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DISCOVER ADVANCEMENTS IN HORMONE RESTORATION THERAPY

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LEARNING OBJECTIVES

PHARMACISTS

1. Review estrogen metabolism.

2. Discuss the differences in the type of information that can be obtained from saliva testing, serum testing, urine testing, and blood spot testing.

3. Evaluate how to utilize personalized medication in the treatment of complex cases, including, cases with a history of breast cancer, food allergies, and gut dybiosis.

4. Discuss methylation as it pertains to estrogen metabolism.

LEARNING OBJECTIVES

PHARMACY TECHNICIANS

1. Review endocrine physiology and hormone biochemistry.
2. Recognize the need for personalized hormone restoration therapy.
3. Evaluate different dosage forms that can best optimize patient care.

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OUTLINE

1

HORMONE TESTING

- Serum
- Saliva
- Urine
- Blood spot

2

ESTROGEN METABOLISM

- Breast cancer
- Bad estrogens
- Good estrogens
- Preventing negative estrogen burden

3

CASE ASSESSMENT

4

METHYLATION

- Methionine cycle
- Folate cycle
- BH4 cycle
- Urea cycle
- Genetic SNPs

5

CASE ASSESSMENT (Continued)

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LET'S BEGIN

HORMONE TESTING

- Serum
- Saliva
- Urine
- Blood spot

ESTROGEN METABOLISM

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CASE ASSESSMENT

METHYLATION

- Methionine cycle
- Folate cycle
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CASE ASSESSMENT (Continued)

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HORMONE TESTING

SERUM TESTING

SALIVA TESTING

URINE TESTING

BLOOD SPOT TESTING

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HORMONE TESTING

SERUM TESTING

Advantages:

- Predominant and conventional method of choice
- Well-established reference ranges
- Ideal for peptide hormones

Disadvantages:

- Limited utility for sex hormones
- Normal ranges are fairly large
- Represents a snapshot in time
- Must be performed in clinical setting
- Difficult to measure at correct times of day (logistics)

- Brambilla DJ et al. (2007). Intraindividual variation in levels of serum testosterone and other reproductive and adrenal hormones in men. *Clin Endocrinol (Oxf)*, 67, 853–862.
- Melmed, S., Polonsky, K. S., Larsen, P. R., & Kronenberg, H. M. (2015). *Williams textbook of endocrinology*. Elsevier Health Sciences.
- Plymate SR et al. (1989). Circadian variation in testosterone, sex hormone binding globulin, and calculated non-sex hormone binding globulin bound testosterone in healthy young and elderly men. *J Androl*., 10, 366–371.

HORMONE TESTING

SALIVA TESTING

Advantages:

- Easy, stress-free, convenient, and non-invasive
- Measure bioavailable unbound hormones[1,2]
- More accurate assessment of transdermal hormones[3]

Disadvantages:

- Restricted to steroid hormones; Cannot measure peptide hormones[1,2]
- Restrictions on eating, drinking, makeup use, and dental hygiene[2,4]
- Precaution needed when transdermal hormones are applied[5,6]
- Not accurate for hormones given sublingually
- Not accepted by all insurance carriers

1. Malamud, D. (2011). Saliva as a diagnostic fluid. *Dental Clinics of North America*, *55*(1), 159-178.
2. Wood, P. (2009). Salivary steroid assays–research or routine?. *Annals of clinical biochemistry*, *46*(3), 183-196.
3. Elshafie M et al. (2007). Transdermal natural progesterone cream for postmenopausal women: inconsistent data and complex pharmacokinetics. *J Obstet Gynecol.,* 27, 655–659.
4. Granger DA et al. (2003). The "trouble" with salivary testosterone. *Psychoneuroendocrinology*, 29, 1229–1240.
5. Lewis JG et al. (2002). Caution on the use of saliva measurements to monitor absorption of progesterone from transdermal creams in postmenopausal women. *Maturitas*, 41, 1–6.
6. O'Leary P et al. (2000). Salivary, but not serum or urinary levels of progesterone are elevated after topical application of progesterone cream to pre- and postmenopausal women. *Clin Endocrinol*., 53, 615–620.

URINE TESTING

Advantages:

- Non-invasive
- Good estimation of total daily production
- Most economical and reliable method for evaluating metabolites

Disadvantages:

- Uncertainty regarding completeness of collection
- Normal ranges are too wide
- More reflective of metabolites

- Kuijper, E. A. M., Houwink, E. J. F., Van Weissenbruch, M. M., Heij, H. A., Blankenstein, M. A., Huijser, J., ... & Lambalk, C. B. (2006). Urinary gonadotropin measurements in neonates: a valuable non-invasive method. *Annals of clinical biochemistry*, *43*(4), 320-322.
- Hourd, P., & Edwards, R. (1994). Current methods for the measurement of growth hormone in urine. *Clinical endocrinology*, *40*(2), 155-170.

HORMONE TESTING

BLOOD SPOT TESTING

Advantages:

- Easy, convenient, and non-invasive.
- Collection and storing protocols are simpler
- Can test a wide range of hormones

Disadvantages:

- Not common practice
- Further efforts required to ensure validity, reliability, accuracy, precision, and limits of these tests.
- Nonstandard diagnostic measure that may not be comparable to established norms for plasma and serum measures
- Small quantity limits number of analytes

- McDade, T.W., Williams, S., & Snodgrass, J.J. (2007). What a drop can do: Dried blood spots as a minimally invasive method for integrating biomarkers into population-based research. *Demography, 44,* 889–925.

NOTE OF CAUTION

Particularly in the case of hormones, reference ranges *vary greatly* from person-to-person.

Treatment protocols need to be formulated on a
PATIENT-SPECIFIC-BASIS = PERSONALIZED MEDICINE

NOTE OF CAUTION

Hormones – A moving target

- *Continually performing assessments assist in adjusting treatment protocols.*

OUTLINE

HORMONE TESTING

- Serum
- Saliva
- Urine
- Blood spot

ESTROGEN METABOLISM

- Breast cancer
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CASE ASSESSMENT

METHYLATION

- Methionine cycle
- Folate cycle
- BH4 cycle
- Urea cycle
- Genetic SNPs

CASE ASSESSMENT (Continued)

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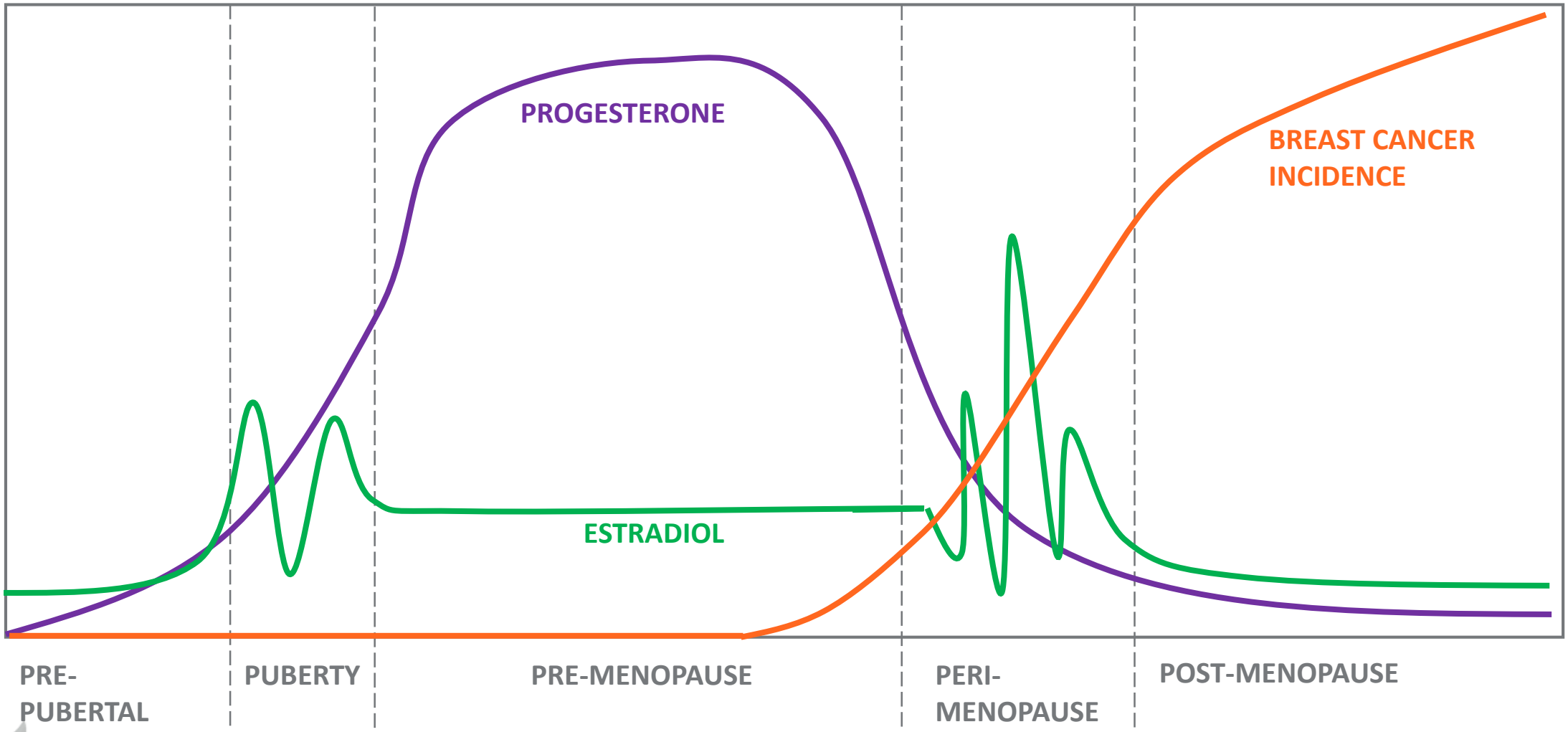
ESTROGEN METABOLISM & BREAST CANCER



ESTROGEN METABOLISM & BREAST CANCER

BREAST CANCER

- In 2014, breast cancer resulted in **40,000 deaths** among individuals in the U.S., with an estimated **232,670 new cases**[1].

