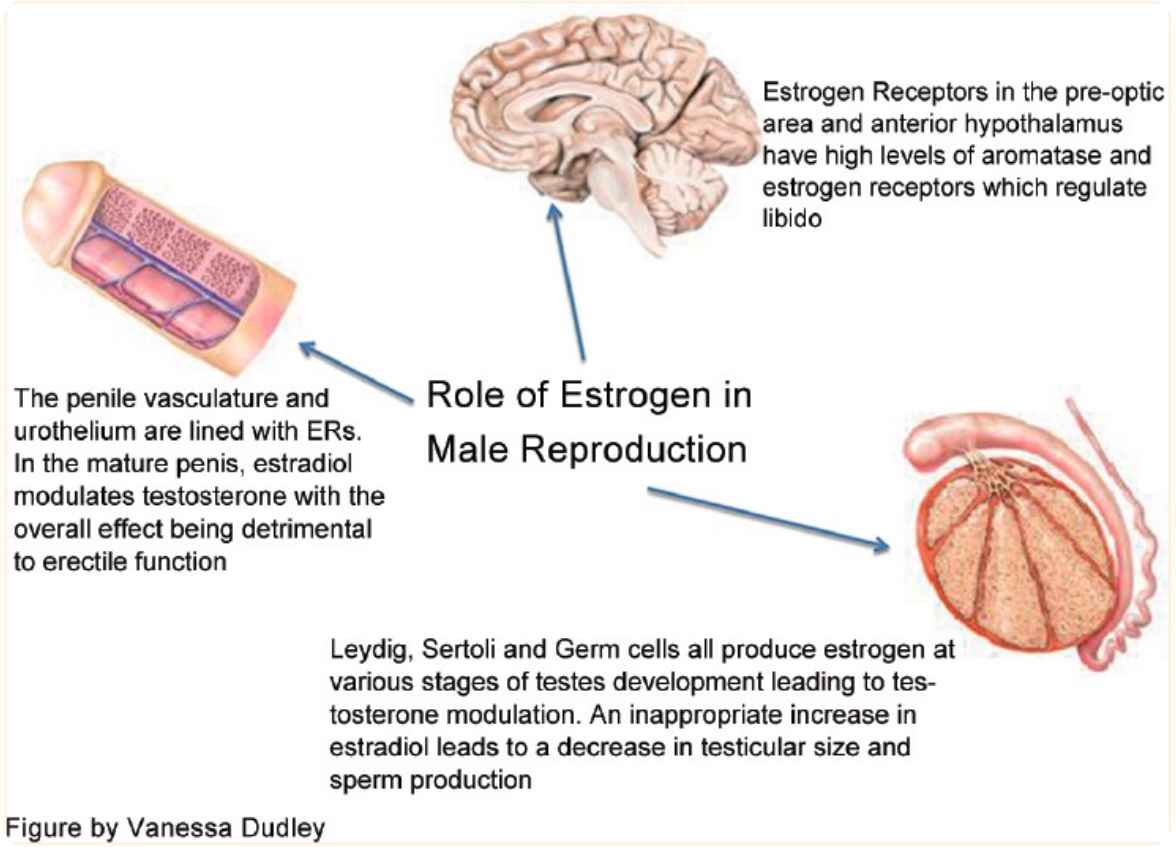


Figure by Vanessa Dudley

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Schulster M, Bernie AM, Ramasamy R. The role of estradiol in male reproductive function. *Asian J Androl*. 2016;18(3):435-440. doi:10.4103/1008-682X.173932

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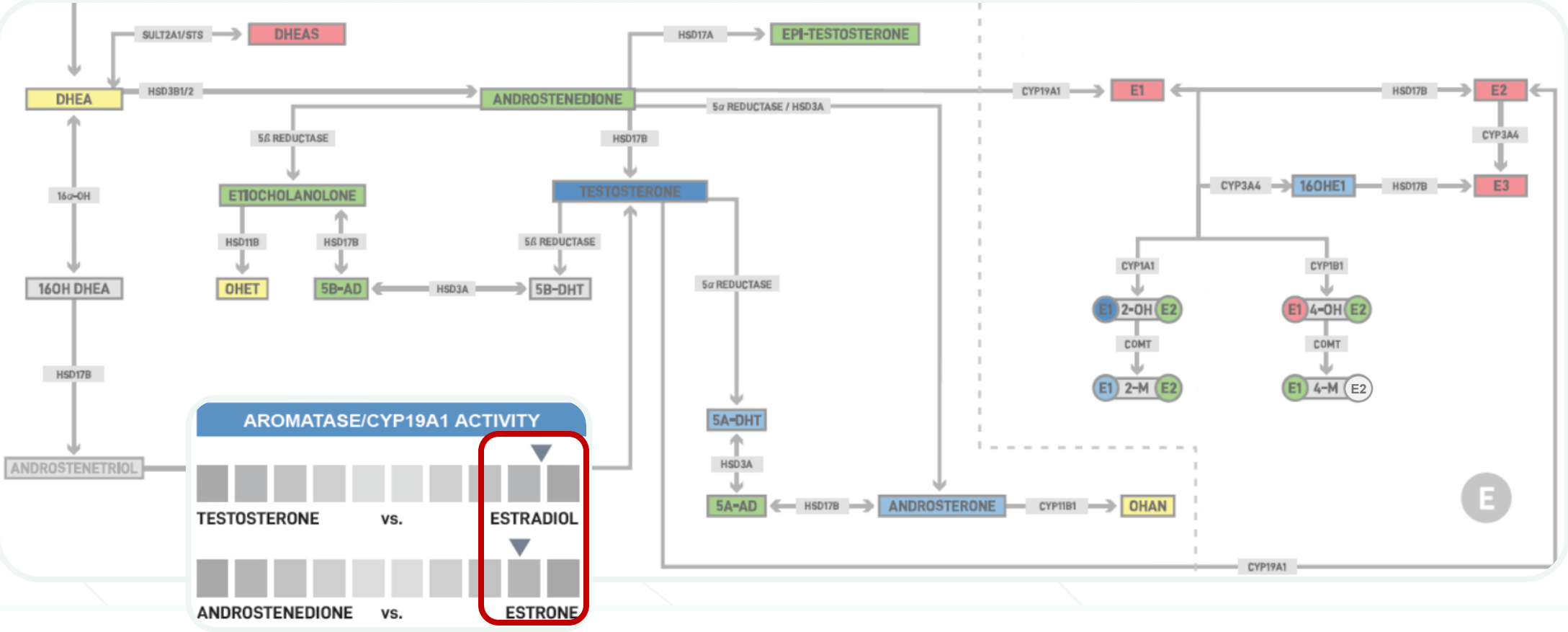
63yo M with Metabolic Syndrome on transdermal testosterone causing gynecomastia!



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Aromatase and Breast Cancer

- Intracellular androgen receptor and the membrane androgen receptor both down-regulate the strongly antiapoptotic protein Bcl-2. *protect
- Estrogen receptor-α and membrane estrogen receptor both up-regulate Bcl-2. *proliferate

- **All of this is consistent with the increase in breast cancer observed in postmenopausal women who had higher serum testosterone levels being due to the resulting increase in the local level of estradiol in the breast tissue. *proliferate**

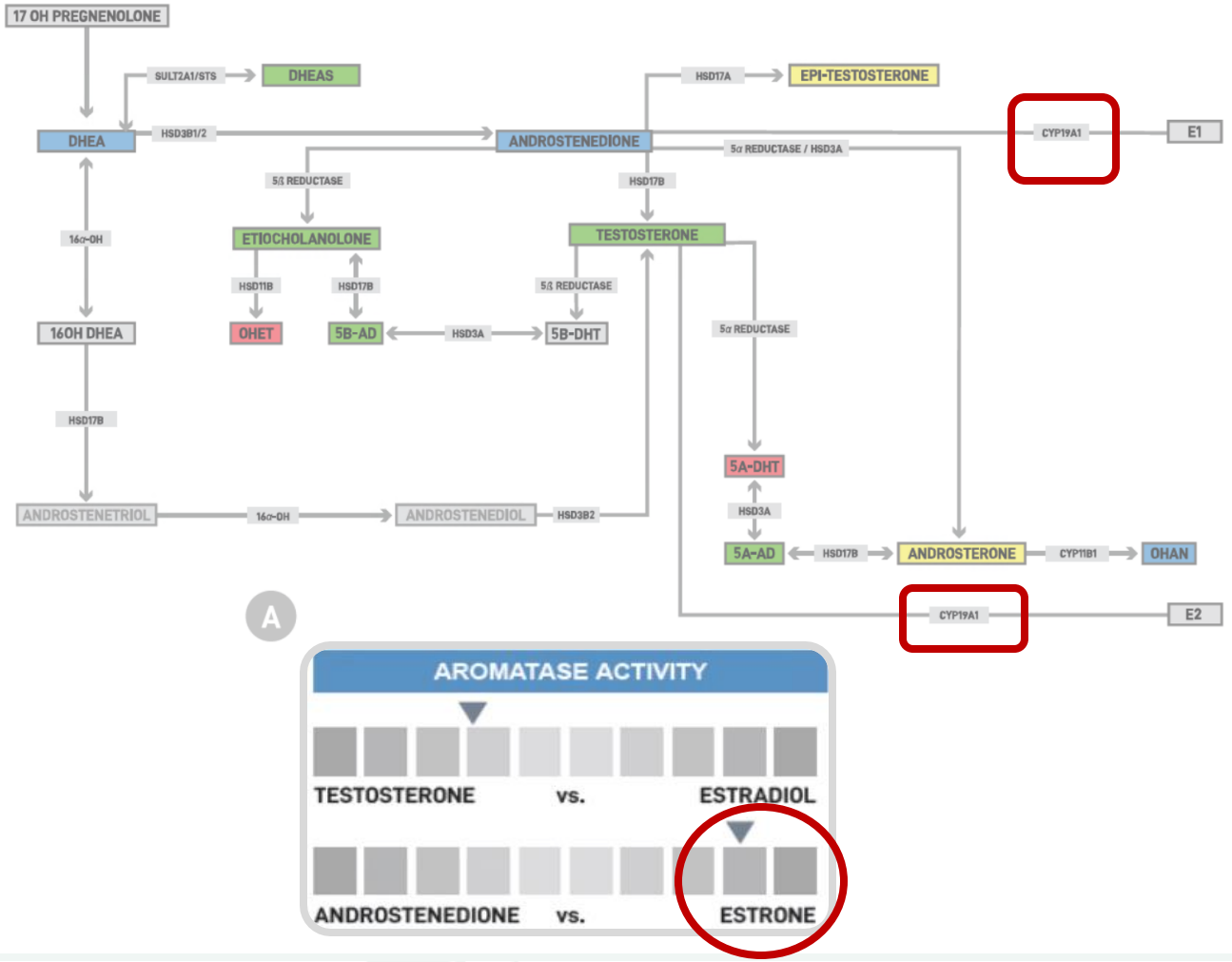
- Friedman AE. Can a single model explain both breast cancer and prostate cancer? *Theor Biol Med Model* 2007;4:28.
- Friedman AE. Aromatase explains why testosterone increases breast cancer rate. Cancer Epidemiol Biomarkers Prev. 2009 Jun;18(6):1942. doi: 10.1158/1055-9965.EPI-09-0157. Epub 2009 May 12. PMID: 19435862.

Aromatase (CYP19A1)

CYP19A1

(-) Chrysin, Zn, nettles, damiana, grape seed, ECGC, resveratrol, licorice, flavonoids, anti-inflammatories

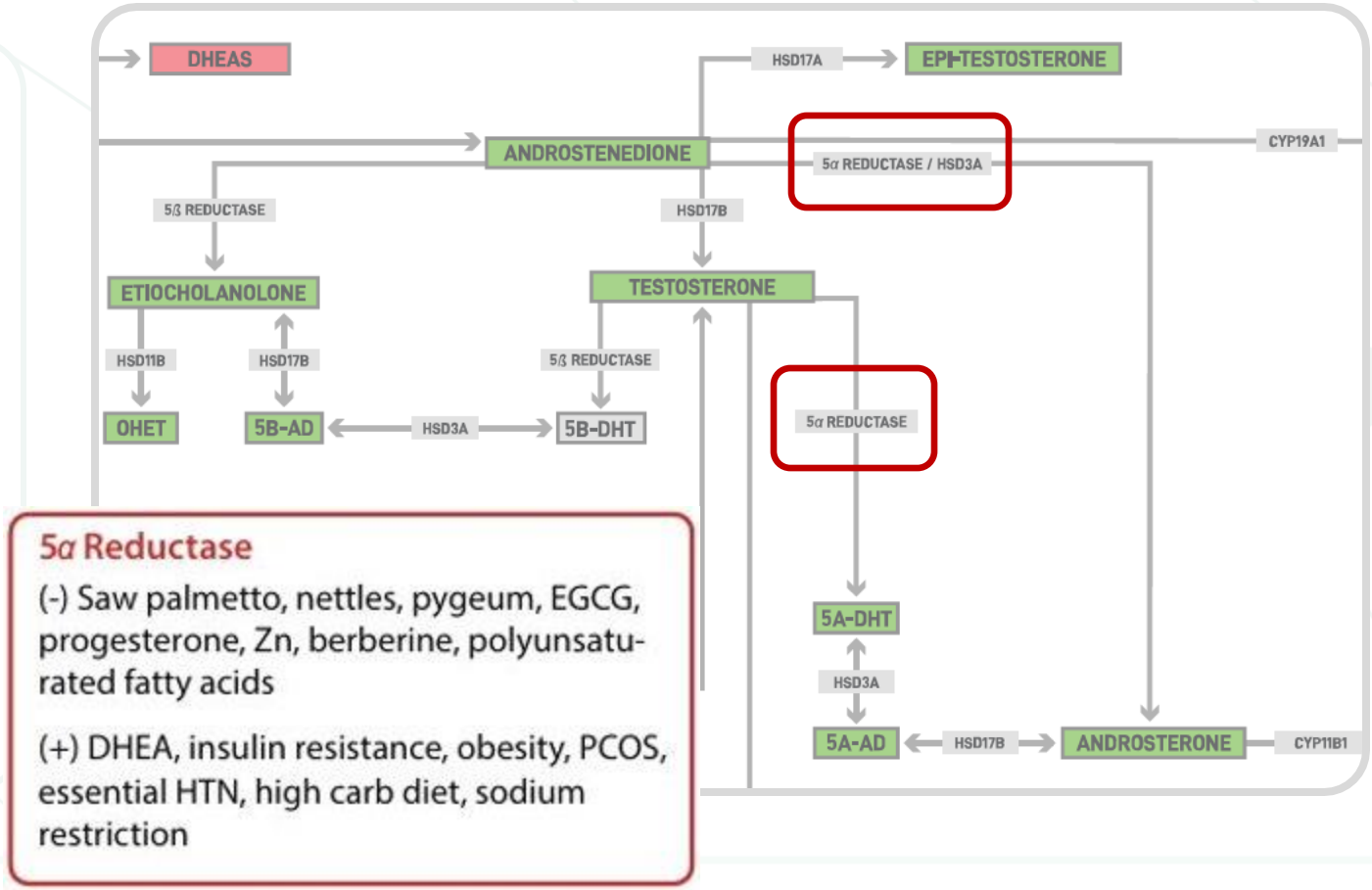
(+) Coleus forskohlii, inflammation, stress, Zn deficiency, excess adipose, high insulin, alcohol



Minich, D., and R. Hodges. "Modulation of metabolic detoxification pathways using foods and food-derived components: A scientific review with clinical application." *Journal of Nutrition and Metabolism,* Vol. 2015 (2015): 760689.

5α-reductase

- Enzyme that converts testosterone to it's more potent form, dihydrotestosterone (5α-DHT)
  - DHT has 2-3 times the affinity for the androgen receptor than testosterone
- May lead to increase in androgenic symptoms in females; acne, scalp hair loss, mood instability
- In males, excess 5α-reductase activity and DHT can be associated with prostate concerns, scalp hair loss



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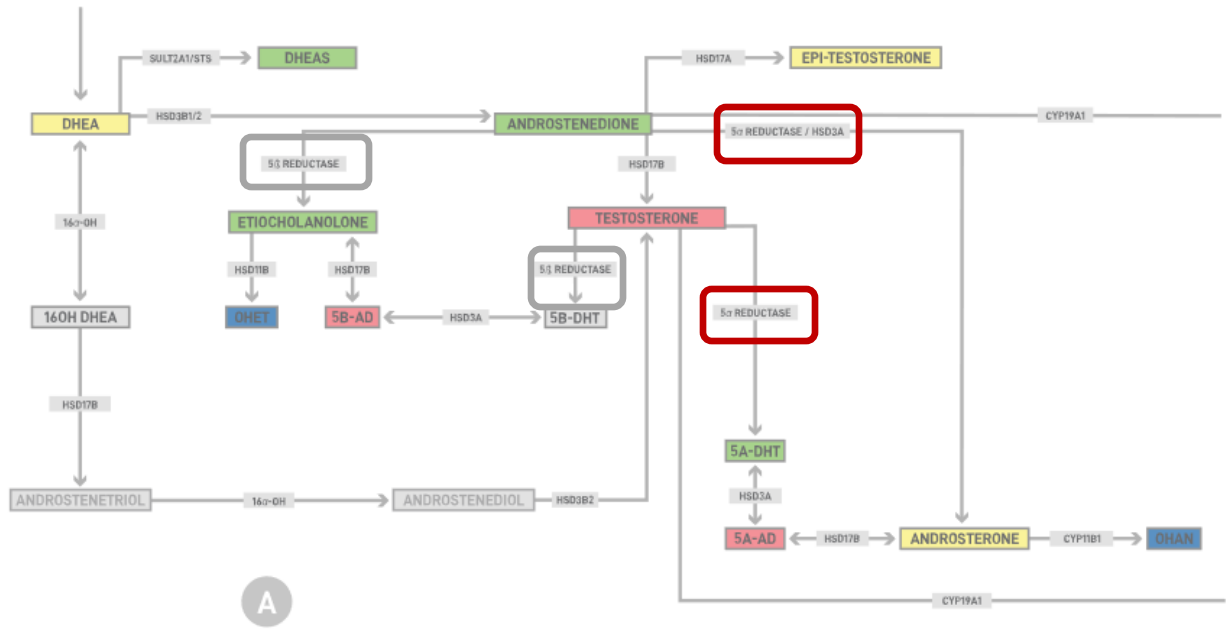
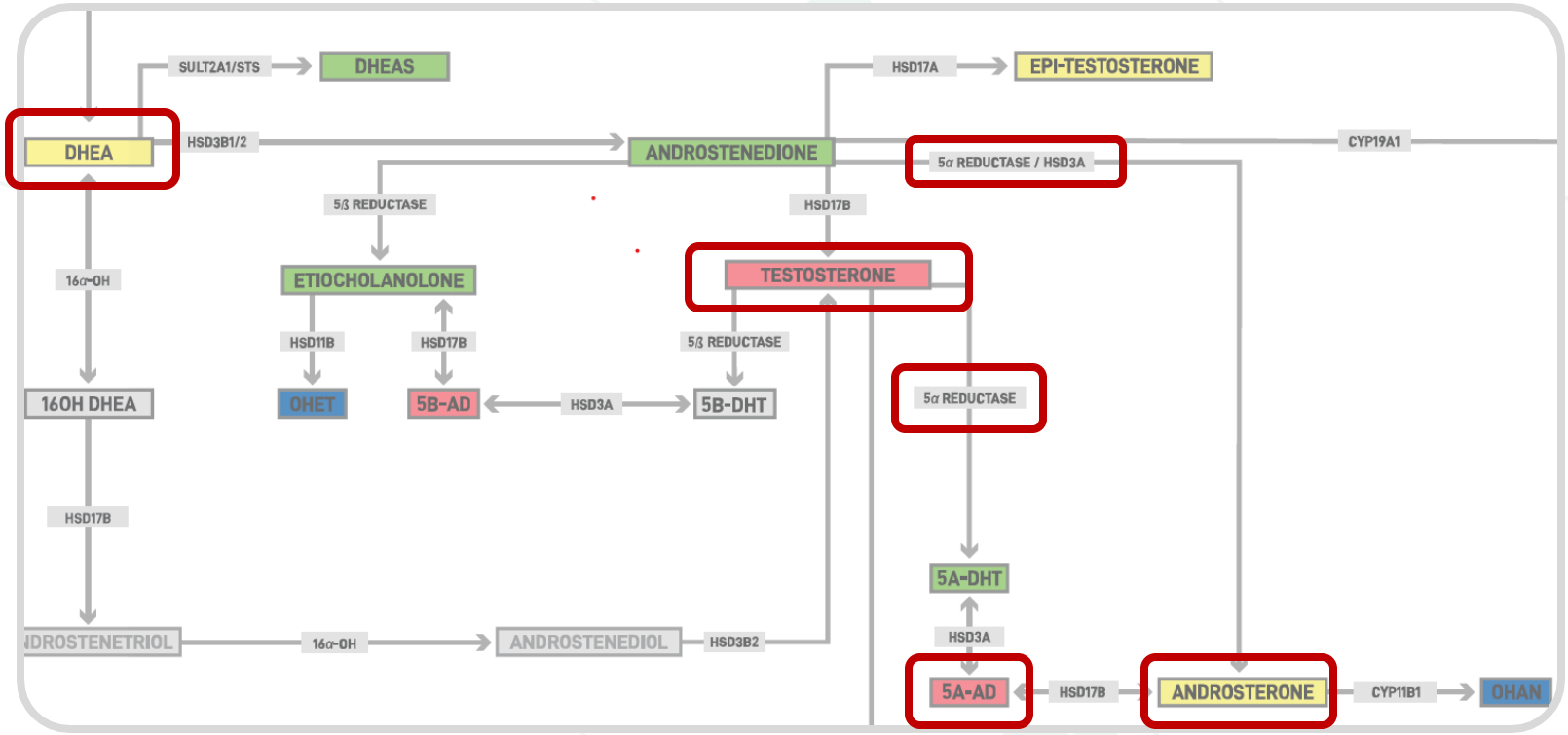
α vs. β: Metabolic Preference of Androgens

- Androsterone (5α) / Etiocholanolone (5β)
  - Alpha (α) metabolism: More potent forms of metabolites
    - May produce more androgenic symptoms
  - Beta (β) metabolism: Less potent forms of metabolites
    - May produce less androgenic symptoms
- 5A-AD and 5B-AD additional analytes that also have alpha and beta metabolism
- Remember other neighborhoods will also display alpha and beta metabolism
  - Progesterone: alpha pregnanediol vs. beta pregnanediol
  - Corticoids: cortisol, cortisone, and corticosterone each have alpha and beta metabolites



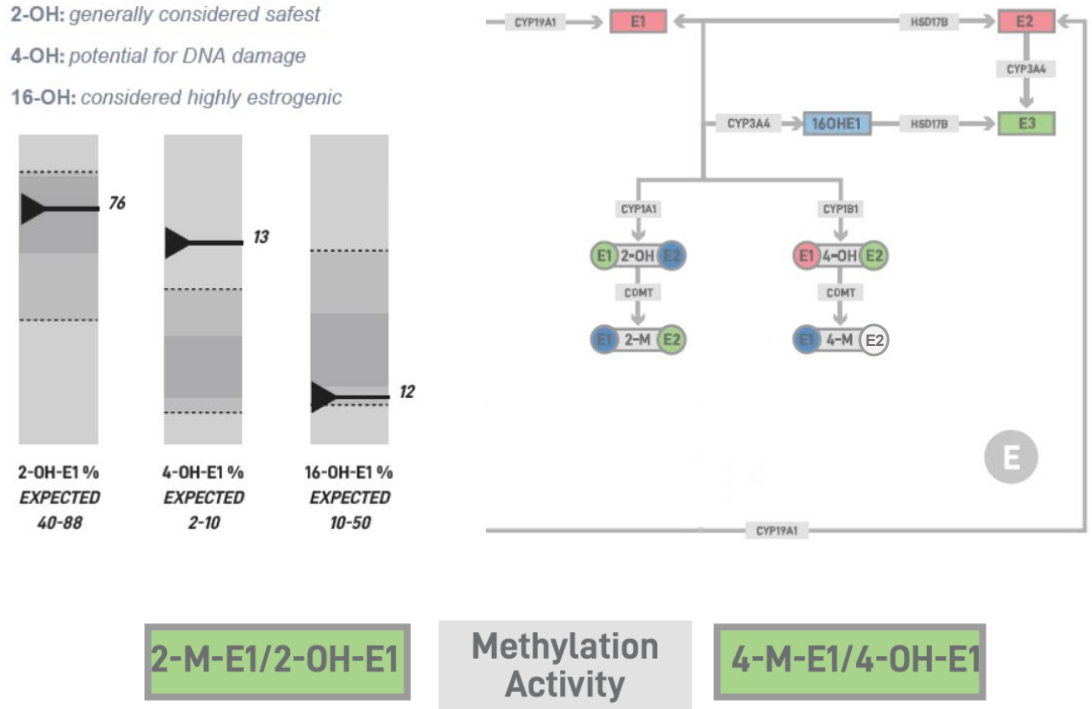
HuMap™ example of a patient with PCOS



Estrogens

Estrogen Neighborhood

- Aromatase activity-
  - E1 and E2
- Evaluation of metabolites
  - Phase 1 metabolism (-OH)
  - Phase 2 metabolism (-M)
- Evaluation of methylation potential (COMT enzyme)
- Evaluation of potential for DNA mutagenesis
- Evaluation of the metabolism of endogenous and exogenous hormones (BHRT)



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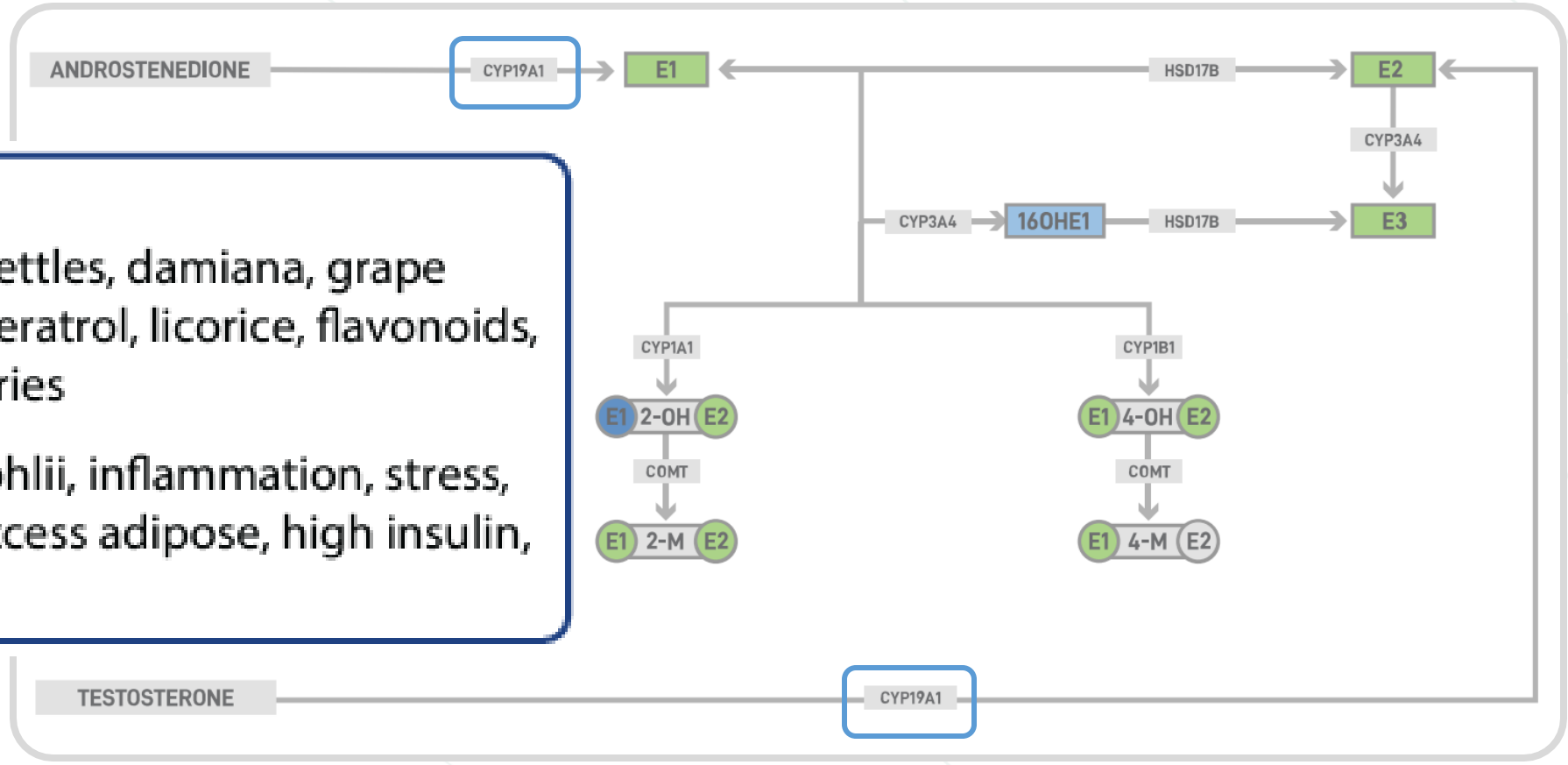
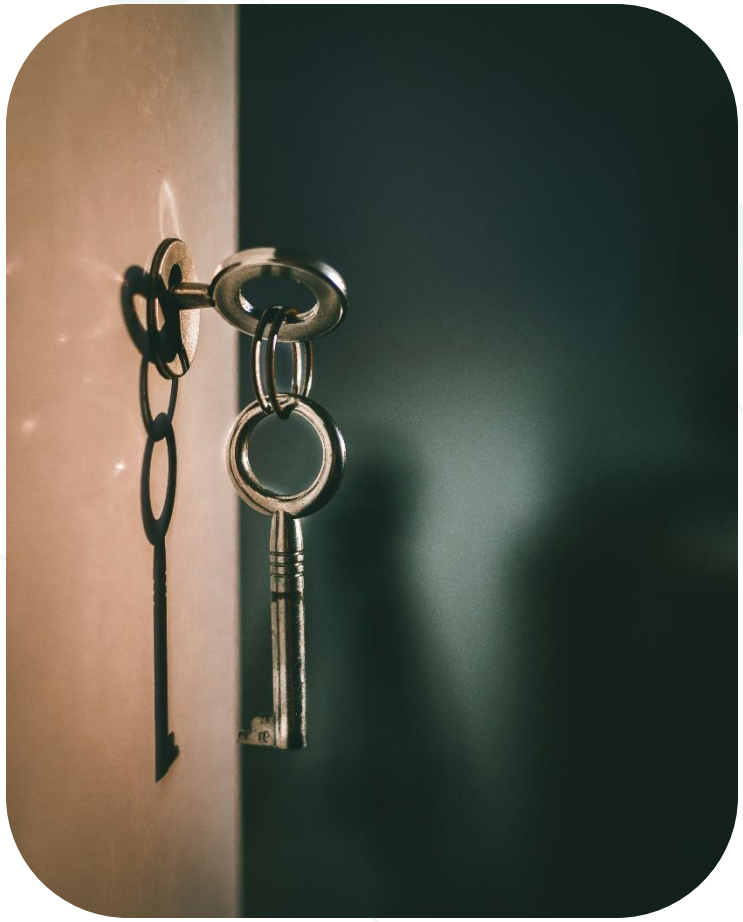
Aromatase / CYP19A1



CYP19A1

(-) Chrysin, Zn, nettles, damiana, grape seed, ECGC, resveratrol, licorice, flavonoids, anti-inflammatories

(+) Coleus forskohlii, inflammation, stress, Zn deficiency, excess adipose, high insulin, alcohol



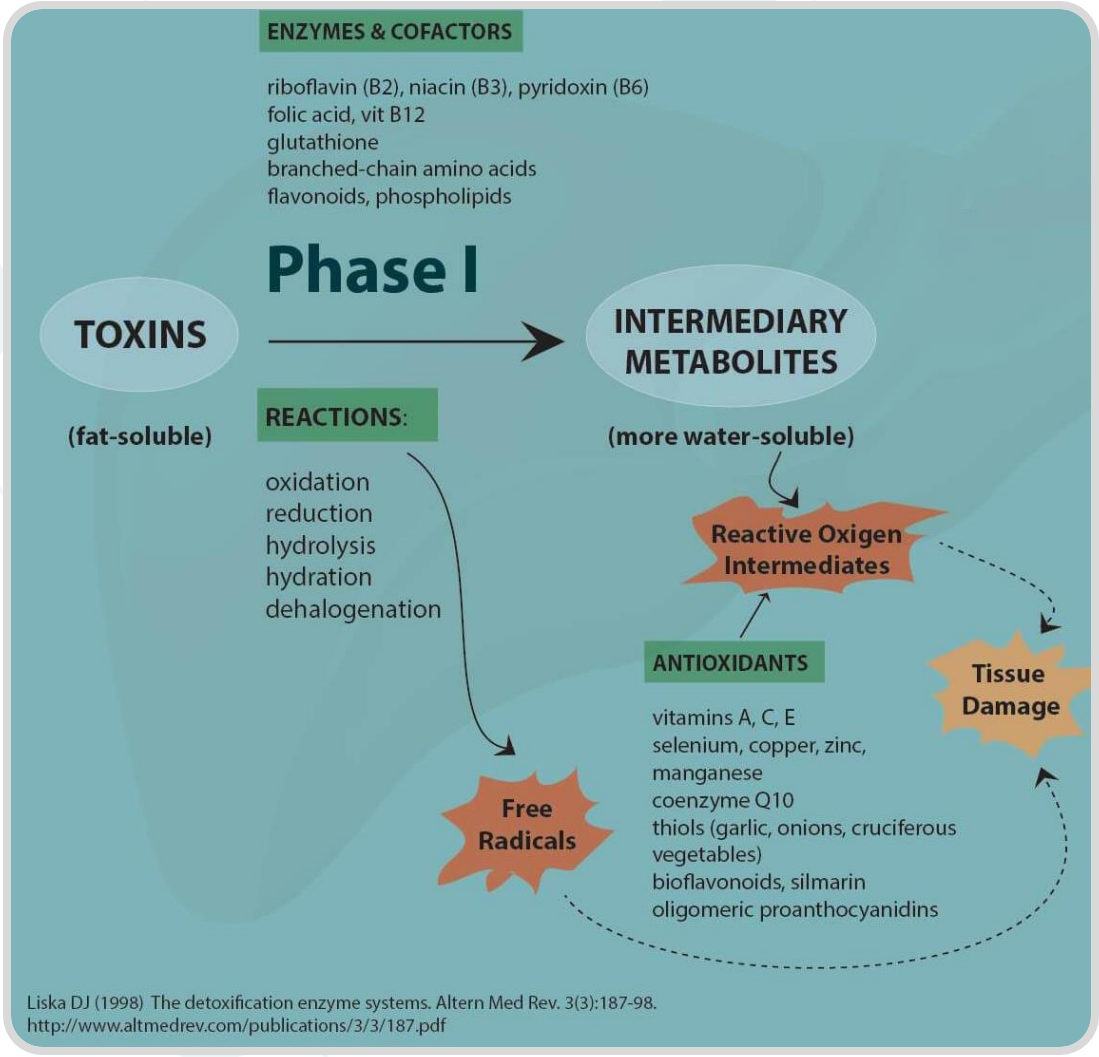
Key Enzymes affecting Estrogen Metabolism