- Contrary to many cancers that begin to surface after 50 years of age, breast cancer **begins to rise at 30 years**.

- Earlier onset is thought to be due to the effects of **ovarian hormone** on breast tissue[2,3].

1. Siegel, R., Ma, J., Zou, Z., & Jemal, A. (2014). Cancer statistics, 2014. *CA Cancer J Clin. 64,* 9–29.
2. Howlader, N., Noone, A.M., Krapcho, M., Garshell, J., Neyman, N., Altekruse, S.F., Kosary, C.L., Yu, M., Ruhl, J., Tatalovich, Z., Cho, H., Mariotto, A., Lewis, D.R., Chen, H.S., Feuer, E.J., & Cronin, K.A. (2013). SEER Cancer Statistics Review, 1975–2010. National Cancer Institute; Bethesda, MD.
3. Hulka, B.S. & Moorman, P.G. (2001). Breast cancer: Hormones and other risk factors. *Maturitas, 38,* 103–116.

BREAST CANCER – RISK FACTORS

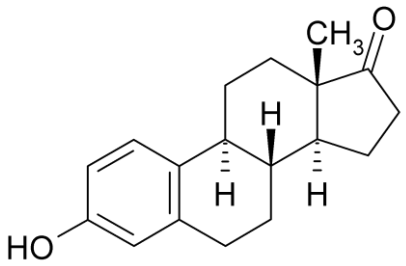
- Age
- BRCA1 and BRCA2 gene mutations
- Family history
- Reproductive history
- Radiation to chest
- High endogenous estrogen levels
- Hormone therapy
- Obesity
- Alcohol

- Samavat, H. & Kurzer, M.S. (2015). Estrogen metabolism and breast cancer. *Cancer Letters,* 356, 231-243.

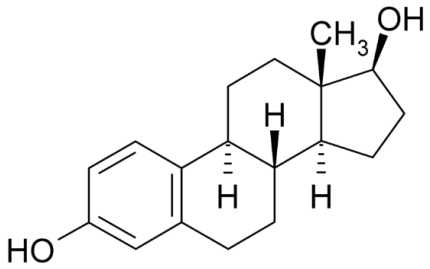
ESTROGEN METABOLISM & BREAST CANCER

ESTROGEN

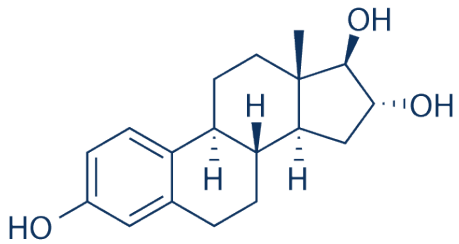
In the human body, there are 3 types of circulating endogenous estrogens:



Estrone (E1)



Estradiol (E2)



Estriol (E3)

- Samavat, H. & Kurzer, M.S. (2015). Estrogen metabolism and breast cancer. *Cancer Letters,* 356, 231-243.

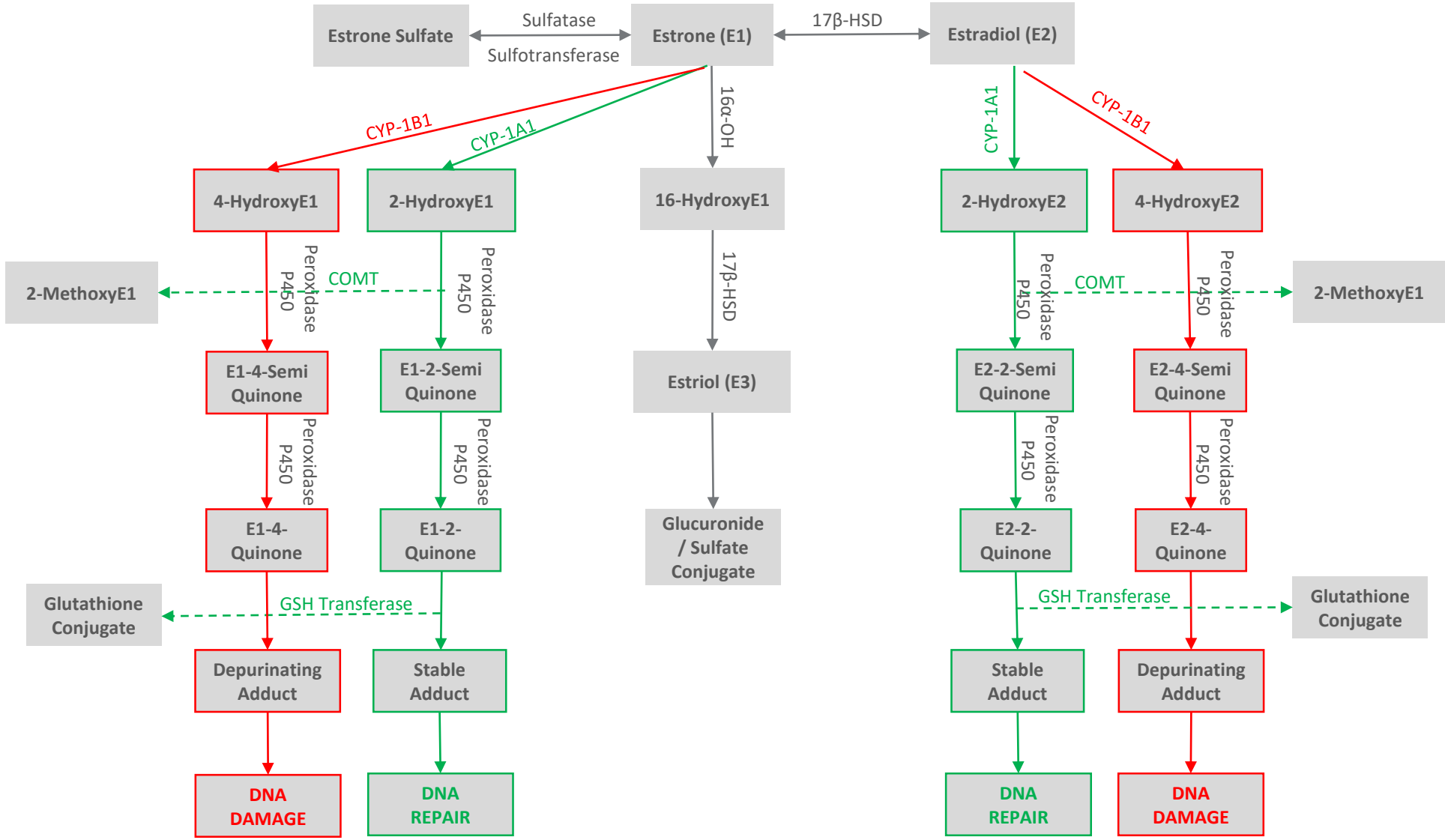
ESTROGEN METABOLISM & BREAST CANCER

ESTROGEN SYNTHESIS

Estrone (E1)	Estradiol (E2)	Estriol (E3)
Primarily synthesized from **androstenedione** by aromatase conversion in peripheral tissues. Reversibly converted into estradiol by enzyme, 17β-hydroxysteroid dehydrogenase Type II.	Primarily synthesized by **developing follicle** in the ovaries. Reversibly converted into estrone by enzyme, 17β-hydroxysteroid dehydrogenase Type I.	Synthesized from **estrone**, which can be converted from the hydroxylation of estradiol or 16-Hydroxyestrone.

- Samavat, H. & Kurzer, M.S. (2015). Estrogen metabolism and breast cancer. *Cancer Letters,* 356, 231-243.