- CYP1A1
- CYP1B1
- CYP3A4
- COMT

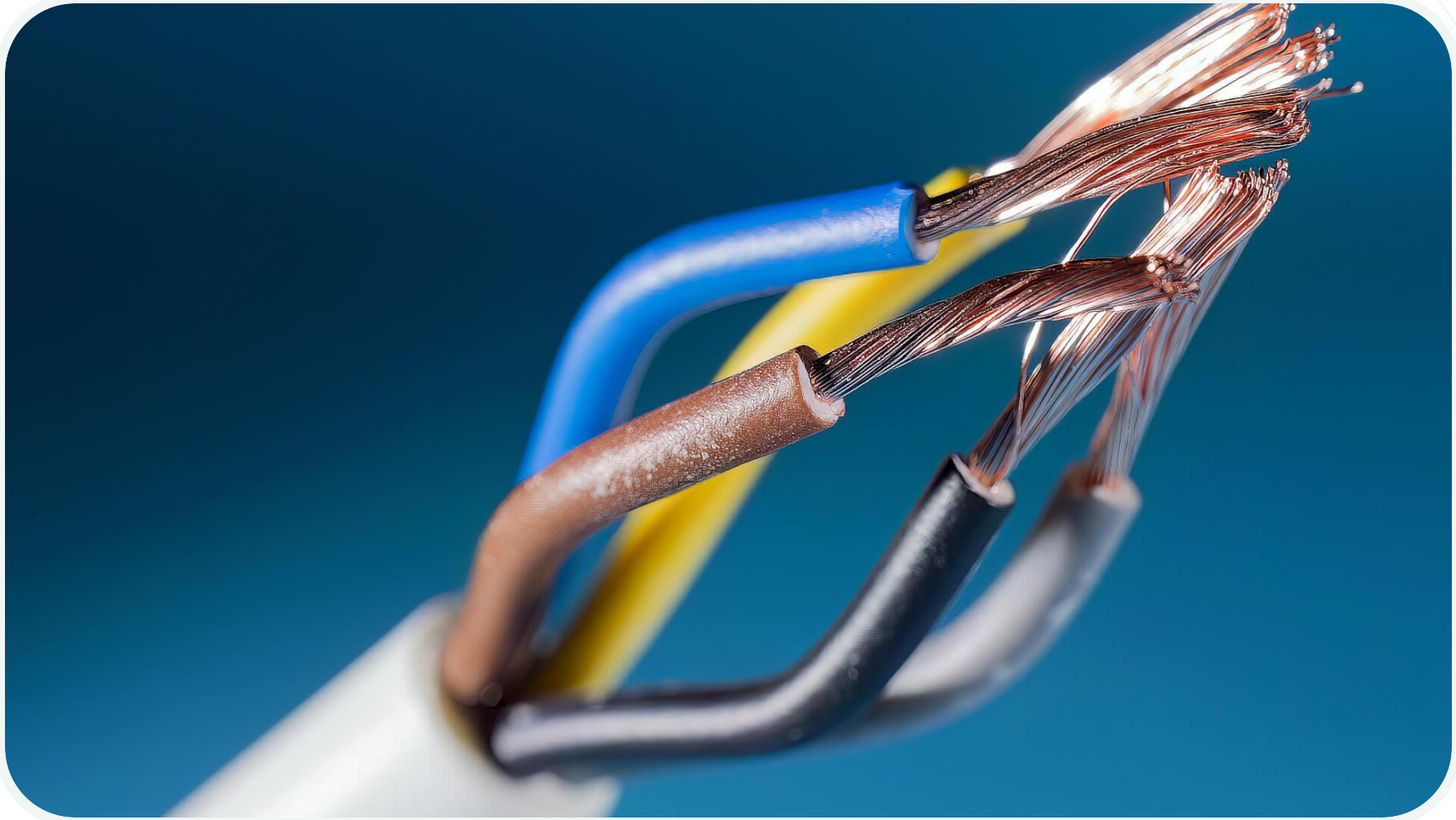
Phase 1

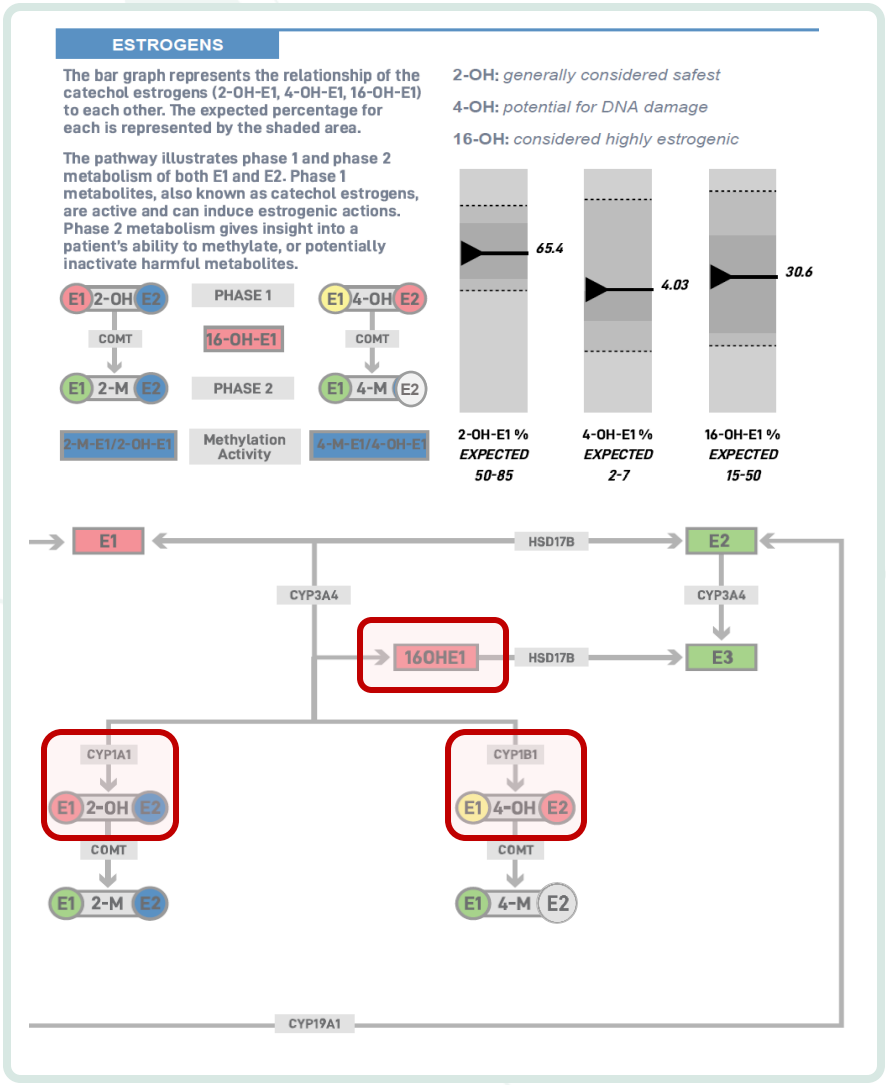
- **Phase 1 enzymes break down *fat-soluble molecules.***
  Phase 1 cytochrome P450 enzymes biotransform harmful substances by adding a hydroxyl, carboxyl, or amino group via either oxidation, reduction, or hydrolysis reactions (REDOX).

  Phase 1 toxins - xenobiotics, antibiotics, ***steroid hormones***, pharmac euticals.



Minich, D., and R. Hodges. "Modulation of metabolic detoxification pathways using foods and food-derived components: A scientific review with clinical application." *Journal of Nutrition and Metabolism,* Vol. 2015 (2015): 760689.





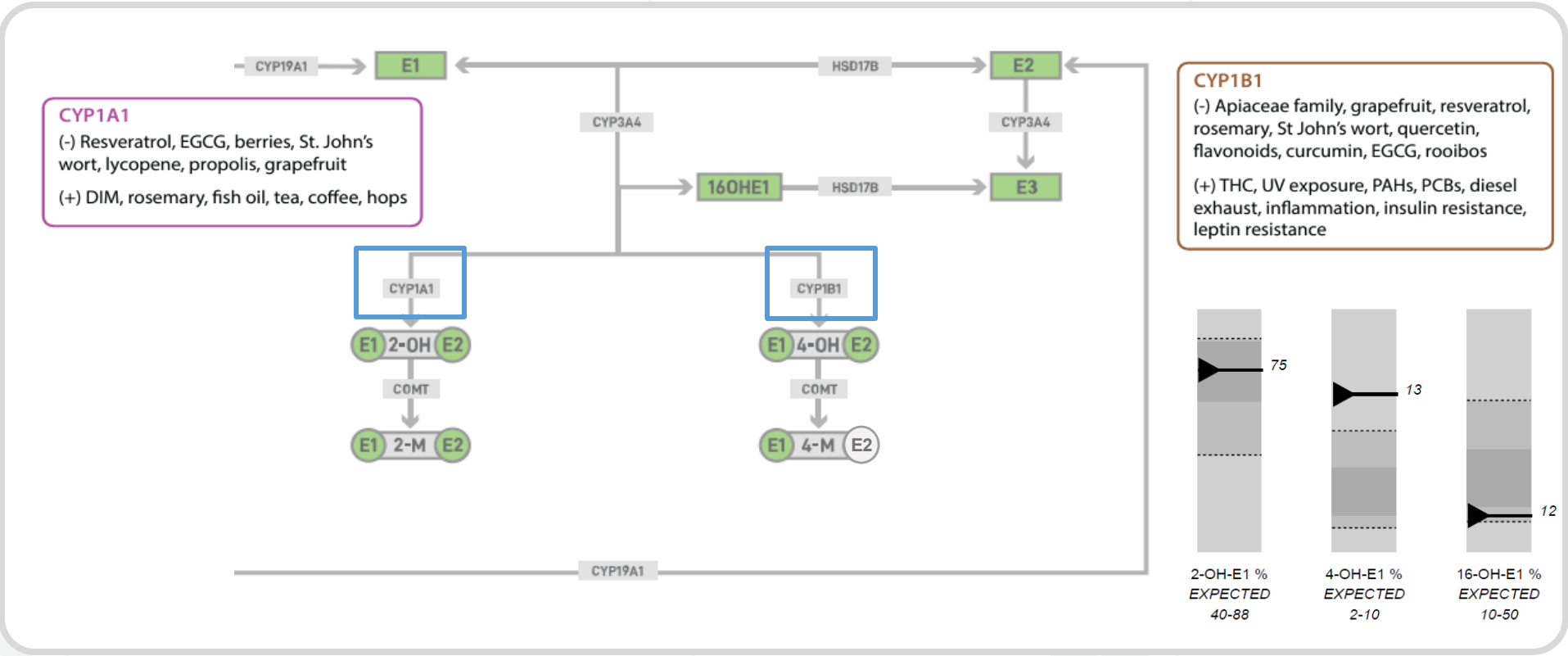
Phase 1 Detox- Estrogen Metabolism

"Catechol Estrogens"

- 2-OH E1,E2- "safe" estrogen (CYP1A1)
- 4-OH E1,E2- DNA damage potential (CYP1B1)
- 16-OH E1- proliferative (CYP3A4)

Fuhrman BJ, Schairer C, Gail M, et al., Estrogen Metabolism and Risk of Breast Cancer in Postmenopausal Women, *JNCI: Journal of the National Cancer Institute*, Volume 104, Issue 4, 22 February 2012, Pages 326–339, https://doi.org/10.1093/jnci/djr531

CYP1A1 and CYP1B1



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Mnemonic

- CYP1A1 – A is awesome!!!

- CYP1B1 – B is bad!!!

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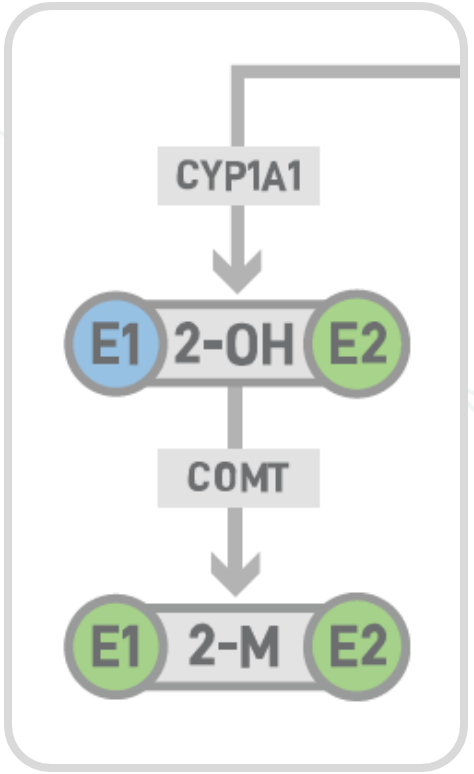
CYP1A1

- Healthy pathway of phase 1
  - Hydroxylates E1 to 2-OH E1
- Also, metabolizes polycyclic aromatic hydrocarbons (PAHs), such as benzo[a]pyrene, released from burning coal, oil, gasoline, trash, tobacco, wood, or charcoal-broiled meat.
- Mainly involved in detoxification, though can sometimes activate cancer-promoting substances such a PAHs PMID: 19531241 PMID: 28074113
- Can also activate aflatoxin B1 (cancer promoting) and tobacco-related carcinogens PMID: 19531241



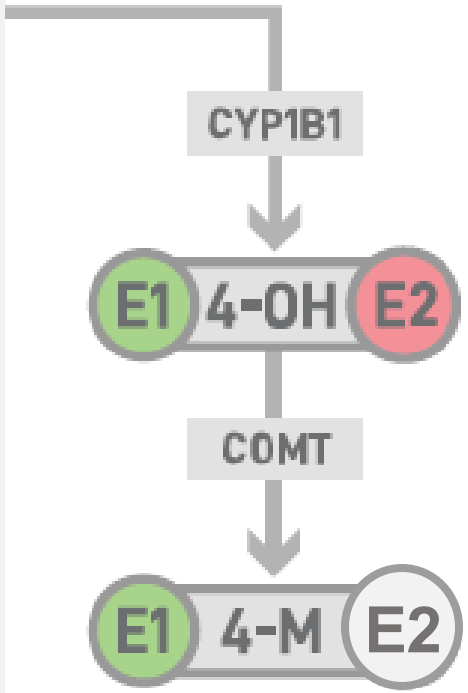
3,3′-Diindolylmethane (DIM)

- DIM supplementation has been shown to enhance the 2-hydroxlyation of estrogen, which is thought to contribute to anti-inflammatory effects in hormone-responsive cell lines
- DIM-treated subjects, relative to placebo, showed a significant **increase in levels of 2-OHE1**
- The influence of DIM results in **reduced production of the carcinogenic 4-hydroxyesterone ($4OHE_1$)**

- Szaefer H, Licznerska B, Krajka-Kuźniak V, Bartoszek A, Baer-Dubowska W. Modulation of CYP1A1, CYP1A2 and CYP1B1 expression by cabbage juices and indoles in human breast cell lines. Nutr Cancer. 2012 Aug;64(6):879-88. doi: 10.1080/01635581.2012.690928. Epub 2012 Jun 20. PMID: 22716309.
- Vivar OI, Saunier EF, Leitman DC, Firestone GL, Bjeldanes LF. Selective activation of estrogen receptor-beta target genes by 3,3'-diindolylmethane. Endocrinology. 2010 Apr;151(4):1662-7. doi: 10.1210/en.2009-1028. Epub 2010 Feb 16. PMID: 20160136; PMCID: PMC2850231.
- Dalessandri KM, Firestone GL, Fitch MD, Bradlow HL, Bjeldanes LF. Pilot study: effect of 3,3'-diindolylmethane supplements on urinary hormone metabolites in postmenopausal women with a history of early-stage breast cancer. Nutr Cancer. 2004;50(2):161-7

CYP1B1

- Takes estrogen down the 4 OH pathway
  - Pushes E1 to 4-OH E1 and E2 to 4-OH E2
- **CYP1B1 is more readily found in tumor tissue compared to normal.**
- Can activate cancer promoting compounds
- Accumulating evidence indicates that modulation of CYP1B1 can decrease adipogenesis and tumorigenesis, and prevent obesity, hypertension, atherosclerosis, and cancer. PMID: 28322972
- Given the role of CYP1B1 in pro-carcinogen and estrogen metabolism, polymorphisms in CYP1B1 could result in modifications in its enzyme activity and subsequently lead to hormone-mediated carcinogenesis.
- Increases fat uptake and can lead to factors of metabolic syndrome



4-OH Estrogens Increase Cancer Risk

- 4-Hydroxylated catechol estrogens possess carcinogenic potential due to their ability to cause DNA damage by forming depurinating adducts, which in turn, generate mutations with subsequent oxidative damage and initiation of breast cancer.
- In microsomal preparations of human mammary adenocarcinoma, formation of 4-**hydroxy**estradiol was four times higher than 2-**hydroxy**estradiol formation, indicating that the ratio of 4-/2-hydroxyestradiol may be used as a biomarker for detection of malignant breast tumors.
- On the other hand, it has been suggested that the 4-**methoxy**estrogens prevent oxidative metabolism of estradiol and oxidative DNA damage.

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Samavat, H; Kurzer, M. Estrogen metabolism and breast cancer. *Cancer Letters*. Vol 356, Issue 2, Part A, 2015, Pages 231-243.

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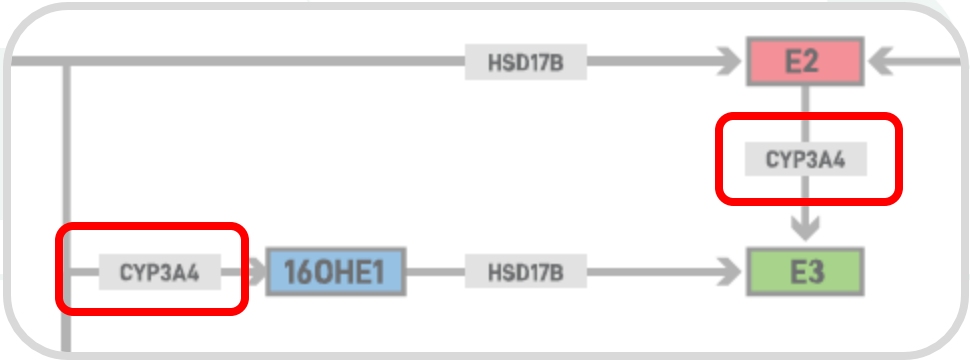
Cancer chemoprevention revisited: Cytochrome P450 family 1B1 as a target in the tumor and the microenvironment

- CYP1B1 converts E_2 and E_1 into 4-hydroxy estradiol (4-OHE_2) or 4-hydroxy estrone (4-OHE_1). 4-OHE_2/E_1 can be further converted into highly potent carcinogens, such as quinones and semiquinones, leading to reactive oxygen species and DNA adducts.
- In contrast, CYP1A1 converts E_2 and E_1 into 2-hydroxy estradiol (2-OHE_2) and 2-hydroxy estrone (2-OHE_1). These metabolites have low affinity for estrogen receptors; although they might also undergo metabolic redox cycling to generate free radicals and reactive semiquinone/quinone intermediates, they are rapidly converted by the enzyme COMT into 2-methoxy estradiol (2-ME_2) or 2-methoxy estrone (2-ME_1), which are known to be protective against tumor formation.
- **CYP1B1 is therefore implicated in the development and progression of estrogen-mediated tumors, as its overexpression is responsible for estrogens conversion into toxic metabolites**

Cancer treatment Reviews: https://www.cancertreatmentreviews.com/article/S0305-7372(17)30183-4/abstract

CYP3A4



Moves E2 to E3 and E1 to 16OHE1
(and metabolizes testosterone)

- CYP3A4 metabolizes about half of all drugs on the market
- Mostly found in the liver, but most active in the gut
- Metabolizes many internal compounds such as cholesterol, fatty acids, prostaglandins, leukotrienes, retinoids and biogenic amines PMID: 25332983
- Detoxifies bile acids PMID: 25332983
- Partially degrades vitamin D PMID: 22985909
- The activity of this enzyme varies and is affected by health, smoking, diet, medication, hormones, and genetics

Estriol

- Estriol is the main estrogen in pregnancy but has received less attention outside gestation
- Non-proliferative estrogen
- Does not convert to E1 or E2
- Immunomodulatory benefits- autoimmune, inflammatory, and neurodegenerative conditions
- Treatment of menopausal symptoms, osteoporosis, cancer, hyperlipidemia, vascular disease, and multiple sclerosis.

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Menopause. 2017 Apr 3. Estriol: emerging clinical benefits.

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16-OH E1-Proliferative / Tissue Growth

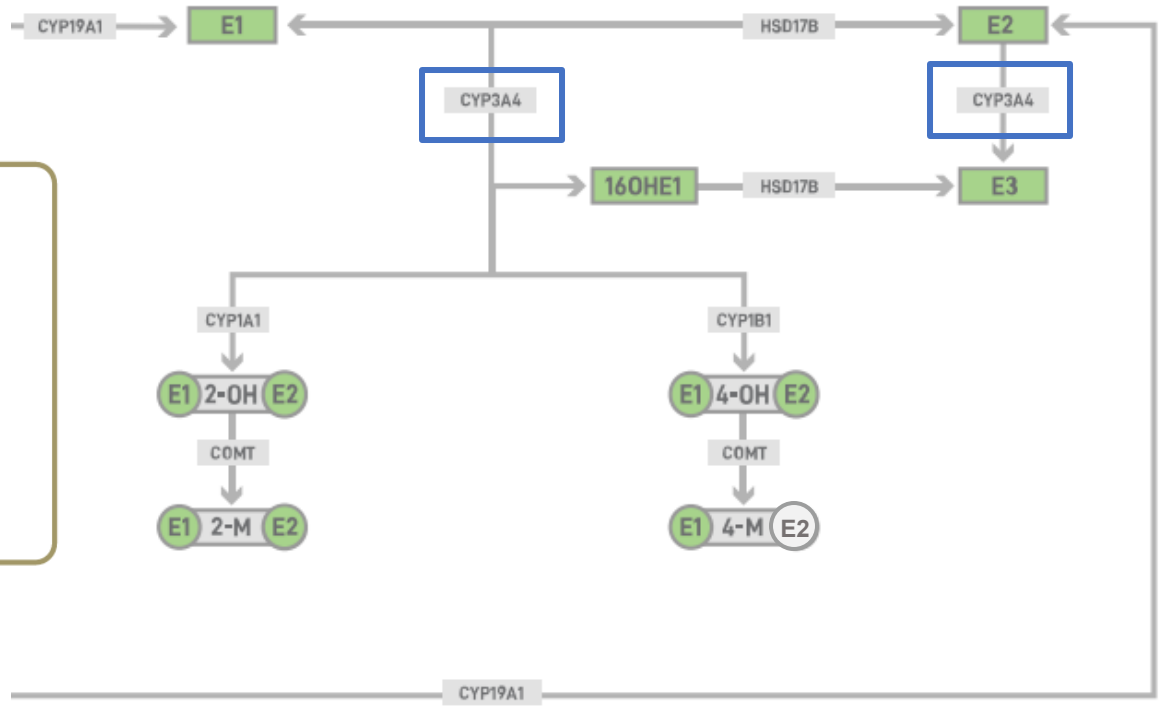
- Good for bones
- Not so good for breast/fibroids/endometriosis
- Possibly more estrogenic symptoms
- Binds most strongly to the estrogen receptor compared to 2OH and 4OH
  - Though much weaker than E1 and E2

CYP3A4

CYP3A4

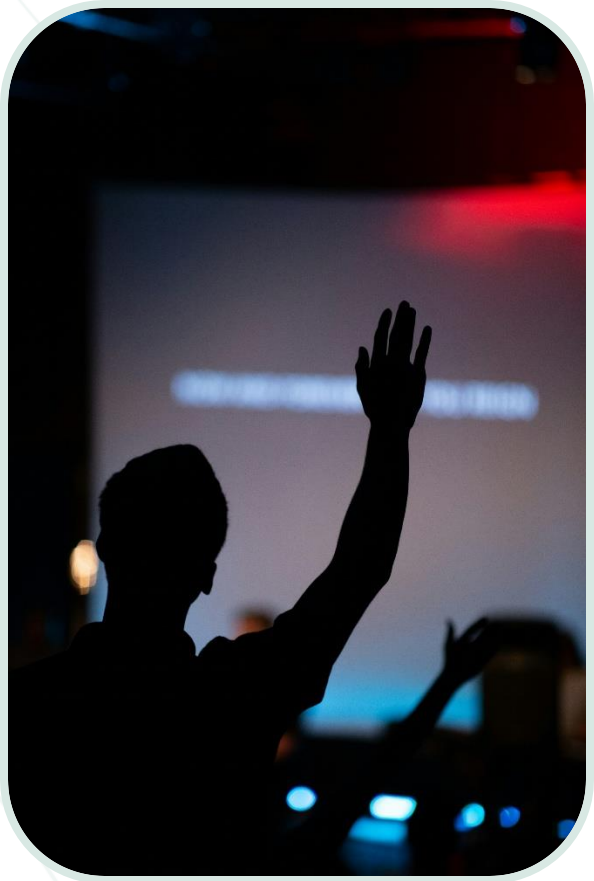
(-) Grapefruit, aloe, polyphenols (i.e. resveratrol), flavonoids, ECGC, coffee, fennel, black pepper, licorice, chrysin, quercetin

(+) St. John's wort, capsaicin, valerian, gingko biloba, fatty acids, Vit D



How do you lower 16-OHE1?

- DIM
- Resveratrol
- Quercetin
- Sulforaphane
- Rosemary



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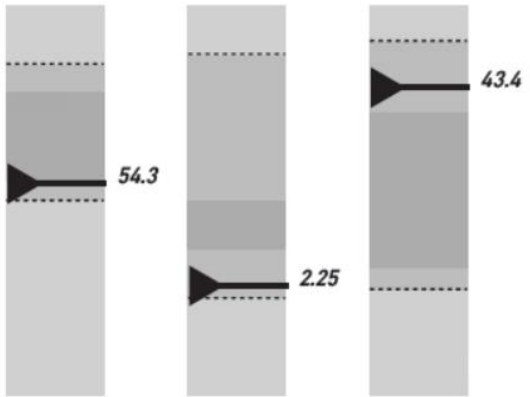
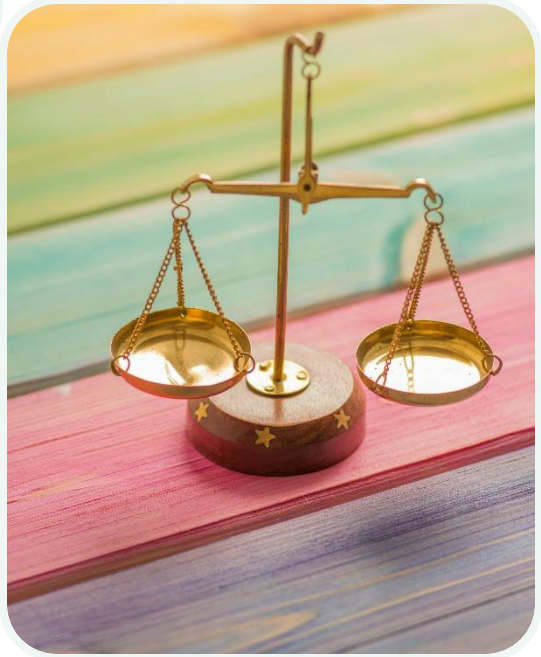
2, 4, 16-OH E1 Compared to Each Other

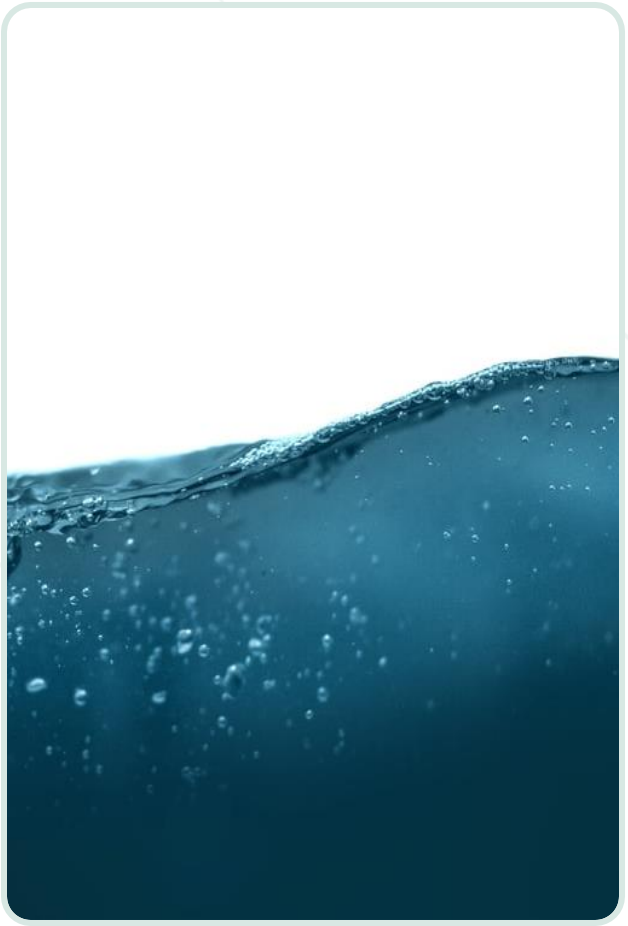
2-OH: *generally considered safest*

4-OH: *potential for DNA damage*

16-OH: *considered highly estrogenic*







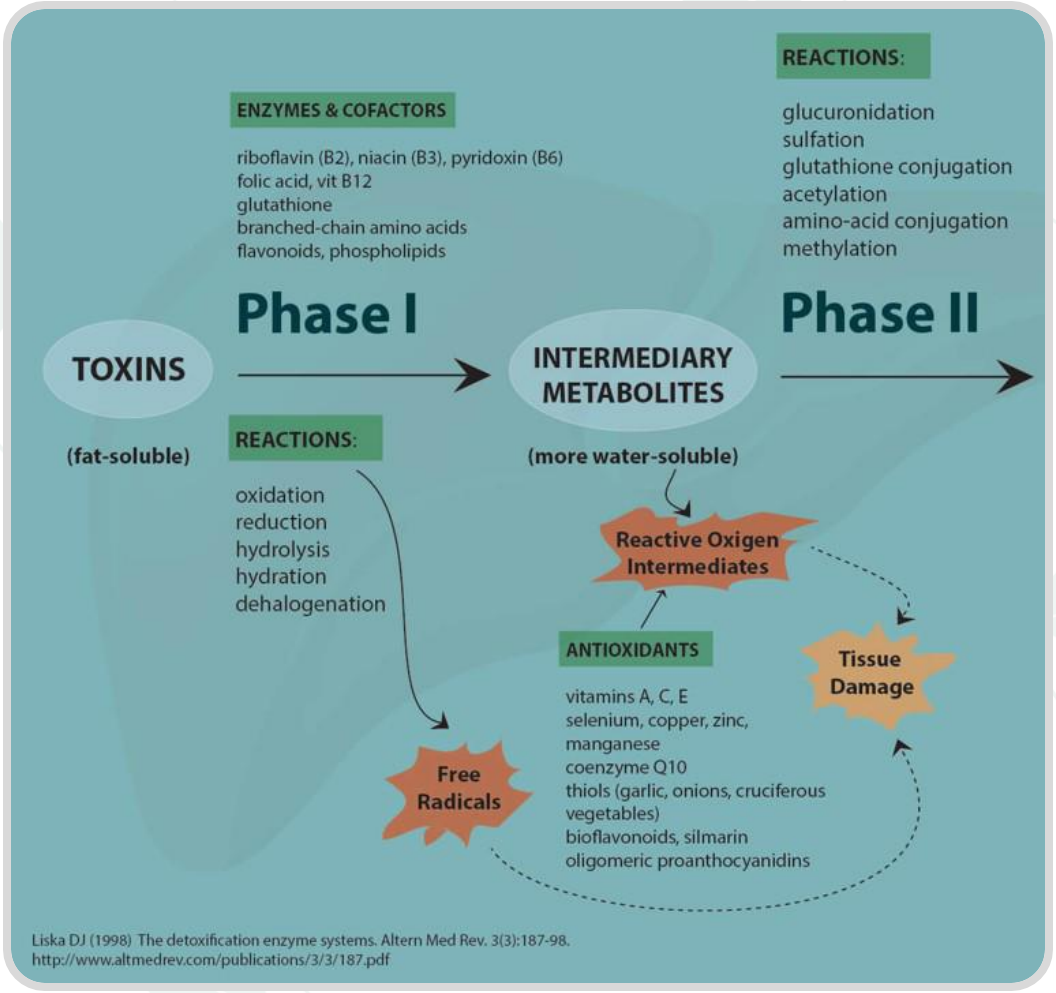
Phase 2 Detoxification

- **Phase 2 enzymes** break down compounds into *water-soluble compounds* for safer excretion.
  - Conjugated with a water- soluble or hydrophilic substance in phase 2.
  - This is completed by adding various groups such as sulfur, glutathione, glucuronic acid, amino acids, or methyl or acetyl groups.
  - Phase 2 enzymes are: UDP-glucuronosyl transferases, sulfotransferases, glutathione transferases, amino acid transferases, N-acetyl transferases, and methyltransferases/catechol-O-methyltransferase.

Minich, D., and R. Hodges. “Modulation of metabolic detoxification pathways using foods and food-derived components: A scientific review with clinical application.” *Journal of Nutrition and Metabolism,* Vol. 2015 (2015): 760689.

Phase 2

- If the 2-OH and 4-OH estrogens are not methylated, they can be converted to highly reactive molecules that could potentially damage DNA.



Wellness Wednesday

Minich, D., and R. Hodges. “Modulation of metabolic detoxification pathways using foods and food-derived components: A scientific review with clinical application.” *Journal of Nutrition and Metabolism,* Vol. 2015 (2015): 760689.

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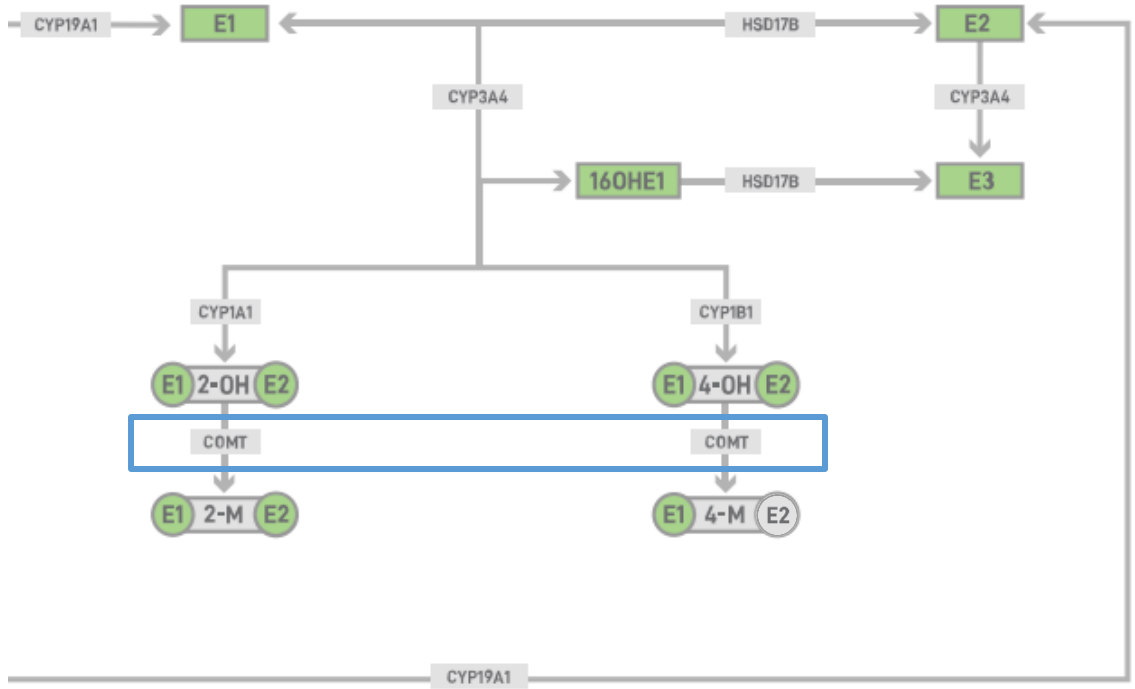
COMT (Catechol-O-Methyltransferase)



COMT

(-) High sucrose diet, leptin resistance, inflammation, bisphenol and PCBs

(+) B12, folate, Mg, methionine, SAMe, betaine, TMG, resveratrol, citrus, rosemary, DIM, rooibos, curcumin

Estrogen Metabolism: Phase 2 Detox

Oxidation or Methylation?