ESTROGEN METABOLISM & BREAST CANCER



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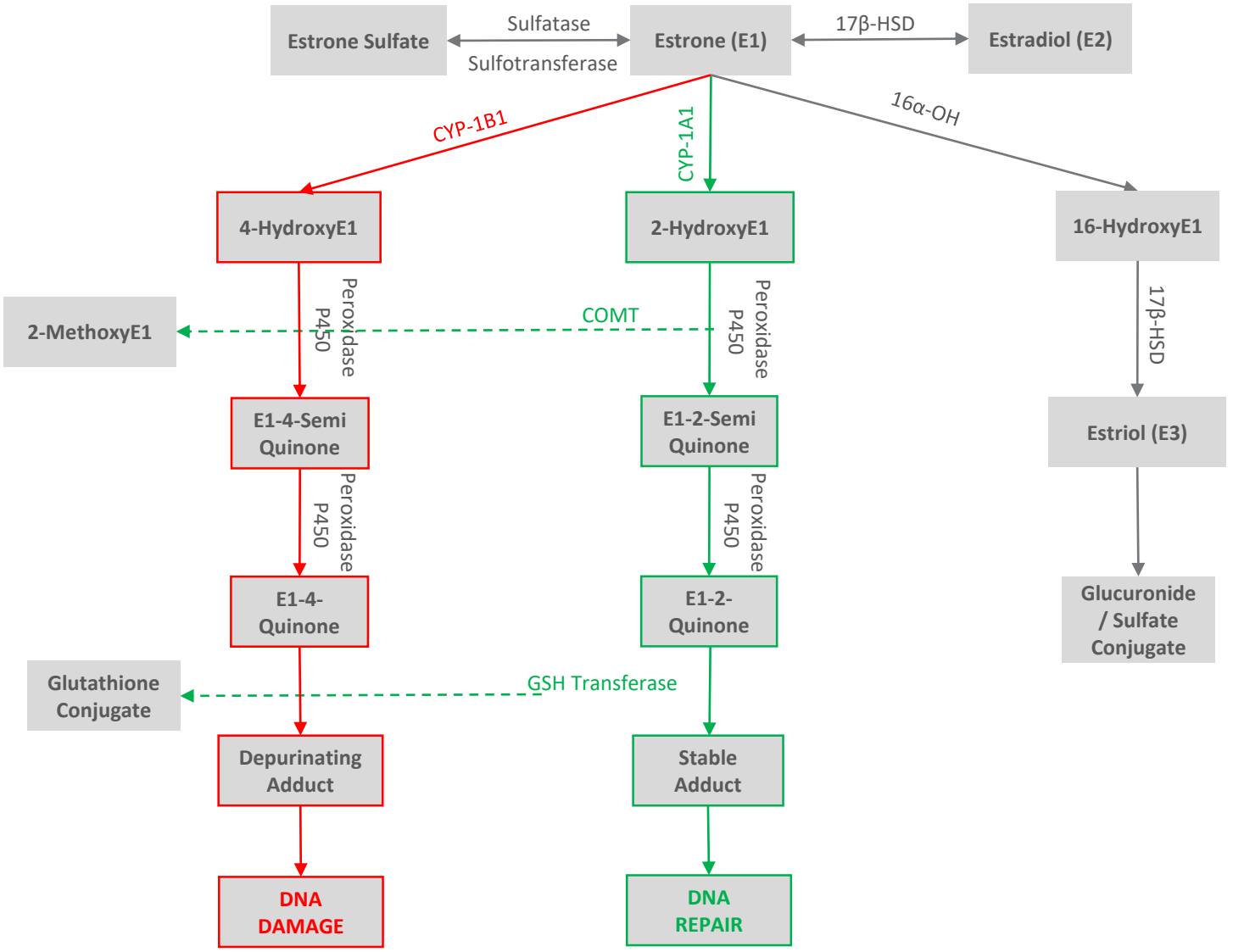
ESTROGEN METABOLISM & BREAST CANCER



ESTROGEN METABOLISM & BREAST CANCER

ESTROGEN PRIMARY FUNCTION

Estrone (E1)	Estradiol (E2)	Estriol (E3)
Predominant estrogen in **postmenopausal** women.	Predominant estrogen in **premenopausal** women. Most biologically active estrogen in women.	Predominant estrogen in **pregnant** women. Most abundant estrogen in urine.

ESTROGEN METABOLITES: THE "GOOD ESTROGENS"

2-HYDROXYESTROGENS:

- Considerable weak with overall low hormonal potency and low binding affinity to estrogen receptors[1].
- 2-hydroxyestrogen have anti-proliferative effects in breast tissue[1,2].

1. Samavat, H. & Kurzer, M.S. (2015). Estrogen metabolism and breast cancer. *Cancer Letters,* 356, 231-243.
2. Gupta, M., McDogal, A., & Safe, S. (1998). Estrogenic and antiestrogenic activities of 16alpha- and 2-hydroxy metabolites of 17 beta-estradiol in MCF-7 and T47D human breast cancer cells. *Journal of Steroid Biochemistry, 32,* 485-492.

ESTROGEN METABOLITES: THE "GOOD ESTROGENS"

METHOXYESTROGENS:

- Methoxyestrogens are deactivated forms of estrogen formed from methylation of catechol estrogens.
- This methylation conjugation prevents the biotransformation of hydroxyestrogens into quinone-DNA adducts (DNA damage) and the byproduct formation of reactive oxygen species.
- Methoxyestrogens also inhibits cell proliferation by inhibiting mitosis[1,2.3].

1. Dawling, S., Roodi, N., & Parl, F.F. (2003). Methoxyestrogens exert feedback inhibition on cytochrome P450 1A1and 1B1. *Cancer Research, 63*, 3127–3132.
2. Lakhani, N.J., Sarkar, M.A., Venitz, J., & Figg, W.D. (2003). 2-methoxyestradiol, a promising anticancer agent. *Pharmacotherapy, 23,* 165–72.
3. Lottering, M., Haag, M., & Seegers, J. (1992). Effects of 17 beta-estradiol metabolites on cell cycle events in MCF-7 cells. *Cancer Research*, *52*(21), 5926-32.

ESTROGEN METABOLITES: THE "BAD ESTROGENS"

4-HYDROXYESTROGEN QUINONE METABOLITES

- Lead to the formation of depurinating adducts[1].
- Women with or at high risk for breast cancer had high levels of adducts in their urine[2].
- In cellular preparations of adenocarcinoma, 4-hydroxyestradiol was 4x higher than 2-hydroxyestradiol[3].

1. Cavalieri, E.L., Stack, D.E., Devanesan, P.D., Todorovic, R., Dwivedy, I., Higginbotham, S., Johansson, S.L., Patil, K.D., Gross, M.L., Gooden, J.K., Ramanathan, R., Cerny, R.L., & Rogan, E.G. (1997). Molecular origin of cancer: catechol estrogen-3,4-quinones as endogenous tumor initiators. *Proc Natl Acad Sci USA, 94*, 10937–10942.
2. Cavalieri, E.L. & Rogan, E.G. (2010). Depurinating estrogen – DNA adducts in the etiology and prevention of breast and other human cancers. *Oncology, 6,* 75-91.
3. Liehr, J.G. & Ricci, M.J. (1996). 4-hydroxylation of estrogens as marker of human mammary tumors. *Proc Natl Acad Sci USA., 93,* 3294–6.

ESTROGEN METABOLITES: THE "BAD ESTROGENS"

16α-HYDROXYESTRONE

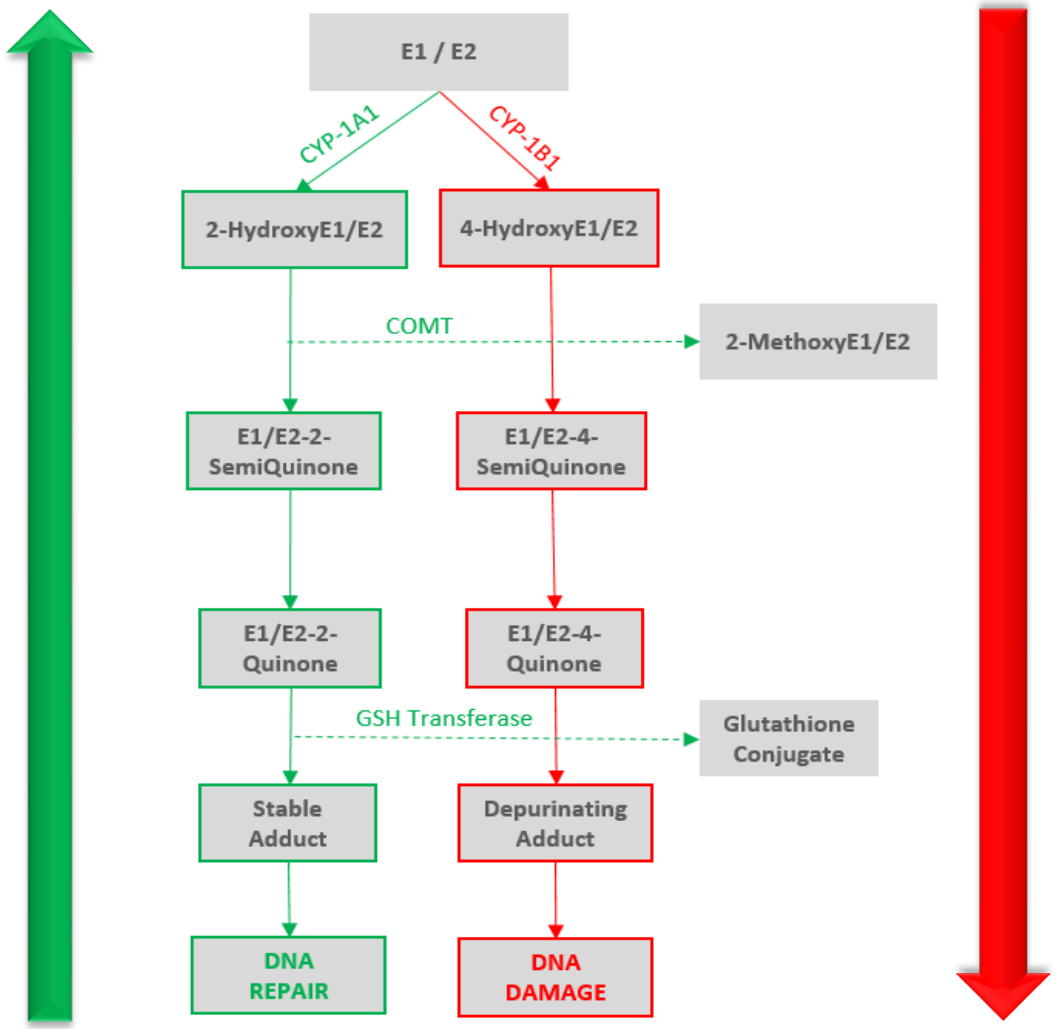
- 16α-Hydroxyestrone is the intermediate between estrone and estriol.
- Higher urinary concentrations of 16α-Hydroxyestrone were associated with mammary cell proliferation in animals[1].
- 16α-Hydroxyestrone has been found to be higher cancer breast tissue relative to normal breast tissue[2].
- 16α-Hydroxyestrone is inversely proportional to 2-hydroxyestrone.
- Recent evidence has drawn into question the significance in the 16α-Hydroxyestrone breast cancer relation[3,4].