- Methylation (COMT)
  - Inactivates catechol estrogens
  - Increases solubility/prepare intermediates for renal and biliary excretion
  - methoxy metabolites →are stable and safely leave the body
- Oxidation
  - CYP peroxidase → quinone and semiquinone formation
    - Glutathionization (GST)
    - Glucuronidation (UGT)
    - Sulfonation (SOD2)
    - Acetylation

COMT

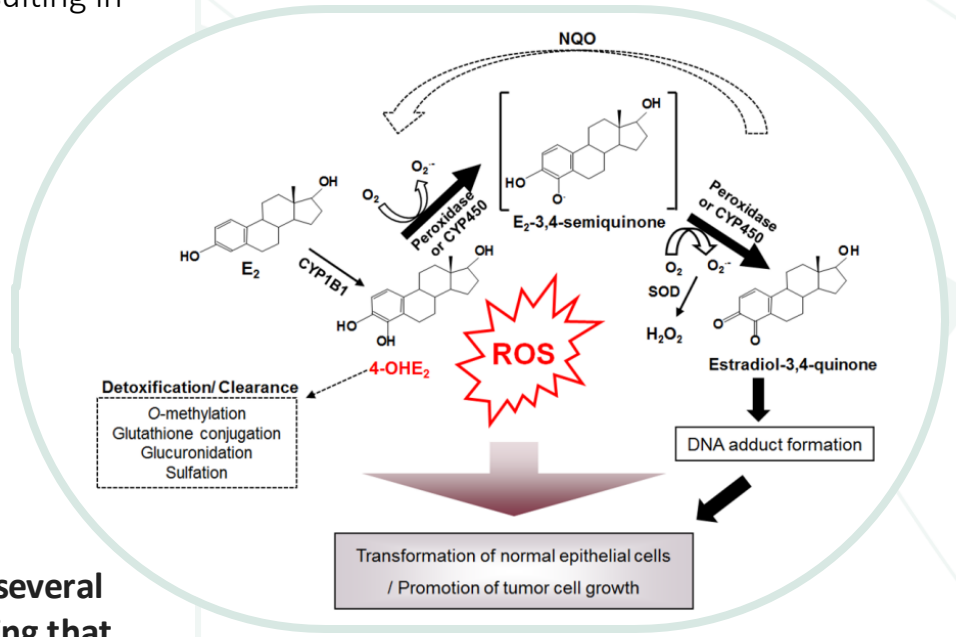
(-) High sucrose diet, leptin resistance, inflammation, bisphenol and PCBs

(+) B12, folate, Mg, methionine, SAMe, betaine, TMG, resveratrol, citrus, rosemary, DIM, rooibos, curcumin

2-M-E1:2-OH-E1‡	(COMT/Methylation activity)	0.22	0.08 – 0.60
2-M-E2:2-OH-E2‡	(COMT/Methylation activity)	0.13	0.06 – 0.80
4-M-E1:4-OH-E1‡	(COMT/Methylation activity)	0.0087	0.004 – 0.10

Estrogen Quinones and Breast Cancer

- Un-methylated 2-OH and 4-OH metabolites can form quinones / semi-quinones, resulting in DNA adduct formation/DNA damage
- Estrogen quinones are highly carcinogenic
- Potentiated by oxidative damage
- Genotoxic: DNA breaks/adducts
- Mutagenic: Depurinated DNA
- Carcinogenic: high levels in BC and HR breast tissue
  - Induction and propagation of BC
  - Increased risk of hormone responsive BC
- **"Increased amounts of estrogen-DNA adducts are found not only in people with several different types of cancer but also in women at high risk for breast cancer, indicating that the formation of adducts is on the pathway to cancer initiation."**



- Yager JD. Mechanisms of estrogen carcinogenesis: The role of E2/E1–quinone metabolites suggests new approaches to preventive intervention – A Review. *Steroids*. 2015;99:56-60. doi:10.1016/j.steroids.2014.08.006
- Cavalieri E, Rogan E. The 3,4-quinones of estrone and estradiol are the initiators of cancer whereas resveratrol and N-acetylcysteine are the preventers. *International Journal of Molecular Sciences*. 2021;22(15):8238. doi:10.3390/ijms22158238
- Park, S-A. Catechol Estrogen 4-Hydroxyestradiol is an Ultimate Carcinogen in Breast Cancer. Biomedical Science Letters 2018, 24(3): 143~149 https://doi.org/10.15616/BSL.2018.24.3.143

Quinone reduction

- NAC
  - Reduce estrogen semiquinones back to catechol estrogens
  - Primary effect is to react with quinones to form conjugates preventing the formation of estrogen-DNA adducts.
- Resveratrol
  - Reduce catechol estrogen semiquinones back to catechol estrogens
  - Induce the estrogen-protective enzyme quinone reductase
  - Modulates CYP1B1, thereby reducing its activity and thus the formation of 4-OHE1(E2)

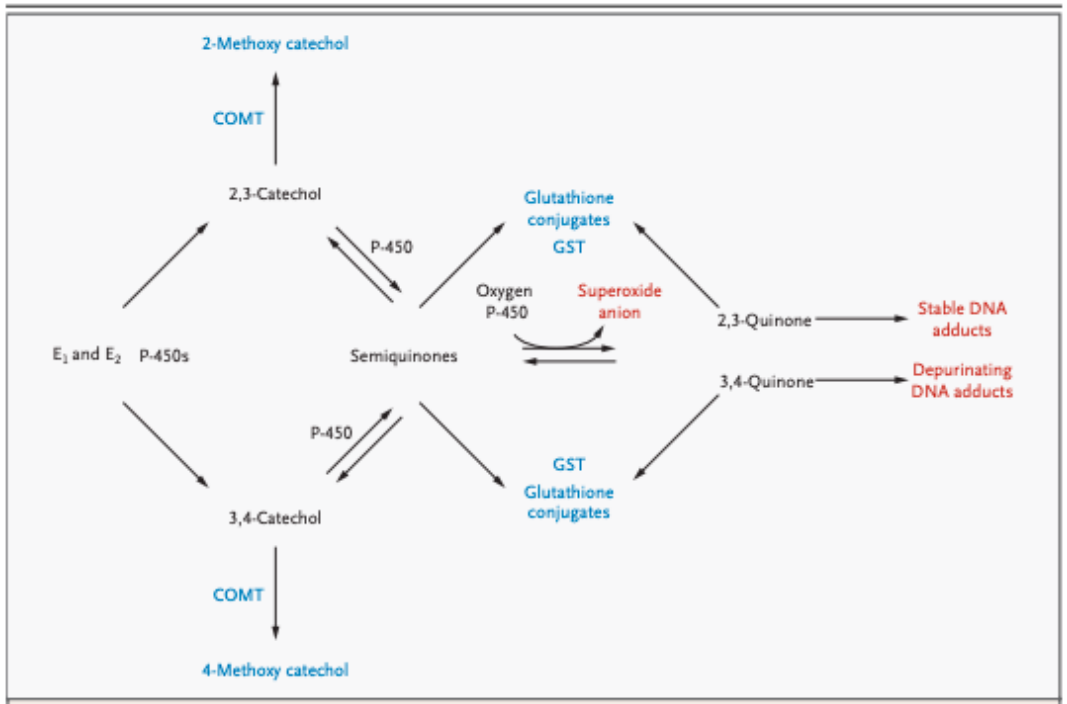
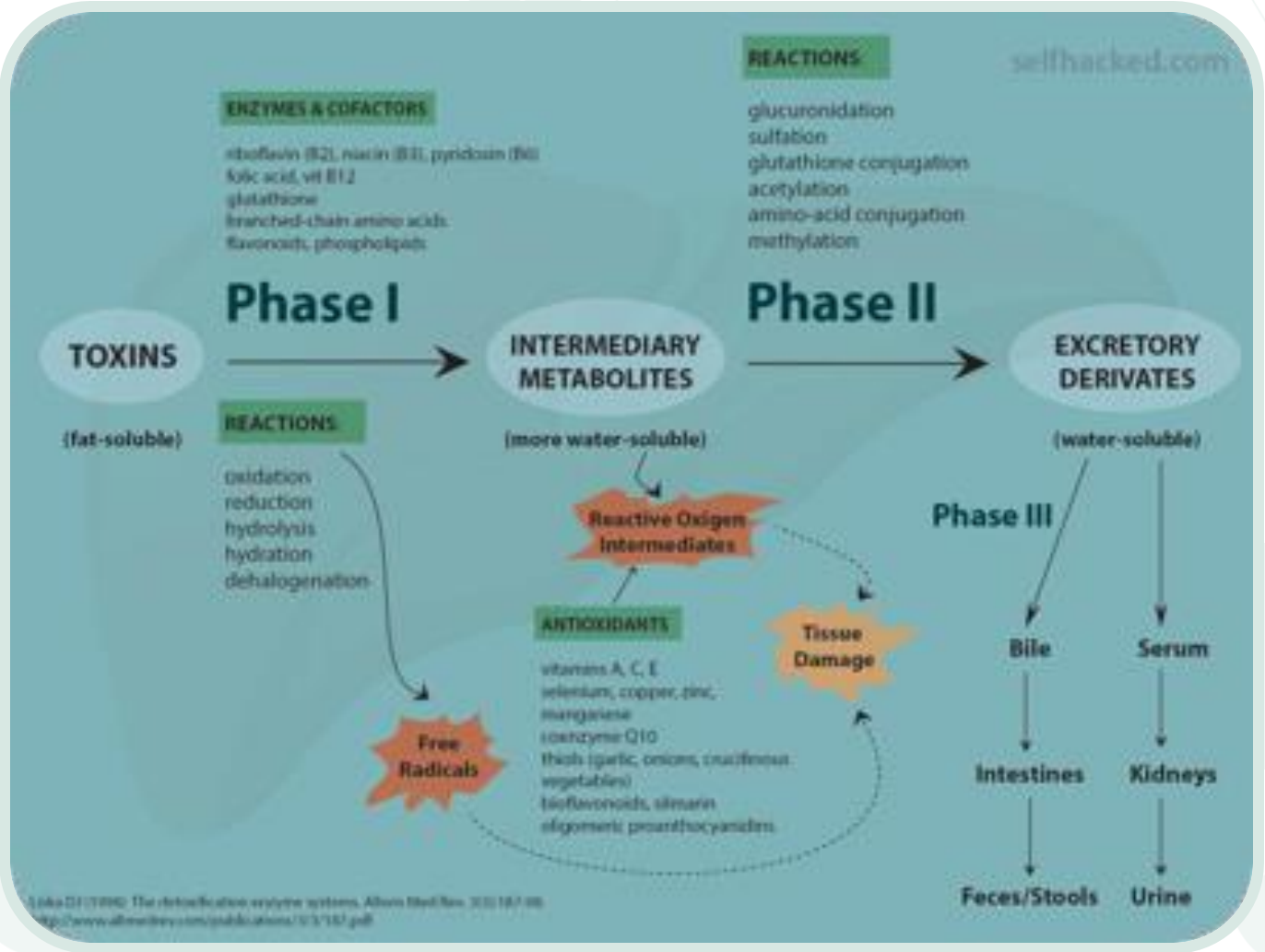


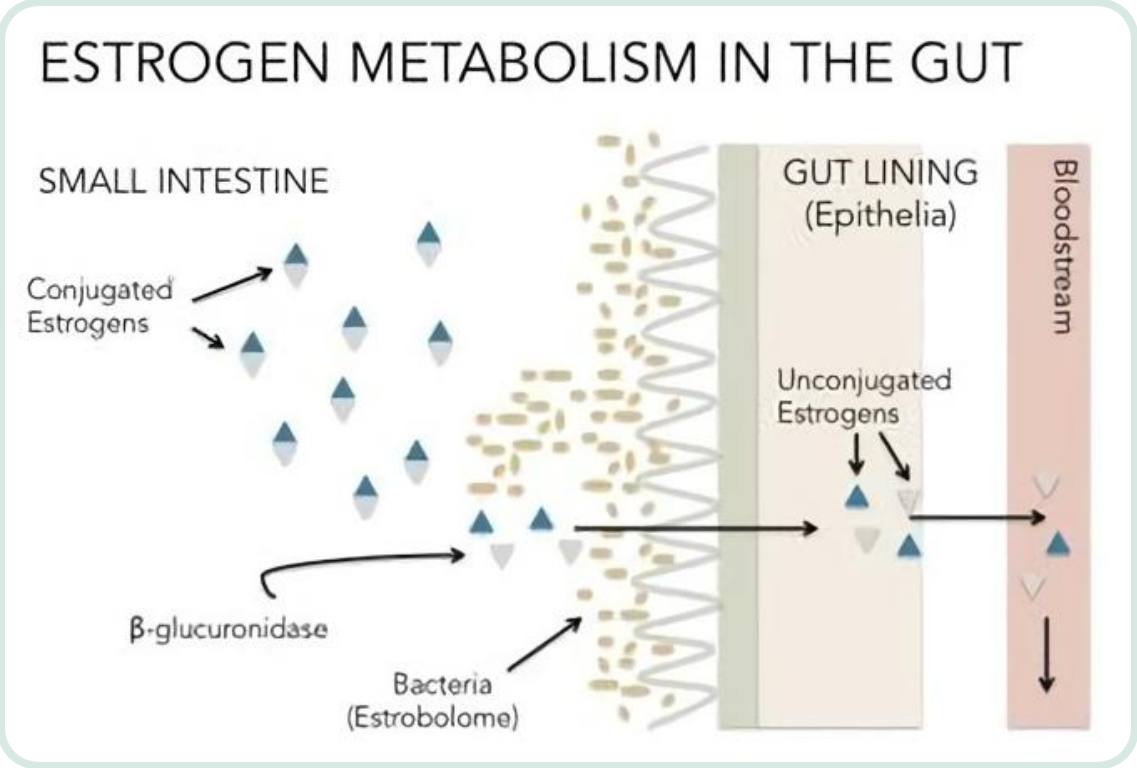
Figure 2. Oxidative Metabolism of Estrogen through the Catechol Pathway.
Data are from Cavalieri et al.[32] E_1 denotes estrone, E_2 estradiol, COMT catechol *O*-methyltransferase, P-450 cytochrome P-450, and GST glutathione S-transferase.

- Yager JD, Davidson NE. Estrogen carcinogenesis in breast cancer. N Engl J Med. 2006;354(3):270-282. doi:10.1056/NEJMra050776
- Cavalieri E, Rogan E. The 3,4-quinones of estrone and estradiol are the initiators of cancer whereas resveratrol and N-acetylcysteine are the preventers. International Journal of Molecular Sciences. 2021;22(15):8238. doi:10.3390/ijms22158238
- Shrivastava N, Parikh A, Dewangan RP, et al. Solid Self-Nano Emulsifying Nanoplatform Loaded with Tamoxifen and Resveratrol for Treatment of Breast Cancer. Pharmaceutics. 2022;14(7):1486. Published 2022 Jul 18. doi:10.3390/pharmaceutics14071486



Phase 3 Detox

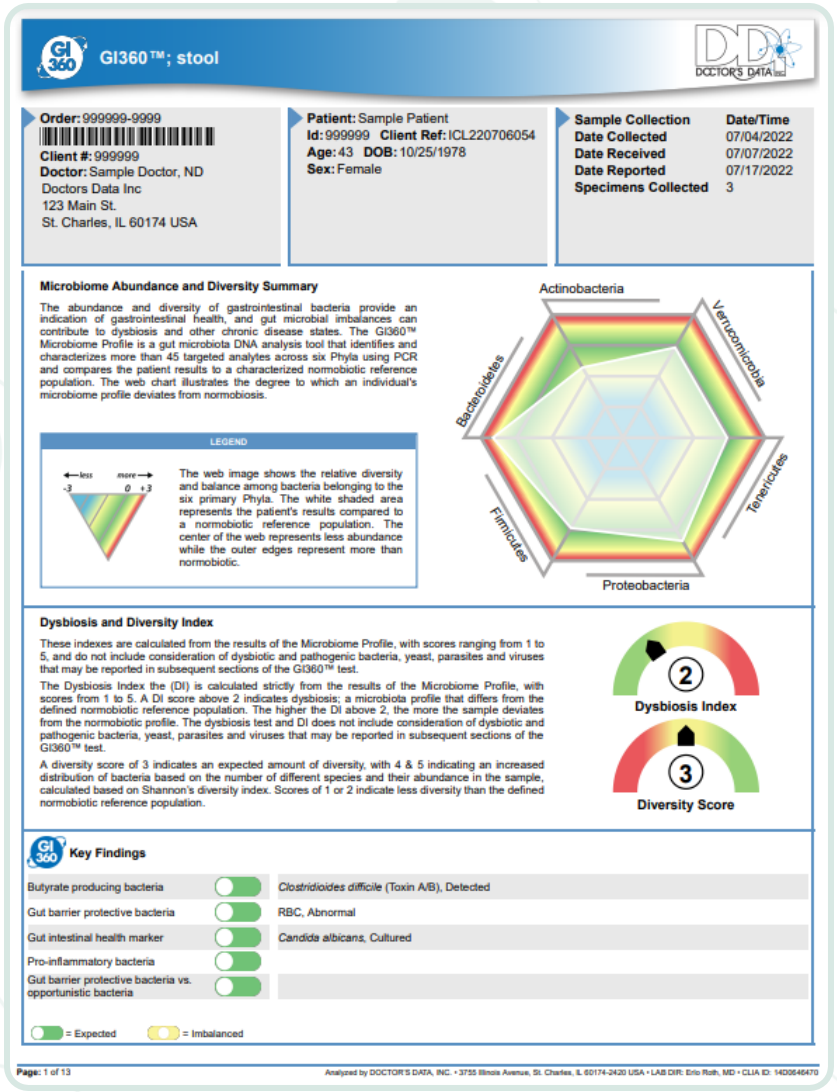
Beta glucuronidase: Elimination or Re-circulation



- Conjugated estrogens pass into the gut for elimination
- Beta-glucuronidase can deconjugate estrogens
- Unconjugated estrogens reabsorbed into circulation
- High levels of beta-glucuronidase could mean more recirculating of estrogens
- Beta-glucuronidase increases with: low fruits and veggies, low fiber, high sugar, processed foods, SAD diet, alcohol, toxicants, antibiotics

Baker, J. M., Al-Nakkash, L., & Herbst-Kralovetz, M. M. (2017). Estrogen–gut microbiome axis: Physiological and clinical implications. *Maturitas 103*, 45-53. doi:10.1016/j.maturitas.2017.06.025

Stool testing: beta glucuronidase



GI360™; stool

DOCTOR'S DATA INC

Order: 999999-9999
Client #: 999999
Doctor: Sample Doctor, ND
Doctors Data Inc
123 Main St.
St. Charles, IL 60174 USA

Patient: Sample Patient
Id: 999999 **Client Ref:** ICL220706054
Age: 43 **DOB:** 10/25/1978
Sex: Female

Sample Collection	Date/Time
Date Collected	07/04/2022
Date Received	07/07/2022
Date Reported	07/17/2022
Specimens Collected	3

Microbiome Abundance and Diversity Summary

The abundance and diversity of gastrointestinal bacteria provide an indication of gastrointestinal health, and gut microbial imbalances can contribute to dysbiosis and other chronic disease states. The GI360™ Microbiome Profile is a gut microbiota DNA analysis tool that identifies and characterizes more than 45 targeted analytes across six Phyla using PCR and compares the patient results to a characterized normobiotic reference population. The web chart illustrates the degree to which an individual's microbiome profile deviates from normobiosis.

LEGEND

less ← → more
-3 0 +3

The web image shows the relative diversity and balance among bacteria belonging to the six primary Phyla. The white shaded area represents the patient's results compared to a normobiotic reference population. The center of the web represents less abundance while the outer edges represent more than normobiotic.

Actinobacteria
Verrucomicrobia
Tenericutes
Proteobacteria
Firmicutes
Bacteroidetes

Dysbiosis and Diversity Index

These indexes are calculated from the results of the Microbiome Profile, with scores ranging from 1 to 5, and do not include consideration of dysbiotic and pathogenic bacteria, yeast, parasites and viruses that may be reported in subsequent sections of the GI360™ test.

The Dysbiosis Index the (DI) is calculated strictly from the results of the Microbiome Profile, with scores from 1 to 5. A DI score above 2 indicates dysbiosis; a microbiota profile that differs from the defined normobiotic reference population. The higher the DI above 2, the more the sample deviates from the normobiotic profile. The dysbiosis test and DI does not include consideration of dysbiotic and pathogenic bacteria, yeast, parasites and viruses that may be reported in subsequent sections of the GI360™ test.

A diversity score of 3 indicates an expected amount of diversity, with 4 & 5 indicating an increased distribution of bacteria based on the number of different species and their abundance in the sample, calculated based on Shannon's diversity index. Scores of 1 or 2 indicate less diversity than the defined normobiotic reference population.