1. Telang, N.T., Suto, A., Wong, G.Y., Osborne, M.P., & Bradlow, H.L. (1992). Induction by estrogen metabolite 16alpha-hydroxyestrone of genotoxic damage and aberrant proliferation in mouse mammary epithelial cells. *Journal of National Cancer Institute, 84*, 634–638.
2. Castagnetta, L.A.M., Granta, O.M., Traina, A., Ravazzolo, B., Amoroso, M., Miele, M., Bellavia, V., Agostara, B., & Carruba, G. (2002). Tissue content of hydroxyestrogens in relation to survival of breast cancer patients. *Clinical Cancer Research, 8,* 3146-3155
3. Obi, N., Vrieling, A., Heinz, J., & Chang-Claude, J. (2011). Estrogen metabolite ratio: Is the 2-hydroxyestrone to 16alpha-hydroxyestrone ratio predictive for breast cancer? *Internation Journal on Womens Health 3,* 37-51.
4. Huang, J., Sun, J., Chen, Y., Song, Y., Dong, L., Zhan, Q., Shang, R., & Abliz, Z. (2012). Analysis of multiplex endogenous estrogen metabolites in human urine using ultra-fast liquid chromatography-tandem mass spectrometry: A case study for breast cancer. *Analytica Chimica Acta, 711,* 60-68.

ESTROGEN METABOLISM & BREAST CANCER

PREVENTING NEGATIVE ESTROGEN BURDEN

Increase
2-HydroxyE
Pathway Activity



Reduce
4-HydroxyE
Pathway Activity

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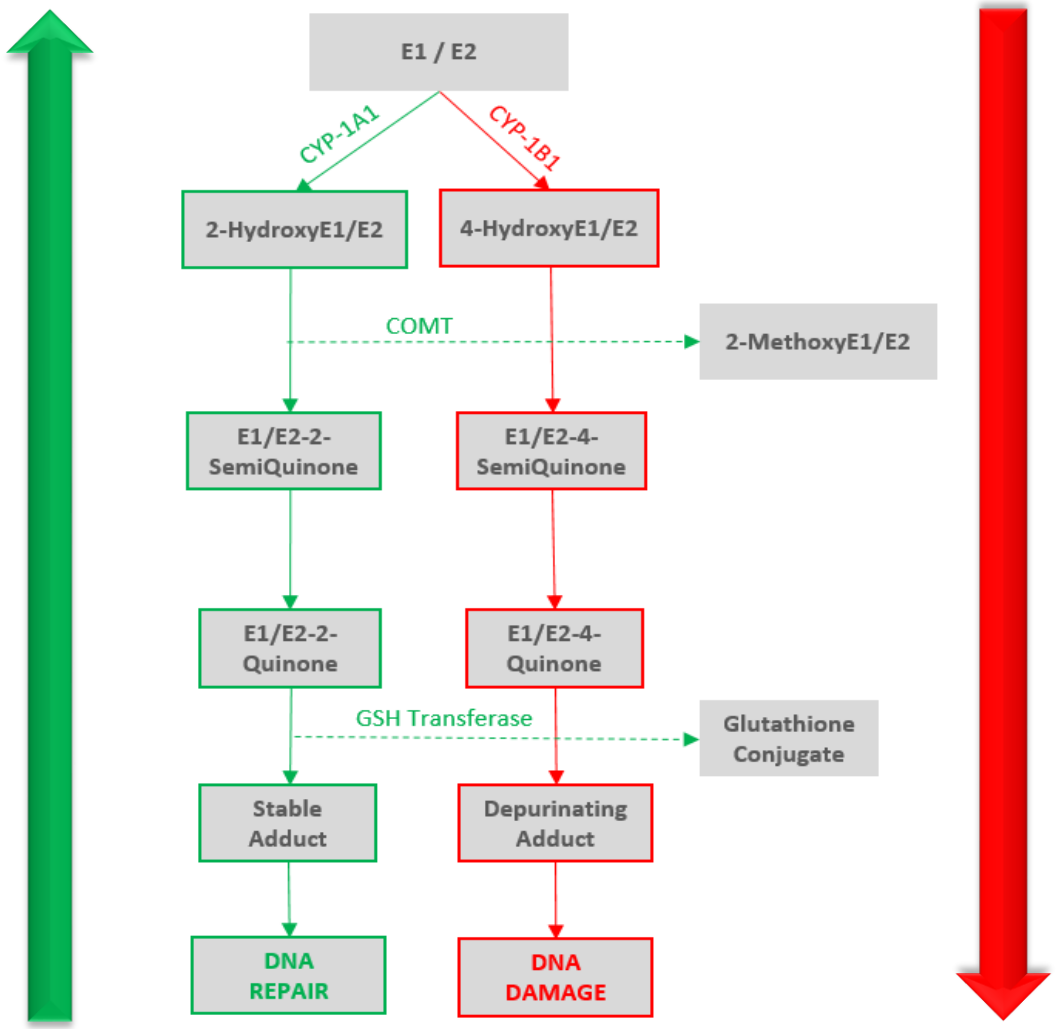
ESTROGEN METABOLISM & BREAST CANCER

PREVENTING NEGATIVE ESTROGEN BURDEN

- Increase CYP 1A1
- Increase COMT
- Increase quinone reductase
- Increase glutathione conjugation



- Reduce CYP-1B1
- Reduce Peroxidase
- Decrease β-glucuronidase activity

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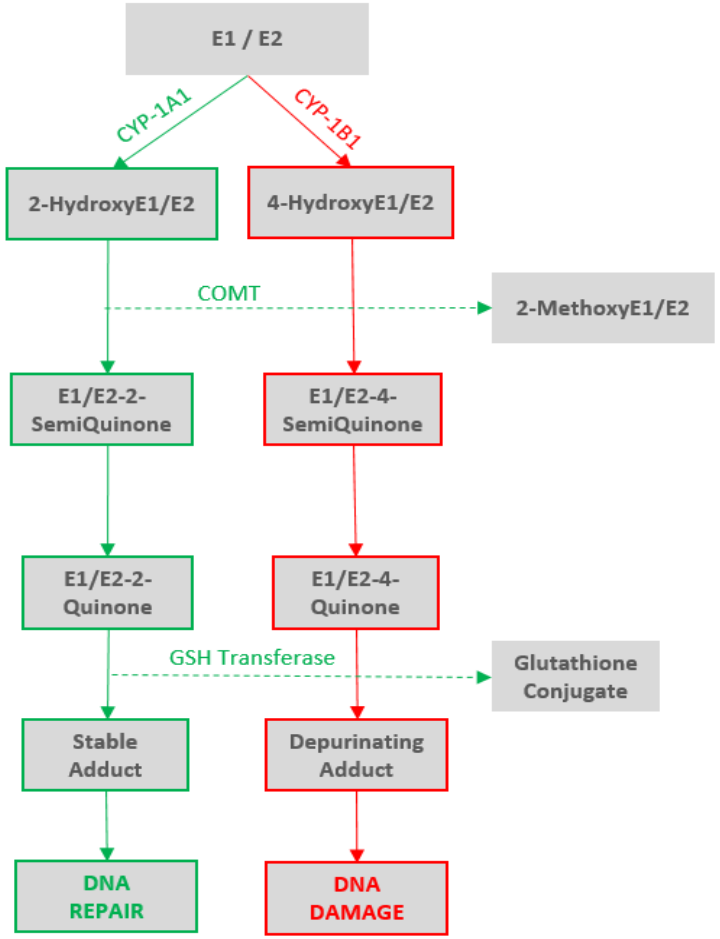
ESTROGEN METABOLISM & BREAST CANCER

PREVENTING NEGATIVE ESTROGEN BURDEN

INSECTICIDES (e.g., endosulfan) has been found to inhibit the expression of CYP-1A1, resulting in reduced activity of the 2-hydroxyE pathway[1].



1. Coumoul, X., Diry, M., Robillot, C., & Barouki, R. (2001). Differential regulation of cytochrome P450 1A1 and 1B1 by a combination of dioxin and pesticides in the breast tumor cell line MCF-7. *Cancer Research, 61,* 3942-3948.

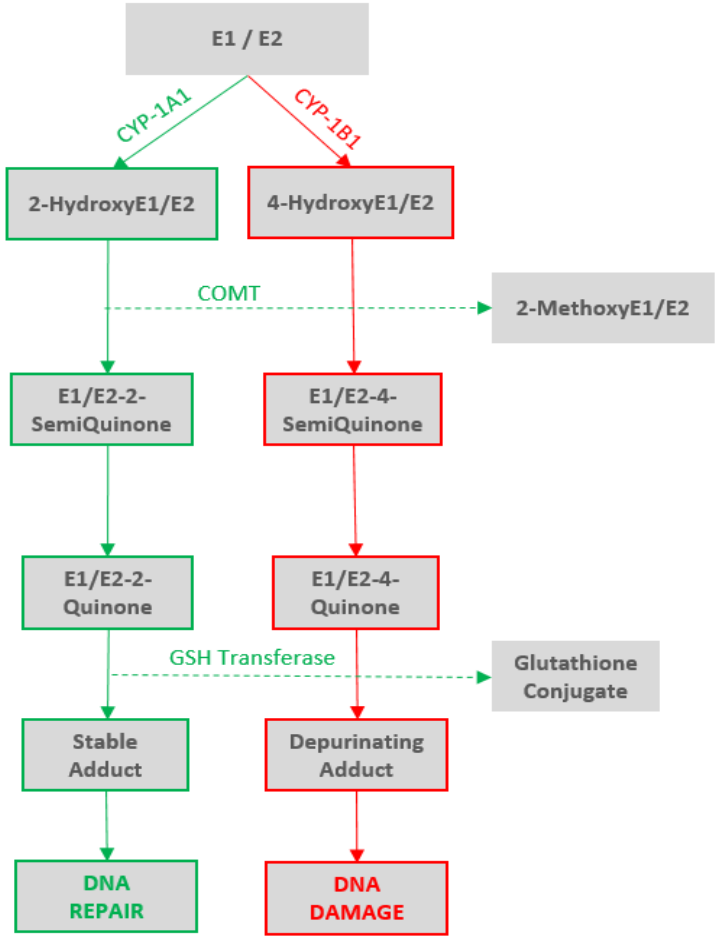
ESTROGEN METABOLISM & BREAST CANCER

PREVENTING NEGATIVE ESTROGEN BURDEN

RESVERATROL prevents the formation of depurinating estrogen DNA adducts in human breast cells treated with E[1].