2 Dysbiosis Index

3 Diversity Score

Key Findings

Butyrate producing bacteria	*Clostridioides difficile* (Toxin A/B), Detected
Gut barrier protective bacteria	RBC, Abnormal
Gut intestinal health marker	*Candida albicans*, Cultured
Pro-inflammatory bacteria	
Gut barrier protective bacteria vs. opportunistic bacteria	

= Expected = Imbalanced

Page: 1 of 13

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Digestion / Absorption	Result	Unit	L WRI H	Reference Interval
Elastase	>500	µg/mL		> 200
Fat Stain	None			None – Few
Carbohydrates†	Negative			Negative
Inflammation	**Result**	**Unit**	**L WRI H**	**Reference Interval**
Lactoferrin	1.6	µg/mL		< 7.3
Lysozyme*	369	ng/mL		≤ 500
Calprotectin	<10	µg/g		≤ 50
Immunology	**Result**	**Unit**	**L WRI H**	**Reference Interval**
Secretory IgA*	34.8	mg/dL		30 – 275
Short Chain Fatty Acids	**Result**	**Unit**	**L WRI H**	**Reference Interval**
% Acetate‡	62			50 – 72
% Propionate‡	17			11 – 25
% Butyrate‡	17			11 – 32
% Valerate‡	3.7			0.8 – 5.0
Butyrate‡	2.4	mg/mL		0.8 – 4.0
Total SCFA's‡	14	mg/mL		5.0 – 16.0
Intestinal Health Markers	**Result**	**Unit**	**L WRI H**	**Reference Interval**
pH	6.1			5.8 – 7.0
β-glucuronidase*	1508	U/L		100 – 1200
Occult Blood	Negative			Negative

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Consider treating phase 3 (elimination) first

- Hydration PMID: 20646222
- Fiber PMID: 26026145
- Herbs to prevent/treat constipation (aloe, ginger, Avipattikar, Triphala) PMID: 30680163 PMID: 28696777
- Magnesium
- Movement
- Calcium D-Glucarate PMID: 2346674

Wellness Wednesday

Genuis SJ. Elimination of persistent toxicants from the human body. Hum Exp Toxicol. 2011 Jan;30(1):3-18. doi: 10.1177/0960327110368417. Epub 2010 Apr 16. PMID: 20400489.

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Assessing oxidative damage: 8-hydroxy-2-deoxyguanosine(8-OHdG)

- Not an estrogen metabolite, but pairs nicely with metabolite information
- Lipids of cellular membranes, proteins, and DNA can incur permanent oxidative damage.
- In nuclear and mitochondrial DNA, 8-OHdG is one of the predominant forms of free radical-induced oxidative lesions and widely used as a biomarker for oxidative stress and carcinogenesis.
- 8-OHdG may be helpful in identifying or confirming DNA damage from harmful metabolites (quinones and DNA adducts)

Oxidative Stress Metabolite		Result	Unit	L WRI H	Reference Interval
8-hydroxy-2'-deoxyguanosine‡	(8-OHdG)	9.08	ng/mg Creat/Day		0 – 7.5

Wellness Wednesday

VALAVANIDIS ATHANASIOS, VLACHOGIANNI THOMAIS, FIOTAKIS CONSTANTINOS. 8-hydroxy-2' -deoxyguanosine (8-ohdg): A critical biomarker of oxidative stress and carcinogenesis. *Journal of Environmental Science and Health, Part C*. 2009;27(2):120-139. doi:10.1080/10590500902885684

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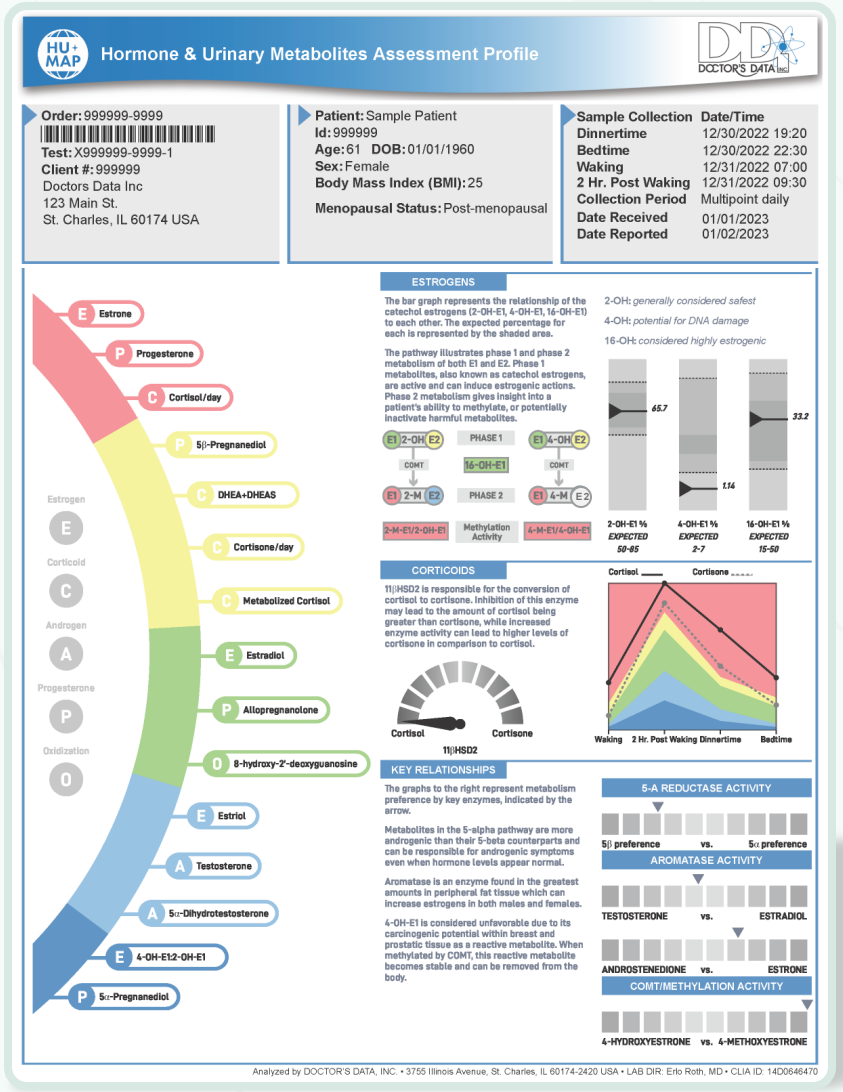
Oxidative stress and disease states

- Chronic stress, Cortisol elevation
- Inflammation
- Insomnia in postmenopausal women
- Degenerative diseases (rheumatoid arthritis, Parkinson's disease, Huntington's disease, Alzheimer's disease)
- Chronic fatigue syndrome
- Major depression
- Hypertension, Cardiovascular disease
- Diabetes type II
- Cystic fibrosis
- Psoriasis
- Chronic hepatitis
- Gastritis
- Irritable bowel disease
- Pancreatitis
- Cancer
- Acute viral infection
- Copper implants
- Toxic exposures (tobacco smoke, methamphetamines, asbestos, heavy metals, polycyclic hydrocarbons).

THE TESTS



Hormone & Urinary Metabolites Assessment Profile

DOCTOR'S DATA Inc

Order: 999999-9999
Test: X999999-9999-1
Client #: 999999
Doctors Data Inc
123 Main St.
St. Charles, IL 60174 USA

Patient: Sample Patient
Id: 999999
Age: 61 DOB: 01/01/1960
Sex: Female
Body Mass Index (BMI): 25
Menopausal Status: Post-menopausal

Sample Collection	Date/Time
Dinnertime	12/30/2022 19:20
Bedtime	12/30/2022 22:30
Waking	12/31/2022 07:00
2 Hr. Post Waking	12/31/2022 09:30
Collection Period	Multipoint daily
Date Received	01/01/2023
Date Reported	01/02/2023

E Estrone
P Progesterone
C Cortisol/day
P 5β-Pregnanediol
C DHEA+DHEAS
C Cortisone/day
C Metabolized Cortisol
E Estradiol
P Allopregnanolone
O 8-hydroxy-2'-deoxyguanosine
E Estriol
A Testosterone
A 5α-Dihydrotestosterone
E 4-OH-E1:2-OH-E1
P 5α-Pregnanediol

Estrogen E
Corticoid C
Androgen A
Progesterone P
Oxidization O

ESTROGENS

The bar graph represents the relationship of the catechol estrogens (2-OH-E1, 4-OH-E1, 16-OH-E1) to each other. The expected percentage for each is represented by the shaded area.

The pathway illustrates phase 1 and phase 2 metabolism of both E1 and E2. Phase 1 metabolites, also known as catechol estrogens, are active and can induce estrogenic actions. Phase 2 metabolism gives insight into a patient's ability to methylate, or potentially inactivate harmful metabolites.

E1 2-OH E2 — PHASE 1 — E1 4-OH E2
COMT → E1 2-M E2 — PHASE 2 — COMT → E1 4-M E2
16-OH-E1
2-M-E1/2-OH-E1 — Methylation Activity — 4-M-E1/4-OH-E1

2-OH: *generally considered safest*
4-OH: *potential for DNA damage*
16-OH: *considered highly estrogenic*

65.7 | 1.14 | 33.2

2-OH-E1 % *EXPECTED 50-85*
4-OH-E1 % *EXPECTED 2-7*
16-OH-E1 % *EXPECTED 15-50*

CORTICOIDS

11βHSD2 is responsible for the conversion of cortisol to cortisone. Inhibition of this enzyme may lead to the amount of cortisol being greater than cortisone, while increased enzyme activity can lead to higher levels of cortisone in comparison to cortisol.

Cortisol — Cortisone
11βHSD2

Cortisol ___ Cortisone - - - -
Waking | 2 Hr. Post Waking | Dinnertime | Bedtime

KEY RELATIONSHIPS

The graphs to the right represent metabolism preference by key enzymes, indicated by the arrow.

Metabolites in the 5-alpha pathway are more androgenic than their 5-beta counterparts and can be responsible for androgenic symptoms even when hormone levels appear normal.

Aromatase is an enzyme found in the greatest amounts in peripheral fat tissue which can increase estrogens in both males and females.

4-OH-E1 is considered unfavorable due to its carcinogenic potential within breast and prostatic tissue as a reactive metabolite. When methylated by COMT, this reactive metabolite becomes stable and can be removed from the body.

5-A REDUCTASE ACTIVITY
5β preference vs. 5α preference
AROMATASE ACTIVITY
TESTOSTERONE vs. ESTRADIOL
ANDROSTENEDIONE vs. ESTRONE
COMT/METHYLATION ACTIVITY
4-HYDROXYESTRONE vs. 4-METHOXYESTRONE

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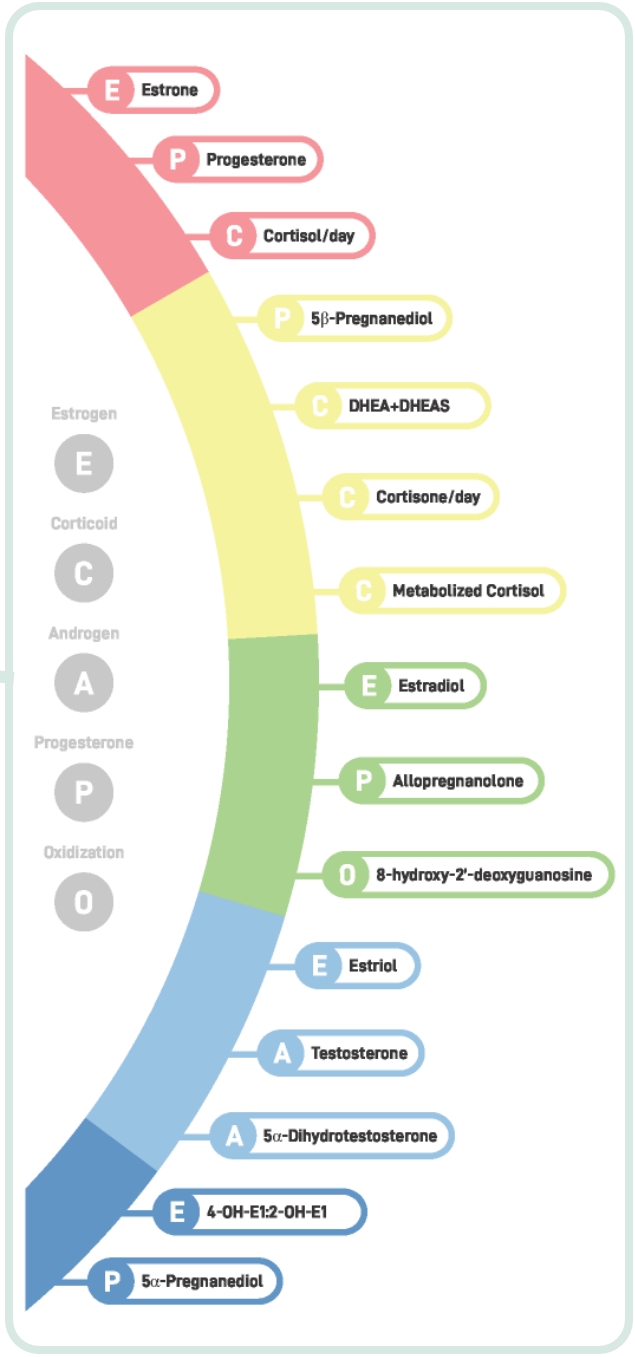
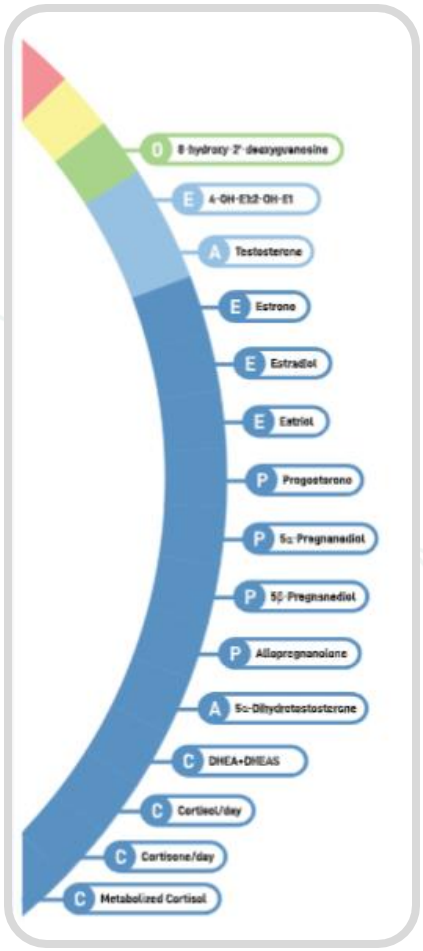
Important, clinically relevant markers are color-coded to respond to an individual's imbalances, providing an at-a-glance format on the summary page.

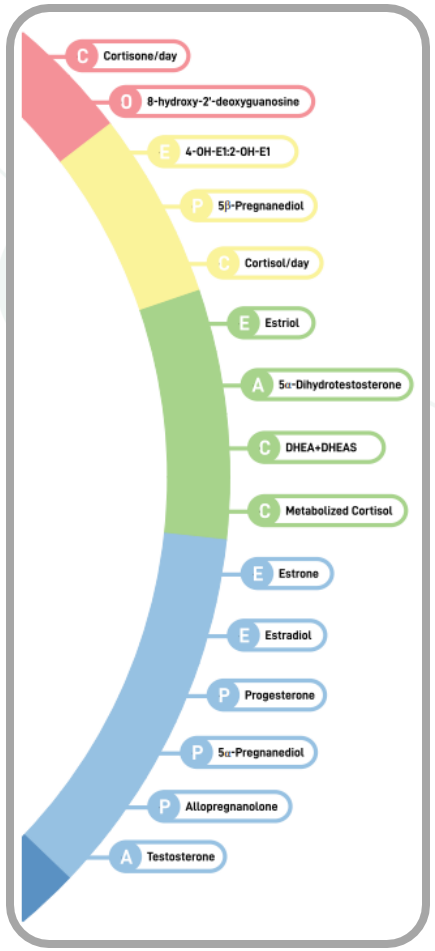


Patient #1



Patient #2

Patient #3



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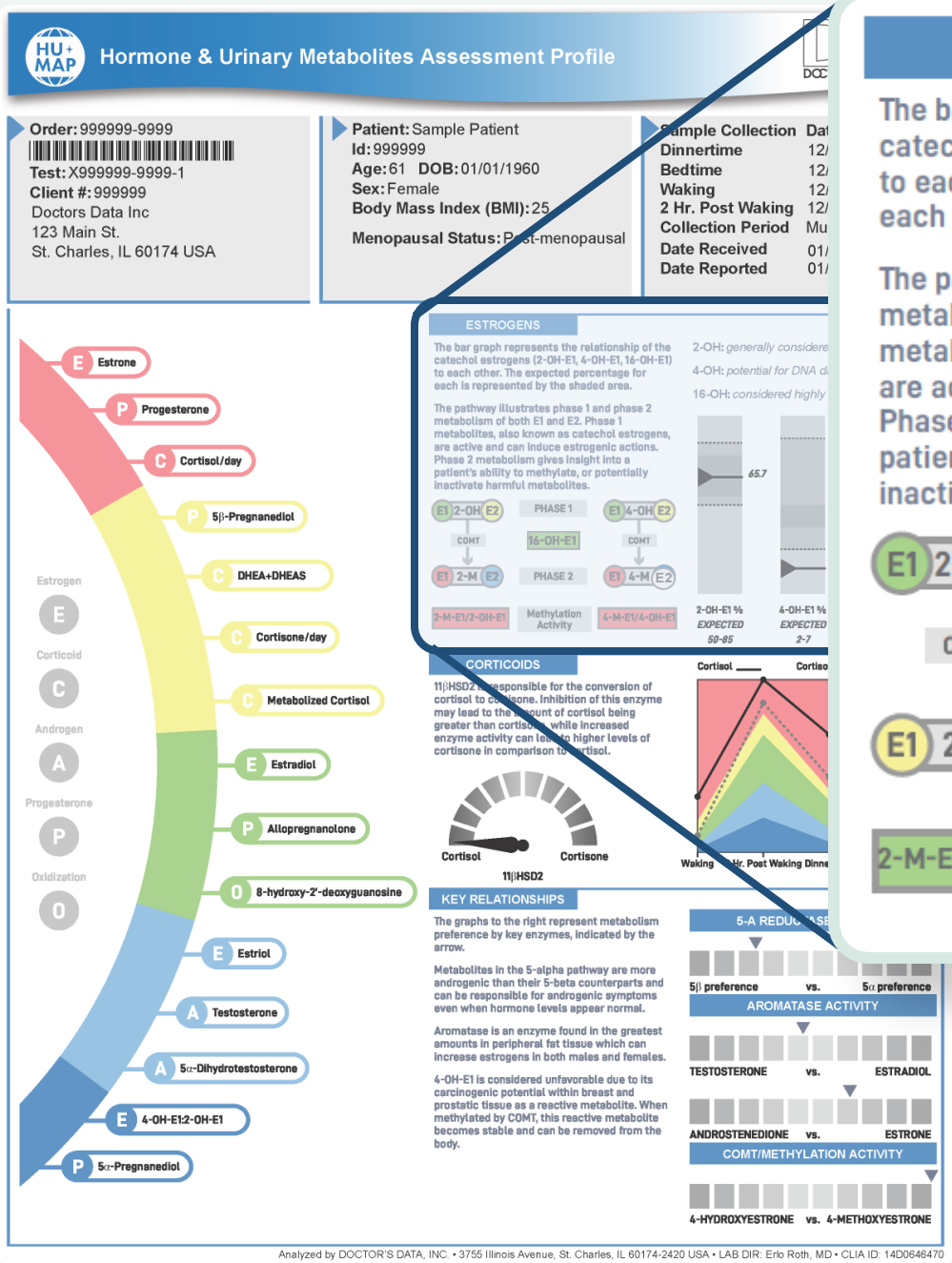

ESTROGENS

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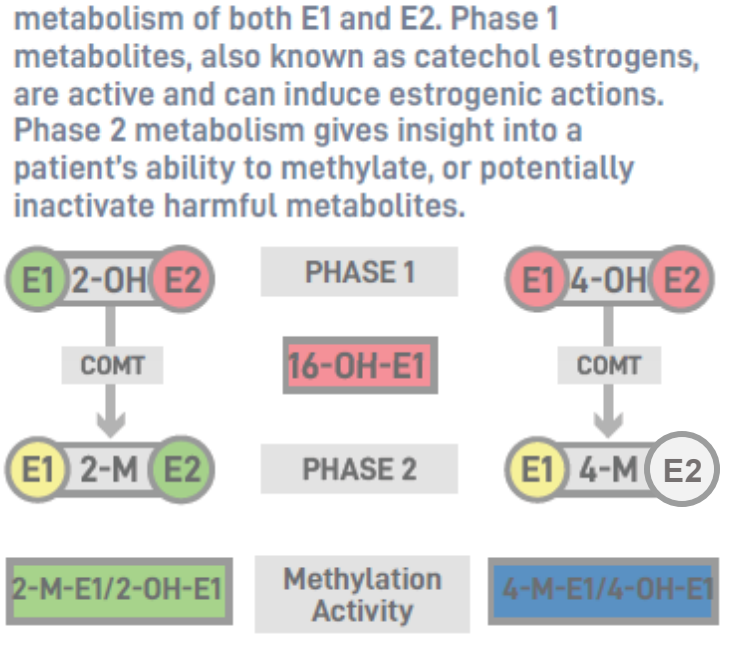
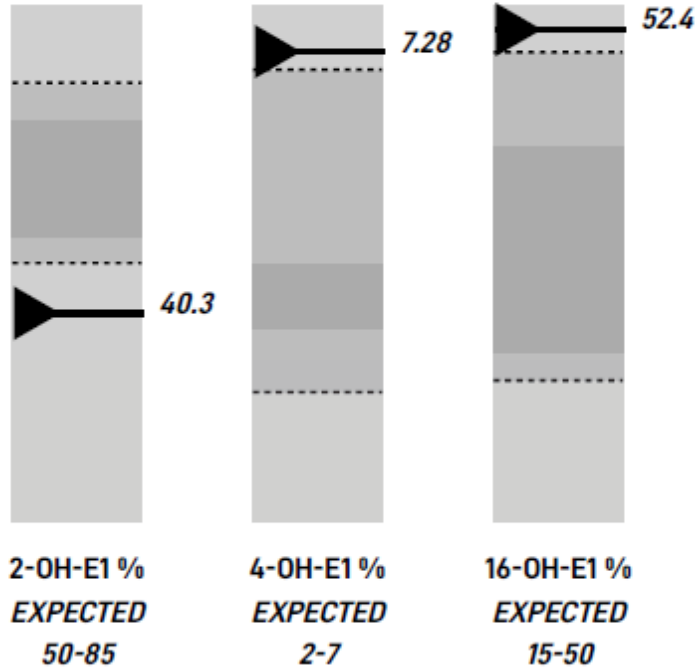
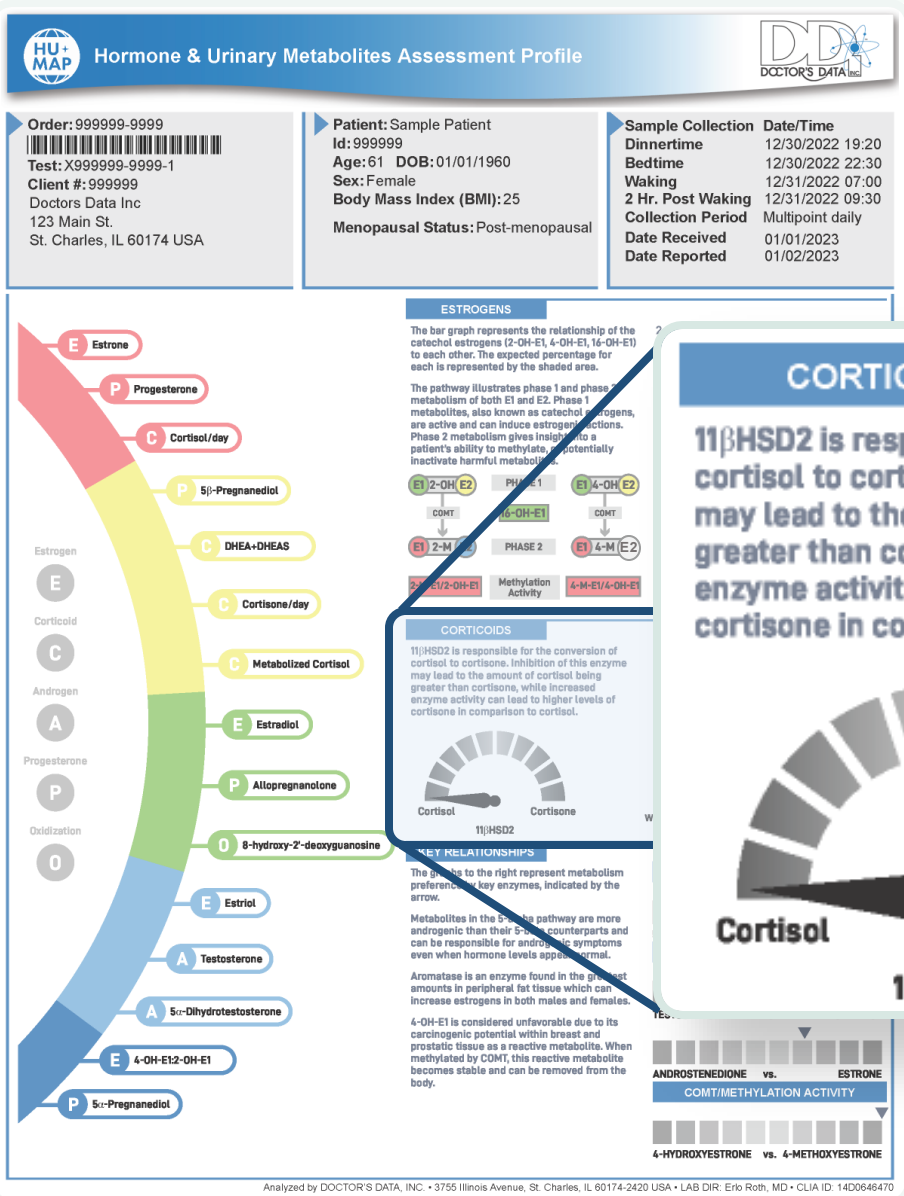
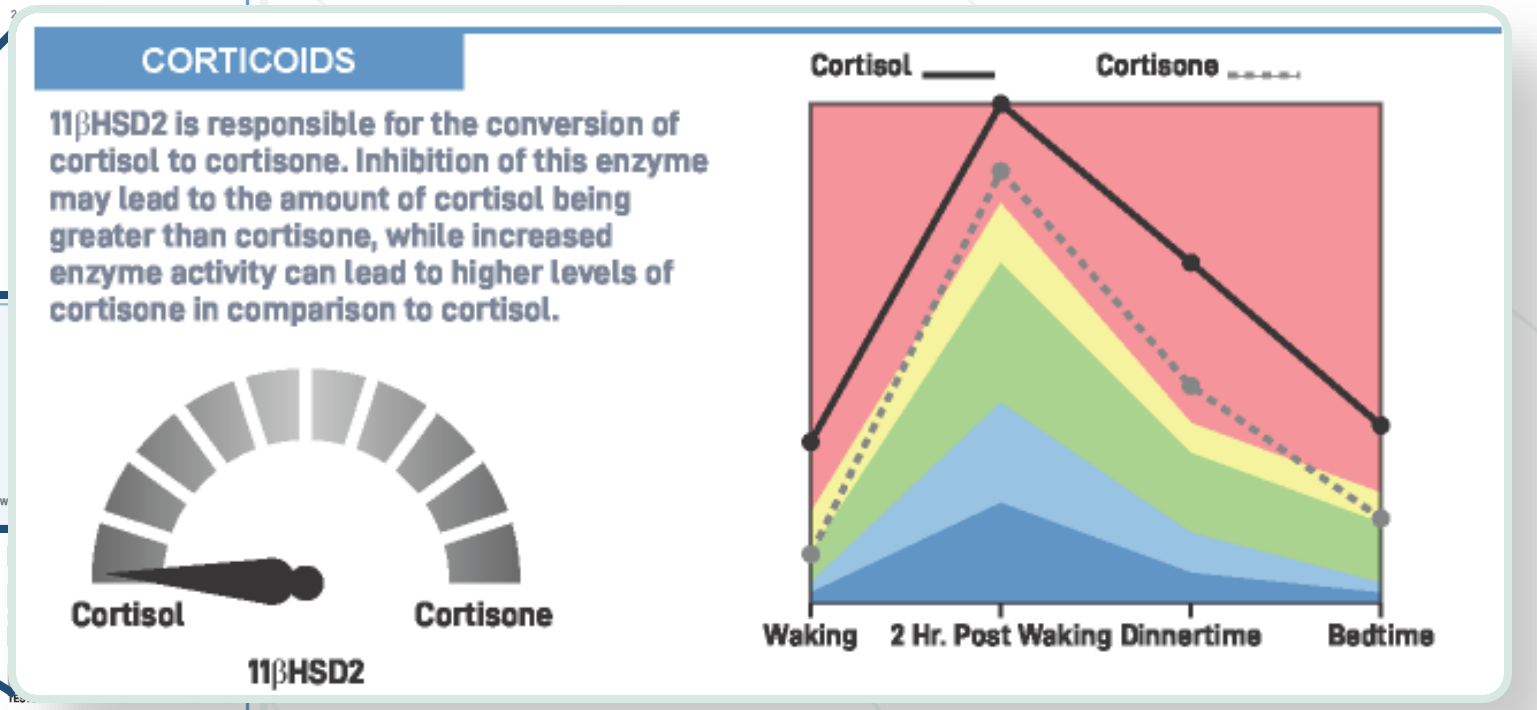




Cortisol and cortisone are plotted on the same graph to quickly identify their relationship to each other.





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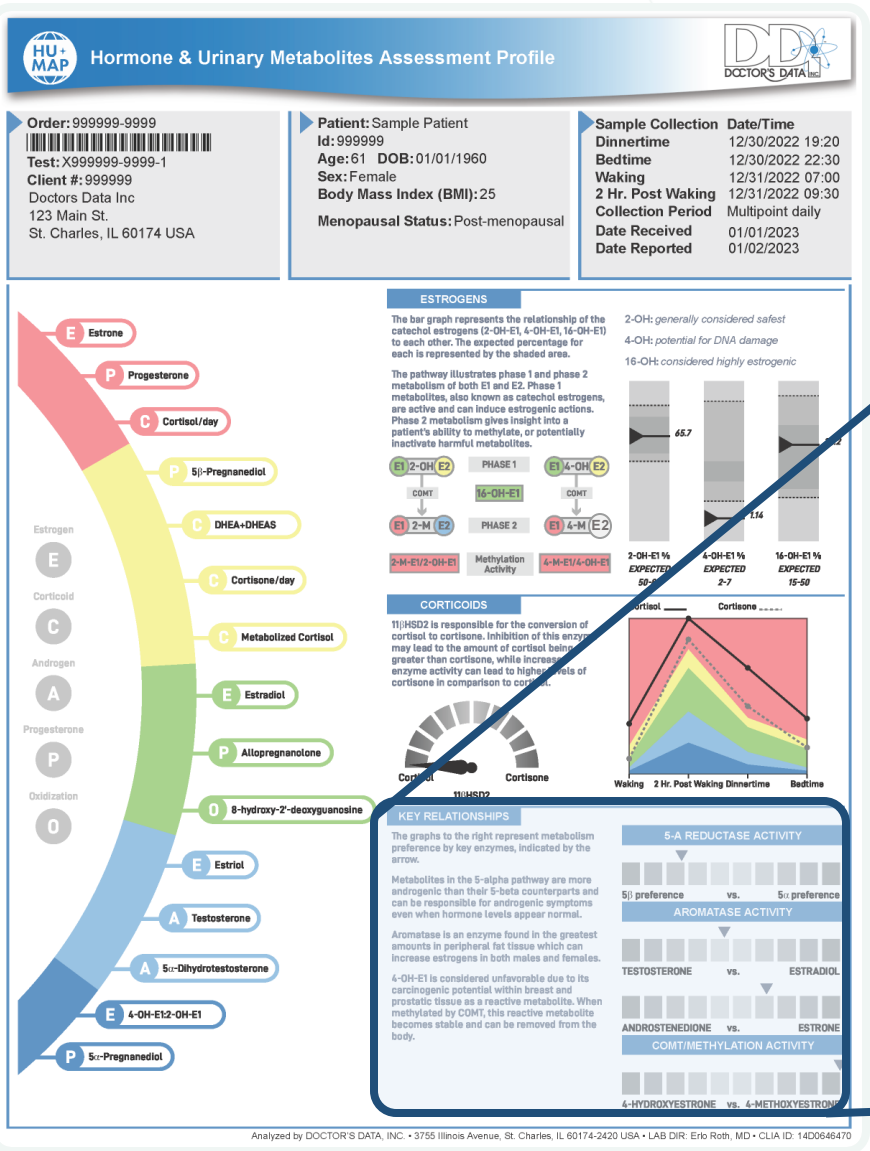

Important relationships are highlighted here, representing metabolism preference by key enzymes.

KEY RELATIONSHIPS

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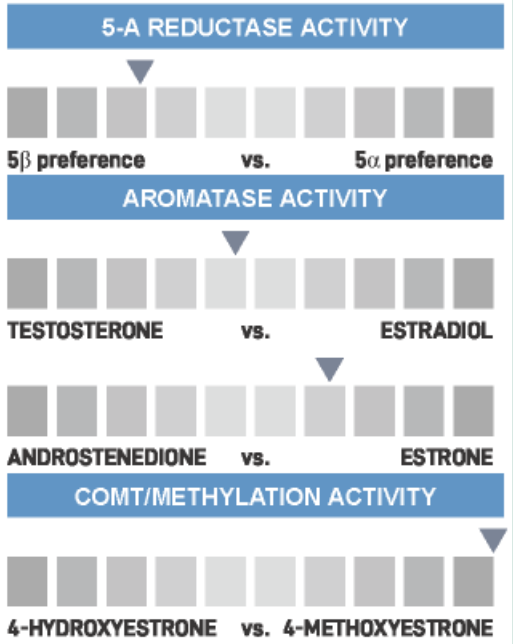

Wellness Wednesday

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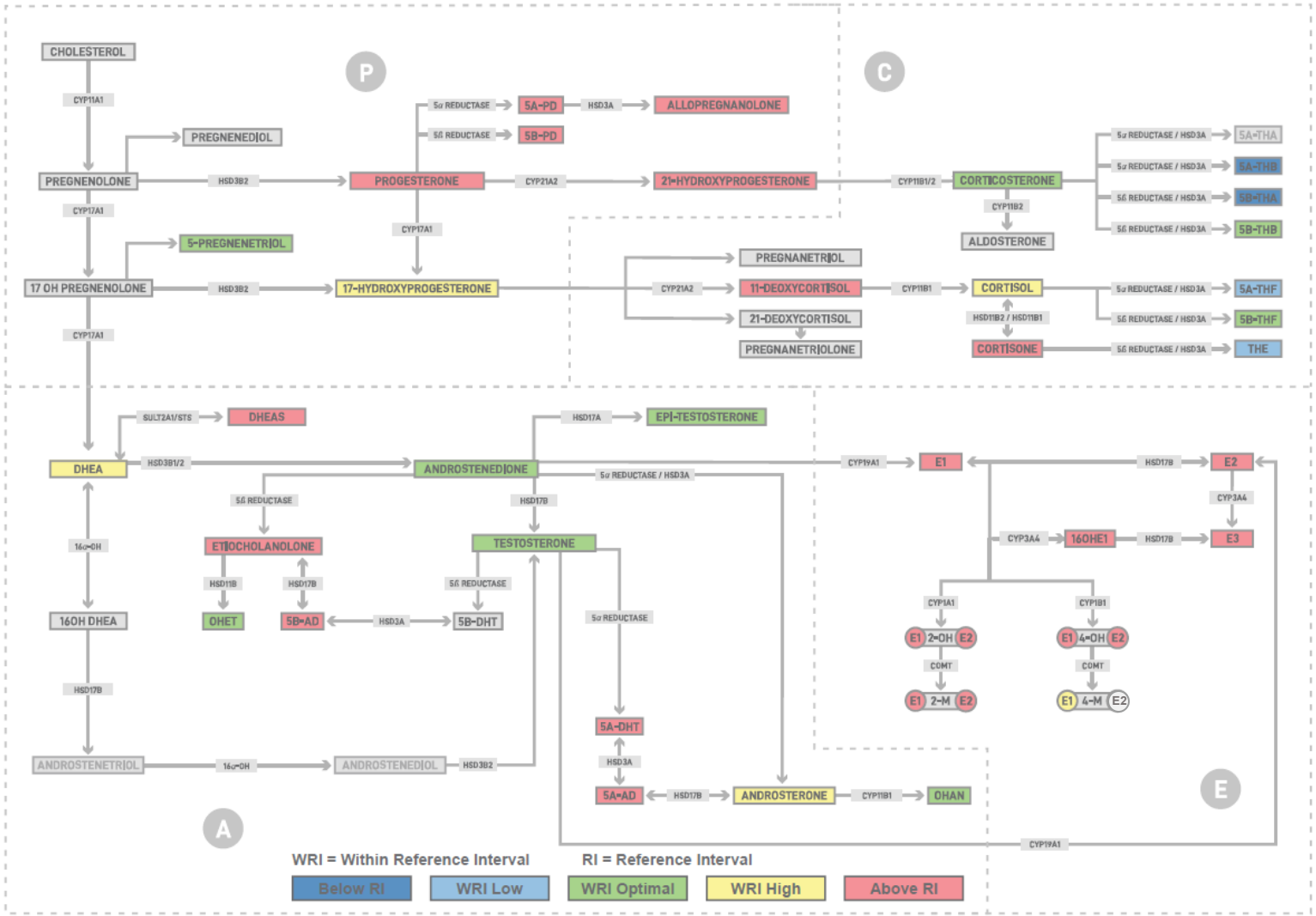

- Dynamic color-coded overview of the entire hormone steroid cascade displaying actual results for your patient.
- Colors are used to easily identify highs and lows for each metabolite.