Resveratrol inhibits peroxidase activity, reducing the formation of catechol estrogen quinones[1].

Resveratrol also increases NDPH quinone reductase activity[2].



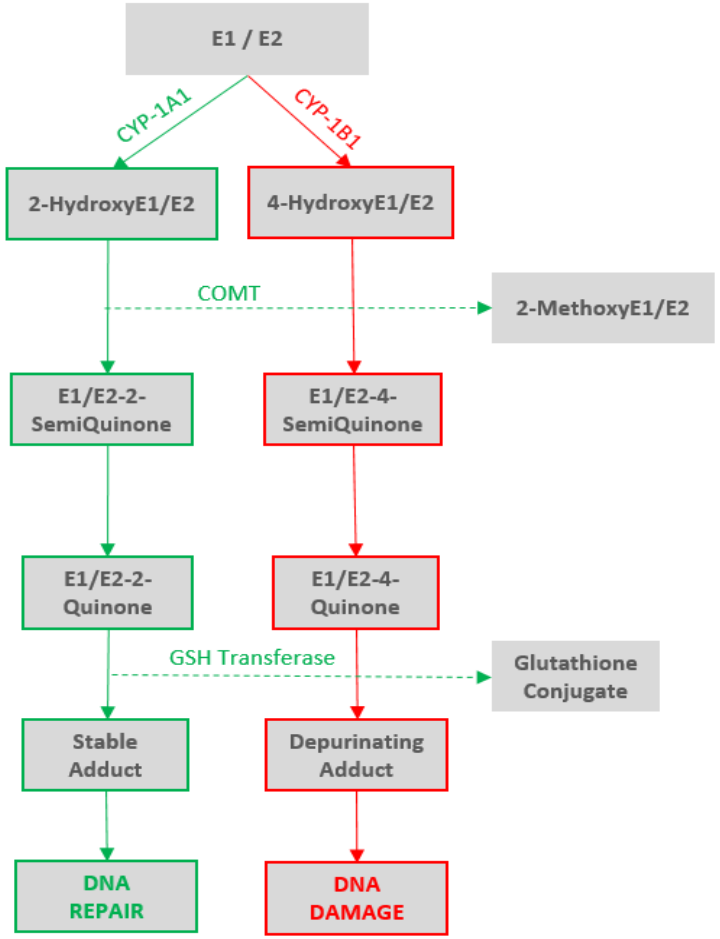
1. Cavalieri, E.L. & Rogan, E.G. (2010). Depurinating estrogen – DNA adducts in the etiology and prevention of breast and other human cancers. *Oncology, 6,* 75-91.
2. Zahid, M., Gaikwad, N.W., Ali, M.F., Lu, F., Saeed, M., Yang, L., Rogan, E.G., & Cavalieri, E.L. (2008). Prevention of estrogen-DNA adduct formation in MCF-10F cells by resveratrol. *Free Radical Biology Medicine, 45,* 136-145.

ESTROGEN METABOLISM & BREAST CANCER

PREVENTING NEGATIVE ESTROGEN BURDEN

N-ACETYLCYSTEINE prevents electrophilic damage to DNA by inhibiting the formation electrophilic quinones.

It has been found that the consumption of N-acetylcysteine for a 1-month period resulted in 55% reduction in urinary levels of estrogen DNA adducts[1].



1. Cavalieri, E.L. & Rogan, E.G. (2010). Depurinating estrogen – DNA adducts in the etiology and prevention of breast and other human cancers. *Oncology, 6,* 75-91.
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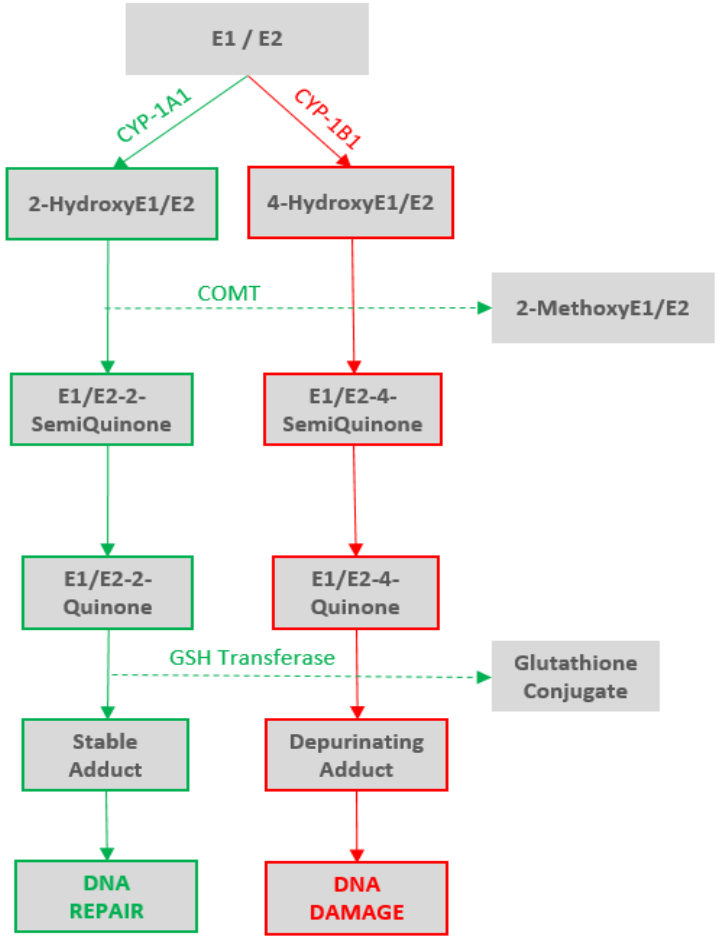
ESTROGEN METABOLISM & BREAST CANCER

PREVENTING NEGATIVE ESTROGEN BURDEN

IODINE plays a critical role in the maintenance and functioning of mammary gland tissue.

There exists high rates of breast cancer among women with thyroid abnormalities[1,2].

Women with breast cancer tend to have larger thyroid volumes than controls, indicating an association between iodine deficiency and breast cancer[1,2].



1. Smyth, P.P.A., Smith, D.F., McDermott, E.W., Murray, M.J., Geraghty, J.G., & O'Higgins, N.J. (1996). A direct relationship between thyroid enlargement and breast cancer. *Journal of Clinical Endocironology and Metabolism, 81,* 937-941.
2. Vassilopoulou-Sellin, R., Palmer, L., Taylor, S., & Cooksley, C.S. (1999). Incidence of breast carcinoma in women with thyroid carcinoma. *Cancer, 85,* 696-705.

ESTROGEN METABOLISM & BREAST CANCER

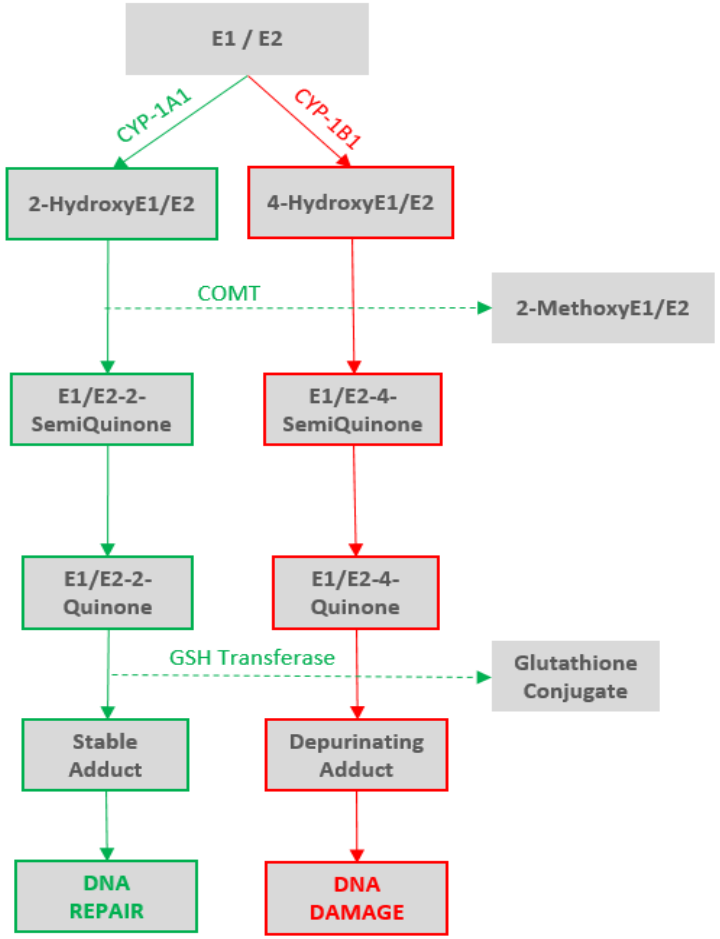
PREVENTING NEGATIVE ESTROGEN BURDEN

IODINE supplementation is effective at diminishing ductal hyperplasia in rats[1].

Patients with benign breast disease that received iodine treatment experienced significant bilateral breast reduction[2].

Japanese communities that consume high amounts of seaweed (high [I]) have reported lower incidences of benign and malignant tissue[3].

Iodine is thought to exhibit its beneficial effects by modulating estrogen metabolism[4,5].