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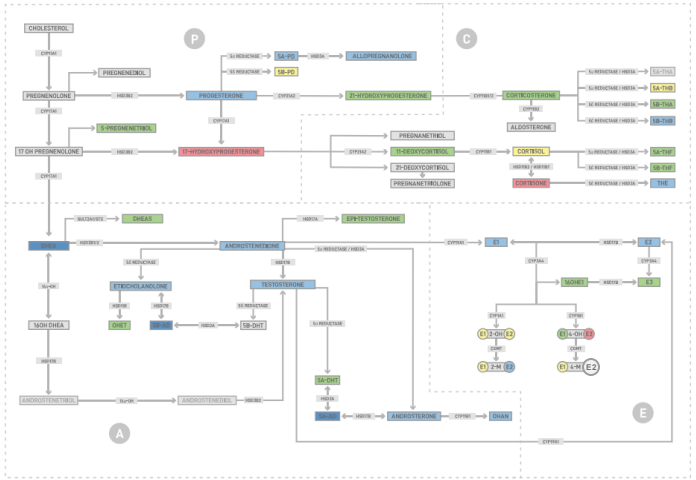
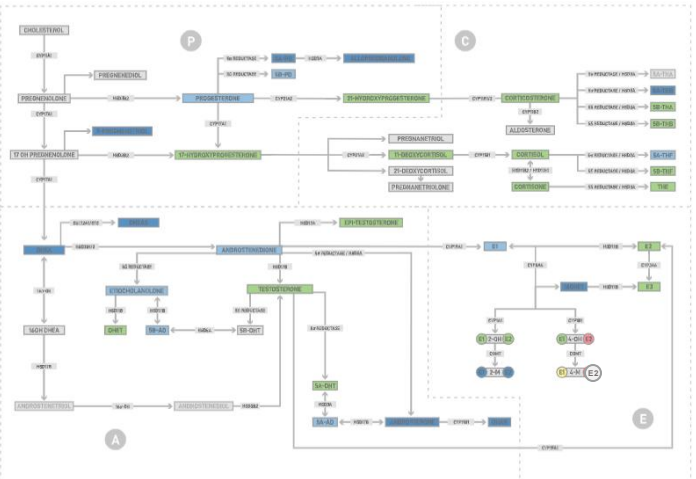
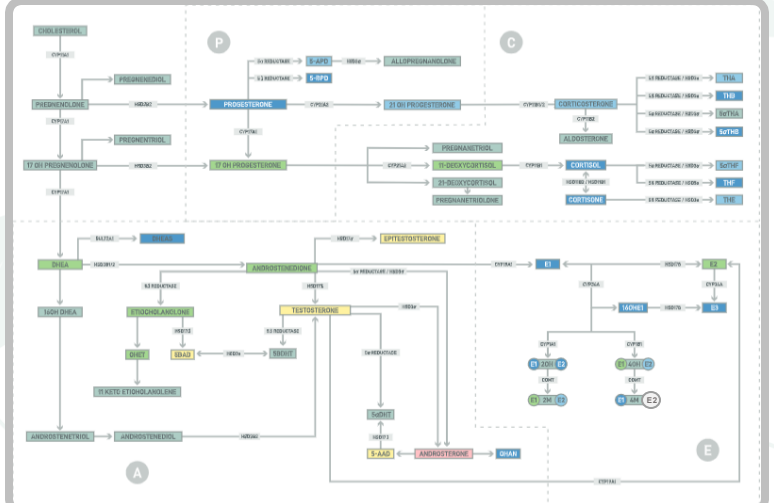
Patient #1

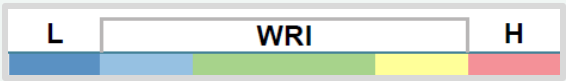


Patient #2



Patient #3





- WRI – Within Reference Interval - represented by bracket and stated ranges on report

- Dark Blue = Below RI
- Light Blue = WRI low
- Green = Optimal
- Yellow = WRI high
- Red = Above RI

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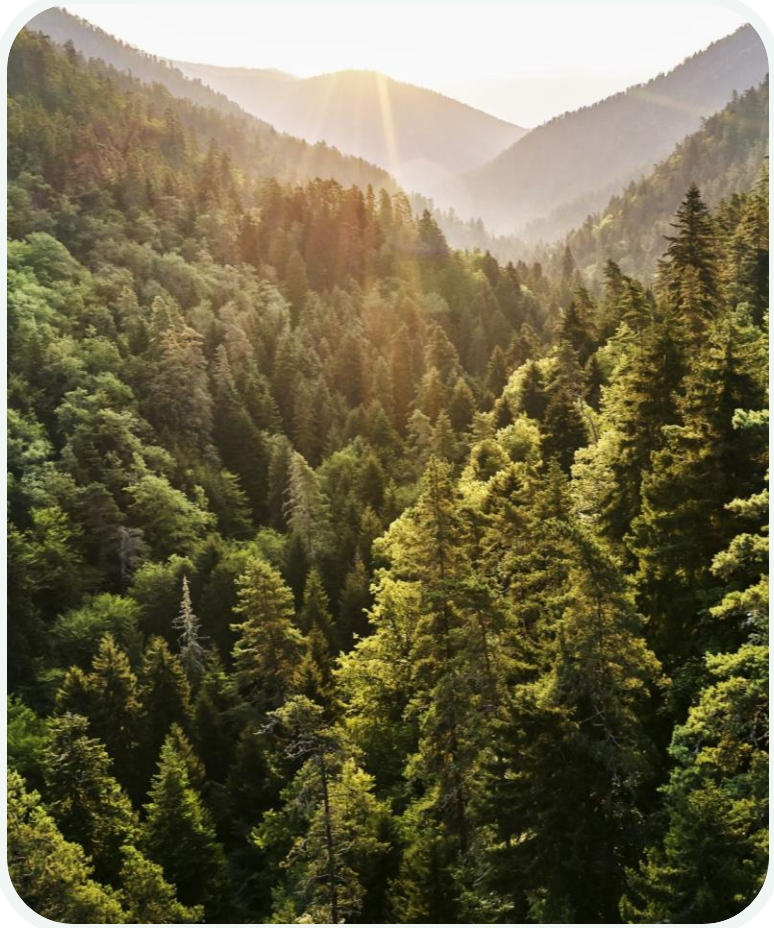
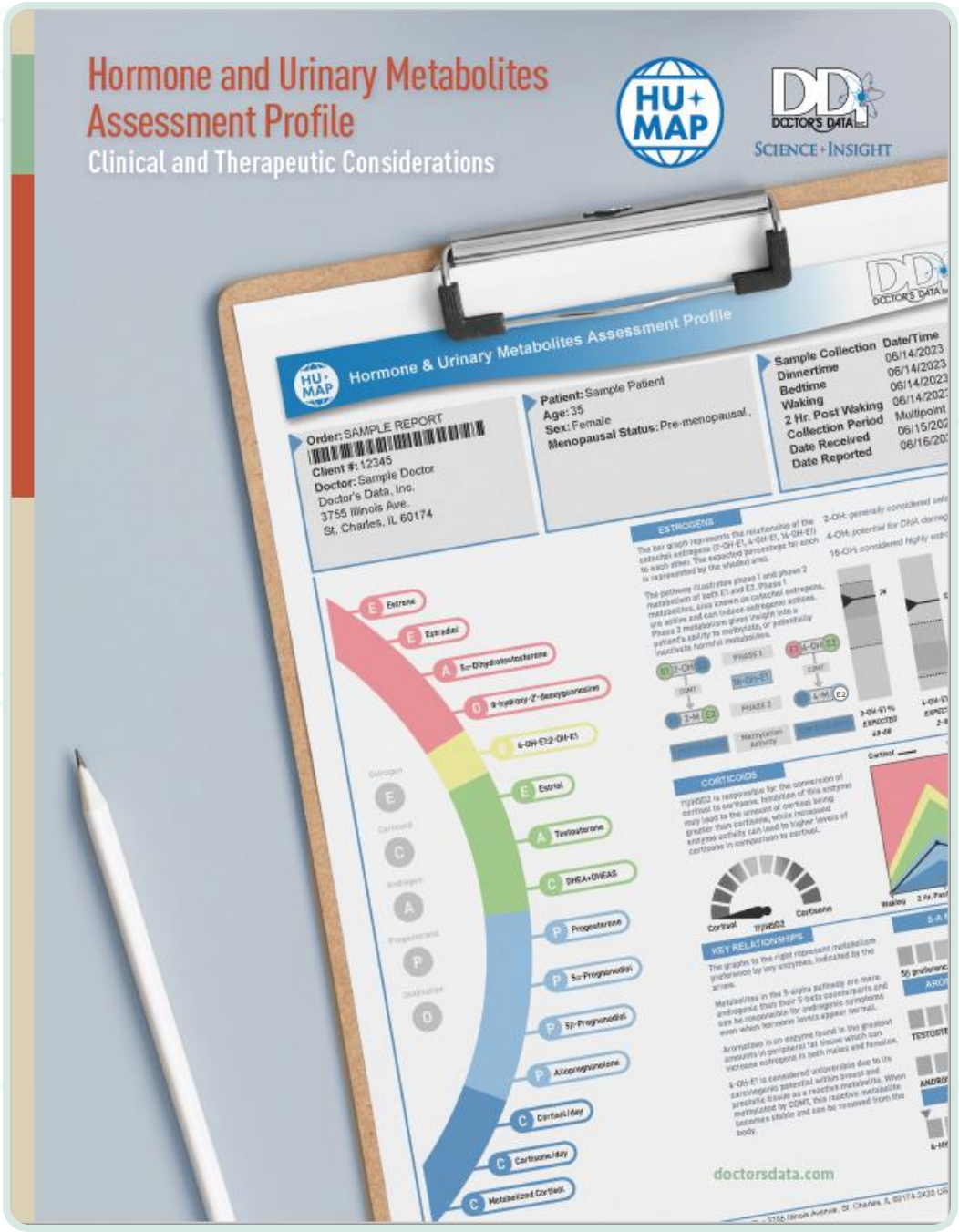


Can’t see the forest for the trees…

- Utilizing urinary hormone testing requires the practitioner to take a step back and look at the pattern of hormone secretion
- Metabolism is complex and will be different for every individual
- **Attempting to bring every analyte within range is not necessarily the goal of this type of testing**



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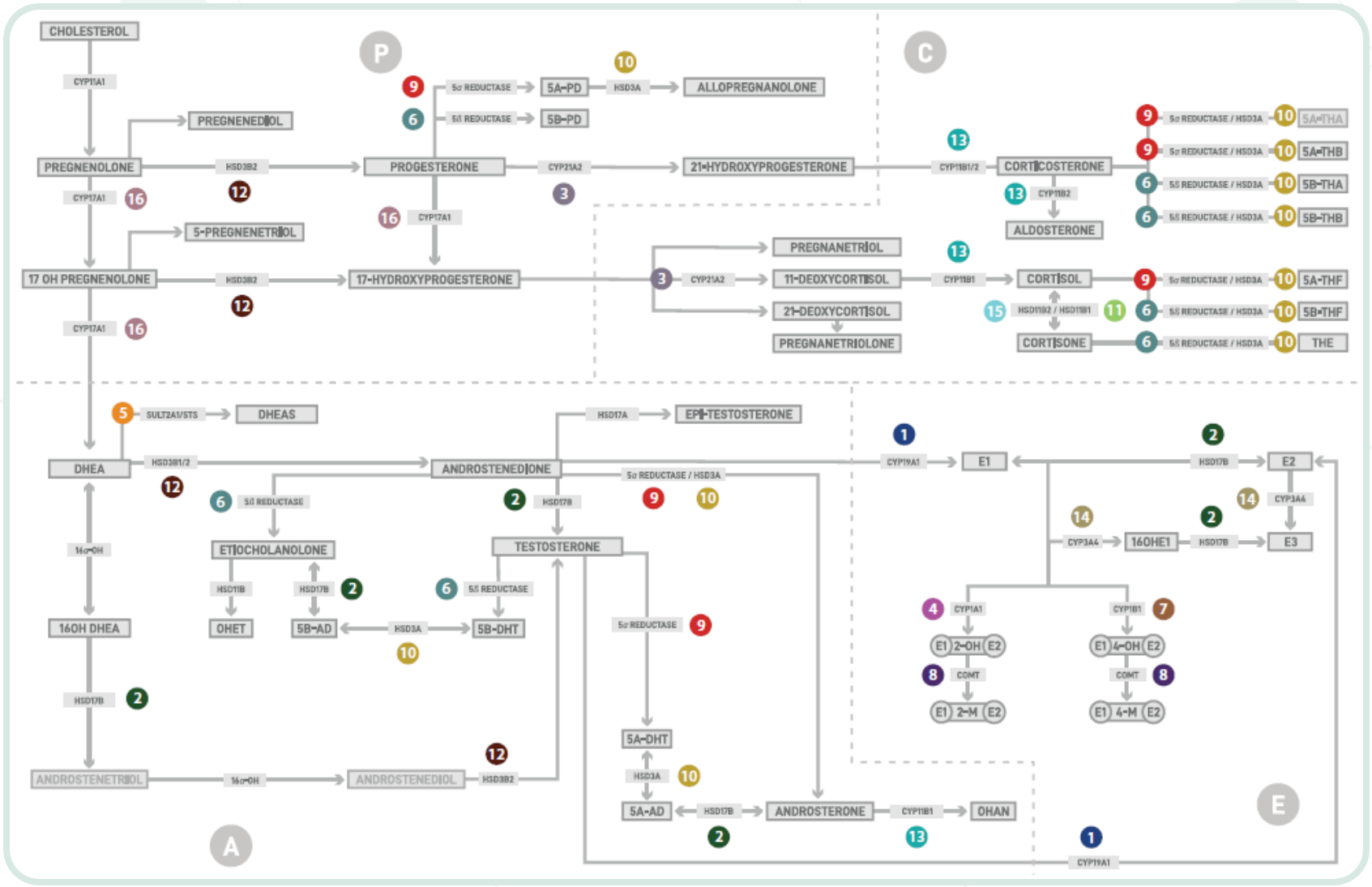
CHOLESTEROL
CYP11A1
PREGNENEDIOL
PREGNENOLONE
HSD3B2
CYP17A1
5-PREGNENETRIOL
17 OH PREGNENOLONE
HSD3B2
CYP17A1
DHEA
SULT2A1/STS
DHEAS
HSD3B1/2
16α-OH
16OH DHEA
HSD17B
ANDROSTENETRIOL
16α-OH
ANDROSTENEDIOL
HSD3B2
A
P
5α REDUCTASE
5A-PD
HSD3A
ALLOPREGNANOLONE
5β REDUCTASE
5B-PD
PROGESTERONE
CYP21A2
21-HYDROXYPROGESTERONE
CYP17A1
17-HYDROXYPROGESTERONE
HSD3B2
ETIOCHOLANOLONE
HSD11B
OHET
HSD17B
5B-AD
HSD3A
5B-DHT
5β REDUCTASE
ANDROSTENEDIONE
HSD17A
EPI-TESTOSTERONE
5α REDUCTASE / HSD3A
HSD17B
TESTOSTERONE
5α REDUCTASE
5A-DHT
HSD3A
5A-AD
HSD17B
ANDROSTERONE
CYP11B1
OHAN
C
CYP11B1/2
CORTICOSTERONE
CYP11B2
ALDOSTERONE
PREGNANETRIOL
11-DEOXYCORTISOL
21-DEOXYCORTISOL
PREGNANETRIOLONE
CYP11B1
CORTISOL
HSD11B2 / HSD11B1
CORTISONE
5α REDUCTASE / HSD3A
5A-THA
5A-THB
5β REDUCTASE / HSD3A
5B-THA
5B-THB
5A-THF
5B-THF
THE
E
CYP19A1
E1
HSD17B
E2
CYP3A4
16OHE1
E3
CYP1A1
E1 2-OH E2
COMT
E1 2-M E2
CYP1B1
E1 4-OH E2
E1 4-M E2

aka Aromatase

Decrease 4-OH estrogen

Phase II detox support

Support 2-OH estrogen

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	coleus forskohlii	curcumin	DIM	EGCG	grape seed	licorice	quercetin	resveratrol	rooibos	rosemary
1 CYP19A1	+			−	−	−		−		
2 HSD17B	+				+	−	−			
3 CYP21A2	+	−						−	−	
4 CYP1A1			+	−				−		+
5 SULT2A1/STS						−	−			
6 5ß Reductase						−				
7 CYP1B1		−		−			−	−	−	−
8 COMT		+	+					+	+	+
9 5α Reductase				−						
10 HSD3A	+									
11 HSD11B1		−		−					−	
12 HSD3B1/2	+							−		
13 CYP11B1/2	+									
14 CYP3A4				−		−	−	−		
15 HSD11B2						−				
16 CYP17A1	+	−				−		−		

doctorsdata.com/humap

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- CardioMetabolic
- Endocrinology
- Environmental Exposure and Detoxification
- Gastrointestinal Health
- Nutritional Status
- Toxic and Essential Elements

Collection Type

URINE

Test Menu / Endocrinology / **Hormone & Urinary Metabolites Assessment Profile**

Hormone & Urinary Metabolites Assessment Profile

The Hormone and Urinary Metabolites Assessment Profile (HuMap™) provides a comprehensive overview of steroid hormones, their metabolites, and the efficiency of the enzymes that metabolize these hormones. This non-invasive test requires only 4 or 5 separate urine collections. Because the breakdown of hormones relies so heavily on processes within the liver, this test can also elucidate areas of interest as it pertains to conjugation of each metabolite. Additionally, testing urinary hormone metabolites can contribute to further understanding of endogenous hormone secretion, supplemental hormone utilization, enzyme activity, oxidative stress, and insight into how your body metabolizes hormones. Patient FAQs and Best Practices for HuMap [LEARN MORE]

Useful for:

- **Female**
- Menopausal symptoms
- Breast Health
- Endometriosis
- PCOS
- PMS/PMDD
- **Male**

Find Out More

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- Collection Instructions
- Resource Guide
- Detailed Information
- Best Practices for Specimen Collection
- Compare Endocrinology Profiles
- HuMap Clinical and Therapeutic Considerations

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QUESTIONS?