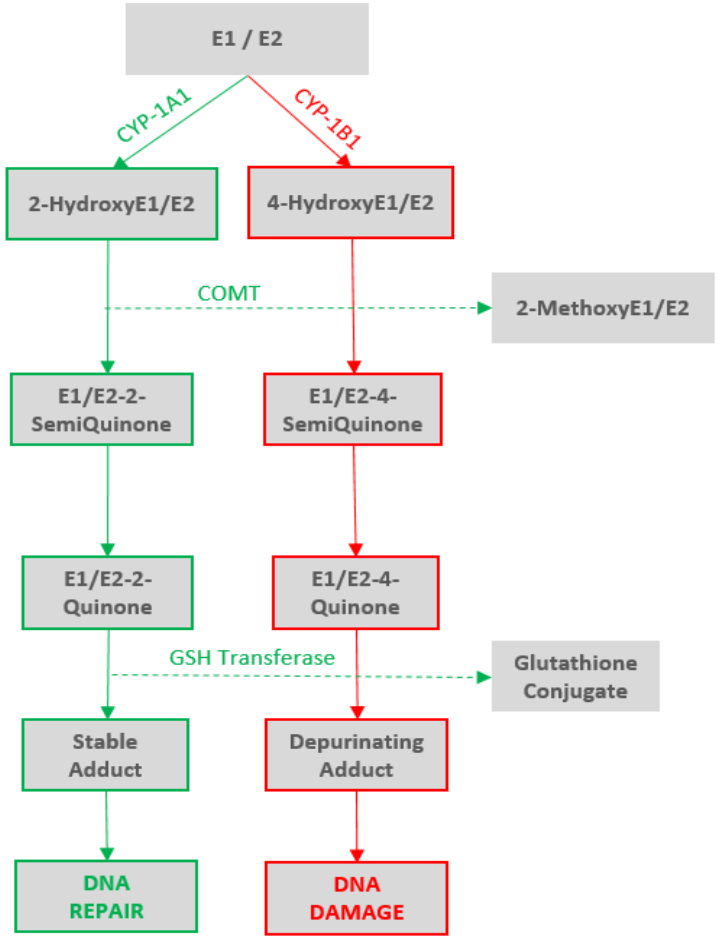
1. Eskin, B.A., Grotkowski, C.E., Connolly, C.P., & Ghent, W.R. (1995). Different tissue responses for iodine and iodide in rat thyroid and mammary gland. *Biological Trace Element Responses, 49,* 9-18.
2. Ghent, W.R., Eskin, B.A., Low, D.A., & Hill, L.P. (1993). Iodine replacement in fibrocystic disease of the breast. *Cancer Journal of Surgery, 36,* 453-460.
3. Cann, S.A., van Netten, J.P., & van Netten, C. (2000). Hypothesis: Iodine, selenium and the development of breast cancer. *Cancer causes Control, 11,* 121-127
4. Smyth, P.P.A. (2003). Role of iodine in antioxidant defence in thyroid and breast disease. *Biofactors, 12,* 121-130.
5. Stoddard II, F.R., Brooks, A.D., Eskin, B.A., & Johannes, G.J. (2008). Iodine alters gene expression in the MCF7 breast cancer cell line: Evidence for anti-estrogen effect of iodine. *International Journal of Medical Science, 5,* 189-196.

ESTROGEN METABOLISM & BREAST CANCER

PREVENTING NEGATIVE ESTROGEN BURDEN

BIFIDOBACTERIUM significantly decreases glucuronidase activity[1].

CALCIUM-D-GLUCARATE is a potent beta-glucuronidase inhibitor that has been shown to exert anticarcinogenic effects[1].



1. Bouhnik, Y., Flourie, B., Andrieux, C., Bisetti, N., Briet, F., & Rambaud, J.C. (1996). Effects of bifidobacterium sp fermented milk ingested with or without inulin on colonic bifidobacteria and enzymatic activities in healthy humans. *European Journal of Clinical Nutrition, 50,* 269-273.
2. Walaszek, Z., Szemraj, J., Narog, M., Adams, A.K., Kilgore, J., Sherman, U., & Hanausek, M. (1997). Metabolism, uptake, and excretion of a D-glucaric acid salt and its potential use in cancer prevention. *Cancer Detection and Prevention, 21,* 178-190.

OUTLINE

HORMONE TESTING

- Serum
- Saliva
- Urine
- Blood spot

ESTROGEN METABOLISM

- Breast cancer
- Bad estrogens
- Good estrogens
- Preventing negative estrogen burden

CASE ASSESSMENT

METHYLATION

- Methionine cycle
- Folate cycle
- BH4 cycle
- Urea cycle
- Genetic SNPs

CASE ASSESSMENT (Continued)

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CASE DESCRIPTION – DECEMBER 2014

Cecilia is a new patient that presents to you for hormone evaluation after recently being diagnosed with **breast cancer**. She is married and has no children (by choice). Cecilia wants to have her hormones checked due to the **estrogen receptor positive tumor** she is diagnosed with (ER 95%; PR 95%; HER2 Negative). She had BRAC testing, which was negative. Cecilia's primary complaints are **fatigue**, **sleep disturbances**, and **headaches** the day before her periods (periods are otherwise normal). Below is a summary of her lab results from a prior practitioner.

- Urinary heavy metals = Negative
- Food allergies = Wheat and Casein IgG was high
- Hemoglobin A1c = 5.1
- TSH = 1.65 (normal)
- Free T4 = 1.3
- Free T3 = 2.7
- Antinuclear antibody (ANA) = 1.1 (negative)

CASE ASSESSMENT

PATIENT EVALUATION

PATIENT VITALS:

- Height: 5’ 4”
- Weight 139.4 lbs
- BP: 129/86 mmHg
- RR: 16

PATIENT MEDICAL HISTORY:

- Gastrointestinal issues, breast cancer (recently diagnosed)

FAMILY MEDICAL HISTORY:

- Atrial fibrillation, Coronary Artery Disease (CAD), High Cholesterol, Arthritis, Kidney Stones

PRIOR INTERVENTIONS:

- Loop Electrosurgical Excision Procedure (LEEP), Lumpectomy

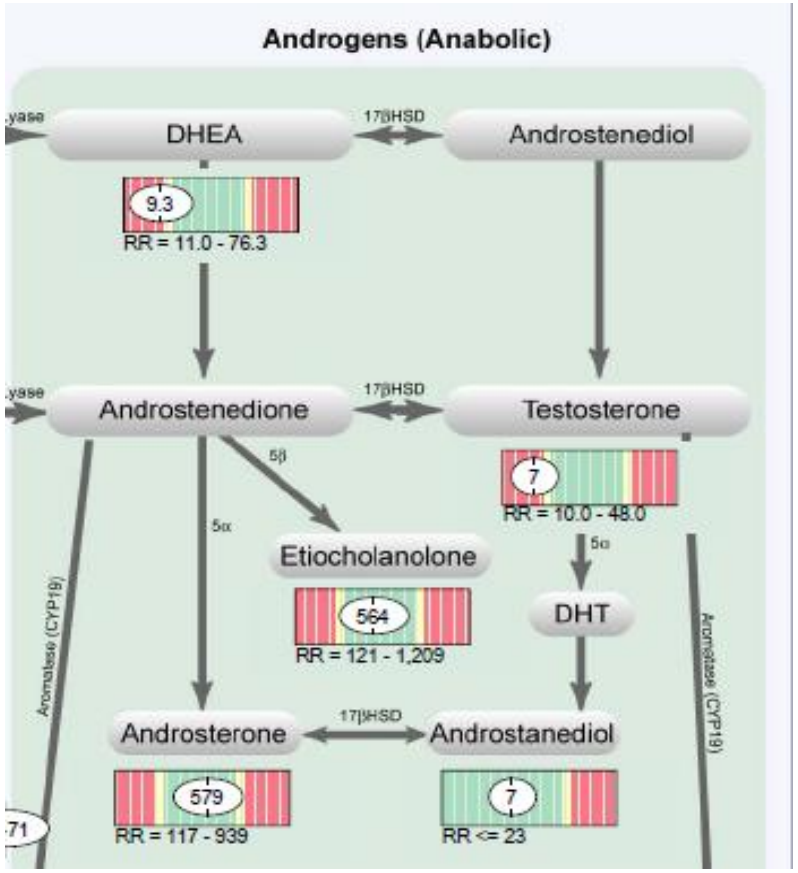
CURRENT MEDICATIONS:

- Vitamin D 5000 IU, Bone Supplement, Probiotic

CASE ASSESSMENT

URINARY HORMONE RESULTS

ANDROGENS (17-Ketosteroids)	
DHEA	9.3
Androsterone	579
Etiocholanolone	564
11-Keto-androsterone	13
11-Keto-etiocholanolone	78
11-Hydroxy-androsterone	137
11-Hydroxy-etiocholanolone	54
17-Ketosteroids, Total*	1,434
Testosterone	7
Androstanediol	7



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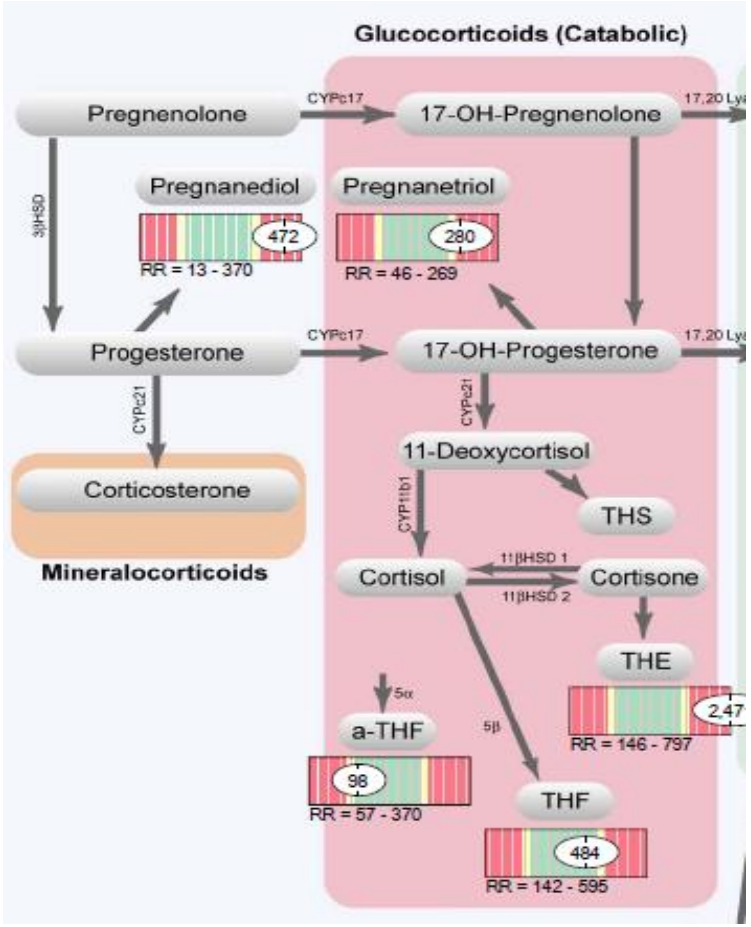
CASE ASSESSMENT

URINARY HORMONE RESULTS

GLUCOCORTICOIDS (17-Hydroxysteroids)	
Pregnanetriol (FMV urine)	280
Allo-Tetrahydrocortisol, a-THF (FMV urine)	98
Tetrahydrodeoxycortisol (THS) (FMV urine)	19.1
Tetrahydrocortisone (THE) (FMV urine)	2,471
Tetrahydrocortisol (THF) (FMV urine)	484
17-Hydroxysteroids, Total*	3,352



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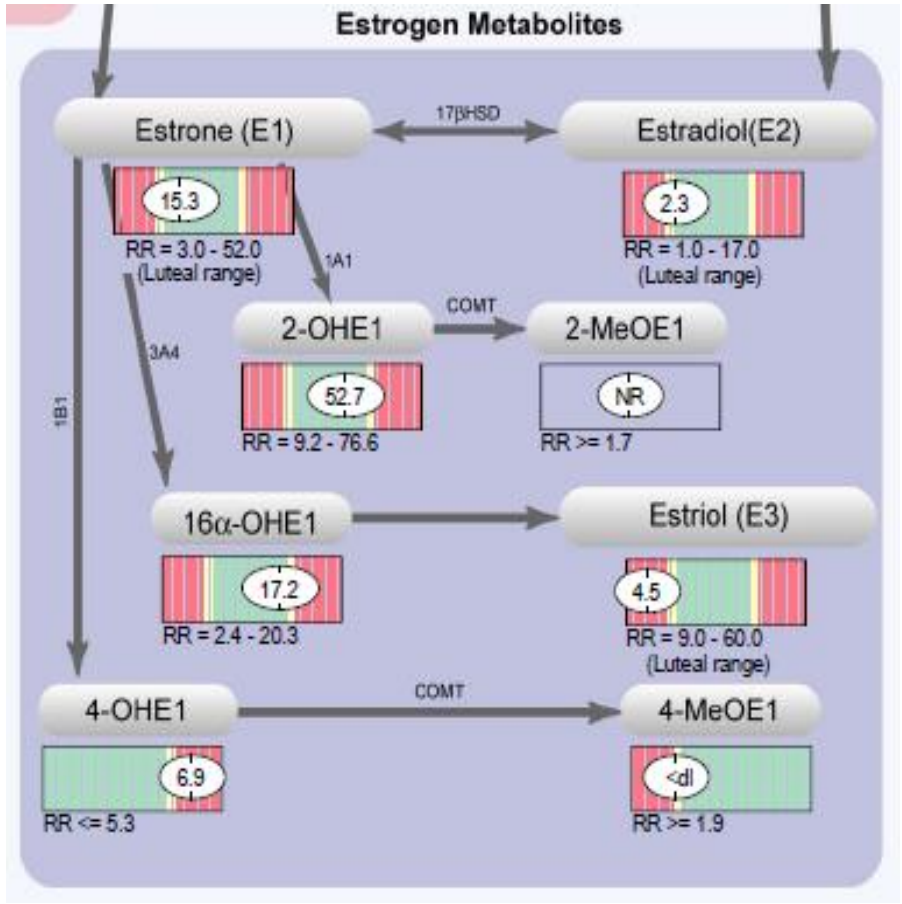
CASE ASSESSMENT

URINARY HORMONE RESULTS

ESTROGENS	
Estrone (E1)	
- Postmenopausal	15.3
Estradiol (E2)	
- Postmenopausal	2.3
Estriol (E3)	
- Postmenopausal	4.5
ESTROGEN METABOLITES	
2-Hydroxyestrone	52.7
16α-Hydroxyestrone	17.2
4-Hydroxyestrone	6.9
2-Methoxyestrone	NR
4-Methoxyestrone	<dl



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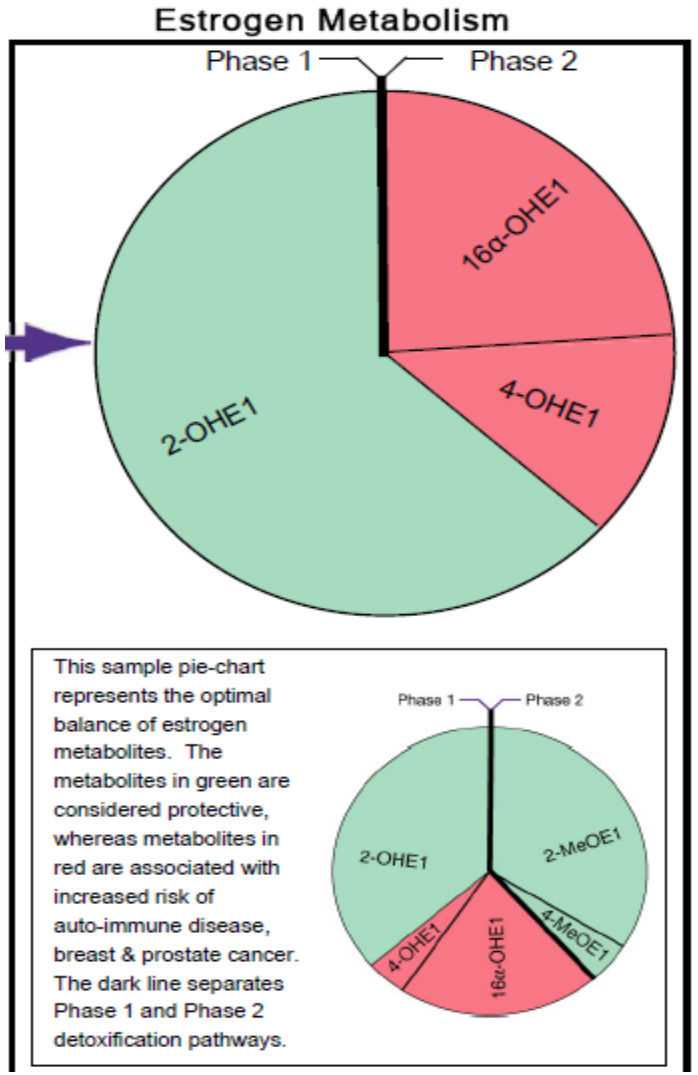
CASE ASSESSMENT

URINARY HORMONE RESULTS

RATIOS			
Anabolic (17-Ketosteroids)/ **Catabolic** (17-Hydroxysteroids) Balance	0.43 Catabolic	Anabolic	
Anabolic (17-Ketosteroids)		1,434	
Catabolic (17-Hydroxysteroids)			3,352
11β-HSD Index ((α-THF+THF)/THE)	0.24 Less cortisol		More cortisol
5α-Reductase Activity (Etiocholanolone/Androsterone)	More 5α-Reductase	0.97	Less 5α-Reductase
Estrogen Metabolism (2-Hydroxyestrone/16α-Hydroxyestrone)	16α-OHE1 (higher risk of breast cancer)	3.1	OHE1 wer risk of breast cancer)
Methylation Activity (2-Methoxyestrone/2-Hydroxyestrone)	Less Methylation		More Methylation



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DIAGNOSIS & THERAPEUTIC PLAN

Diagnosis?

- Low Androgens, Low Cortisol, Estrogen Metabolism Issue, Hypothyroid, Premenstrual Syndrome, Breast Cancer (ER Positive Tumor)

Pharmaceutical Therapy?

- Tamoxifen

Nutraceutical Therapy?

- Resveratrol, Alpha-Lipoic Acid, Adrenal Support

OUTLINE

HORMONE TESTING

- Serum
- Saliva
- Urine
- Blood spot

ESTROGEN METABOLISM

- Breast cancer
- Bad estrogens
- Good estrogens
- Preventing negative estrogen burden

CASE ASSESSMENT

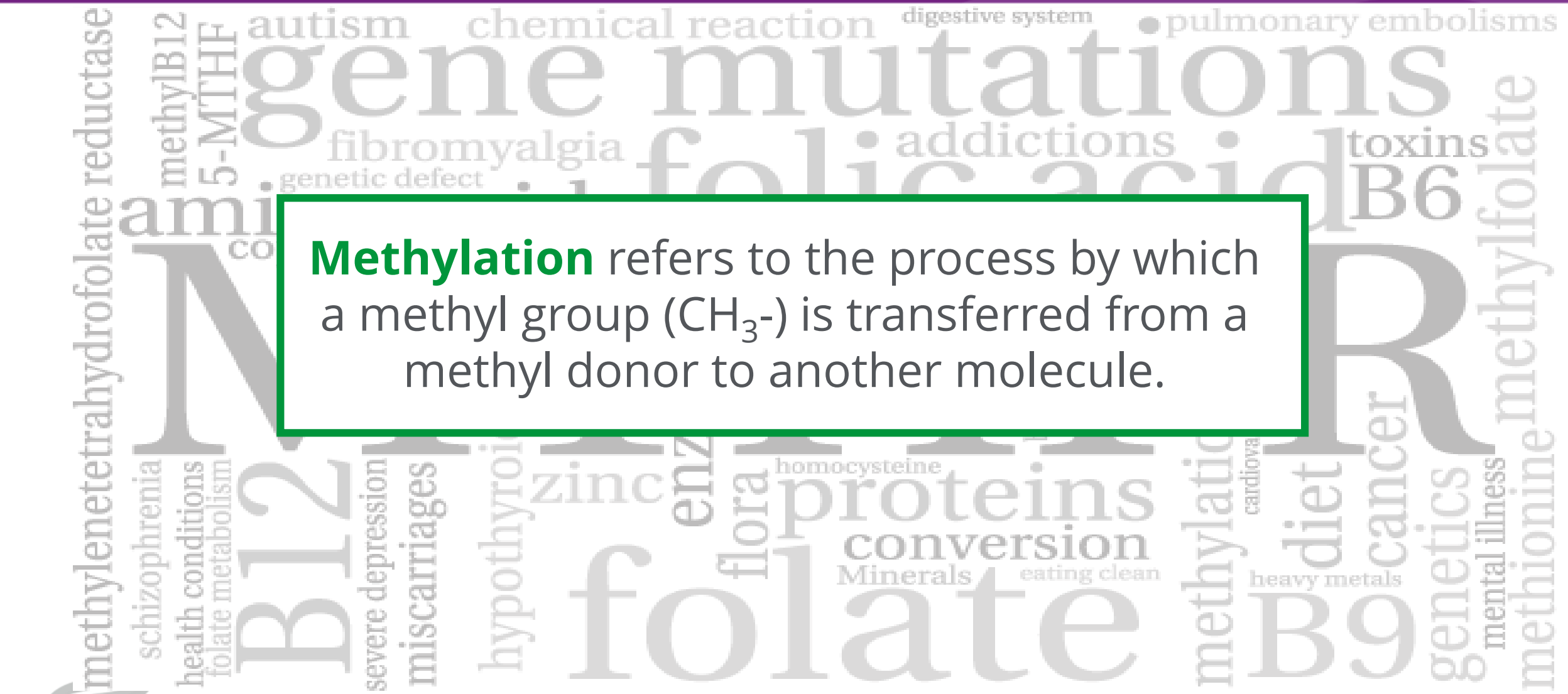
METHYLATION

- Methionine cycle
- Folate cycle
- BH4 cycle
- Urea cycle
- Genetic SNPs

CASE ASSESSMENT (Continued)

WCC 2018

METHYLATION



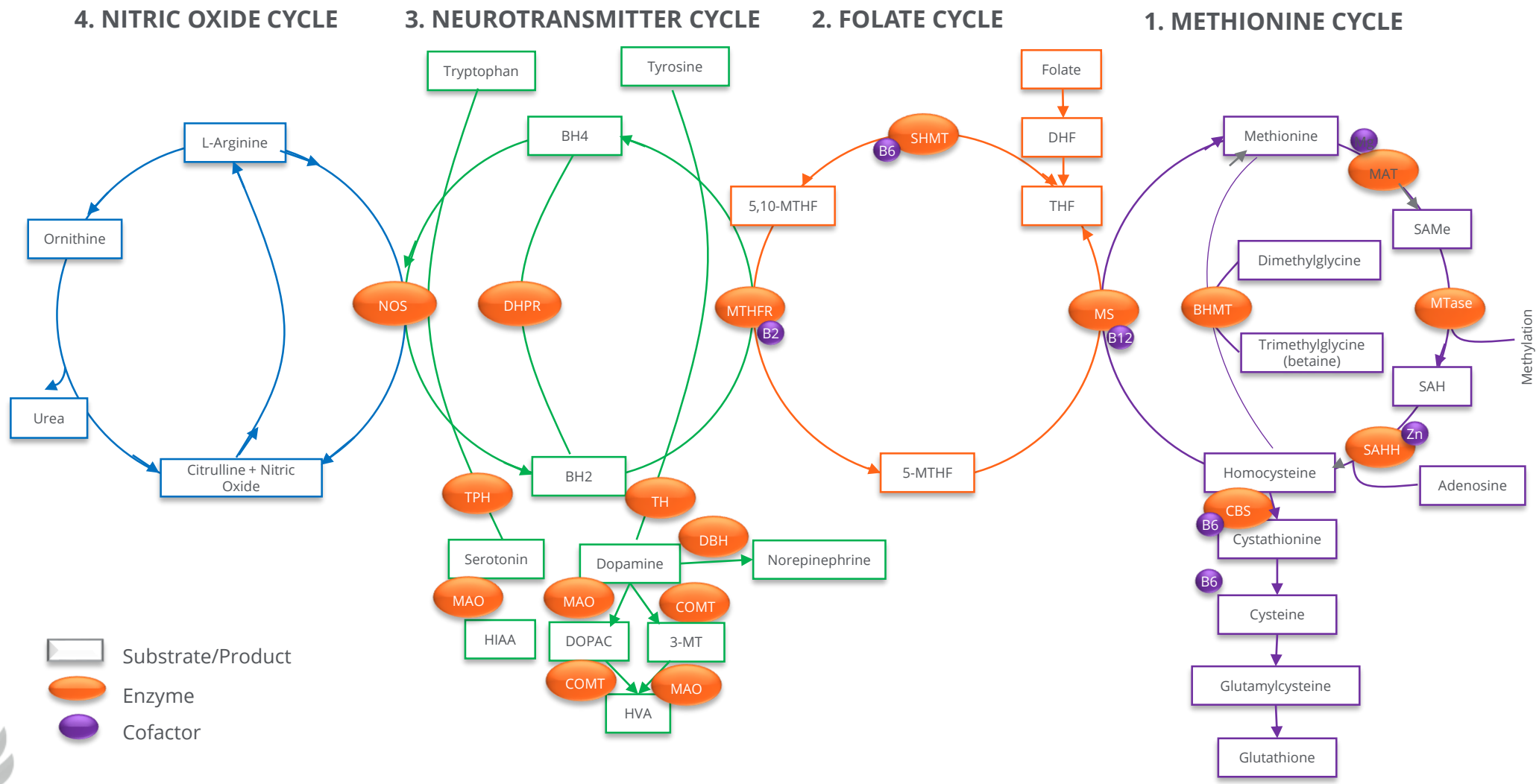
Methylation refers to the process by which a methyl group (CH_3-) is transferred from a methyl donor to another molecule.

METHYLATION

Methylation is involved in a number of essential biological processes:

- Detoxification
- Epigenetic Modification
- Neurotransmitter Synthesis
- Pyrimidine and Purine Synthesis

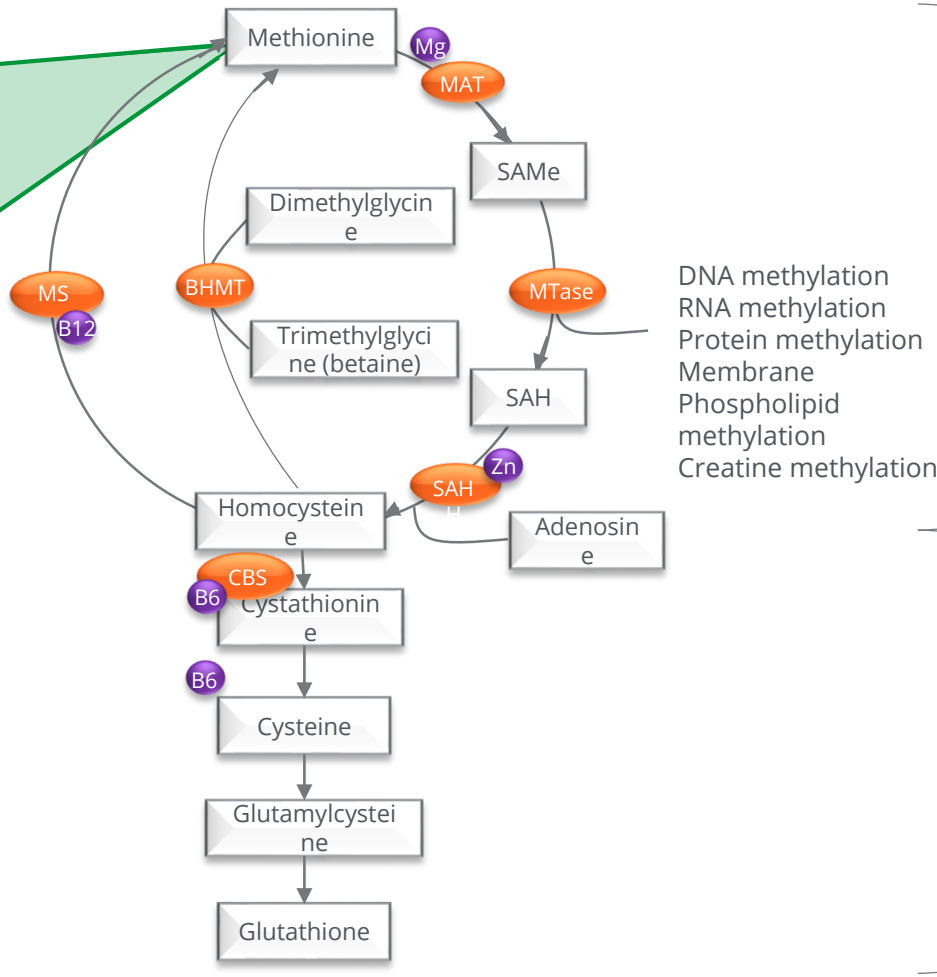
METHYLATION



METHYLATION

1. METHIONINE CYCLE

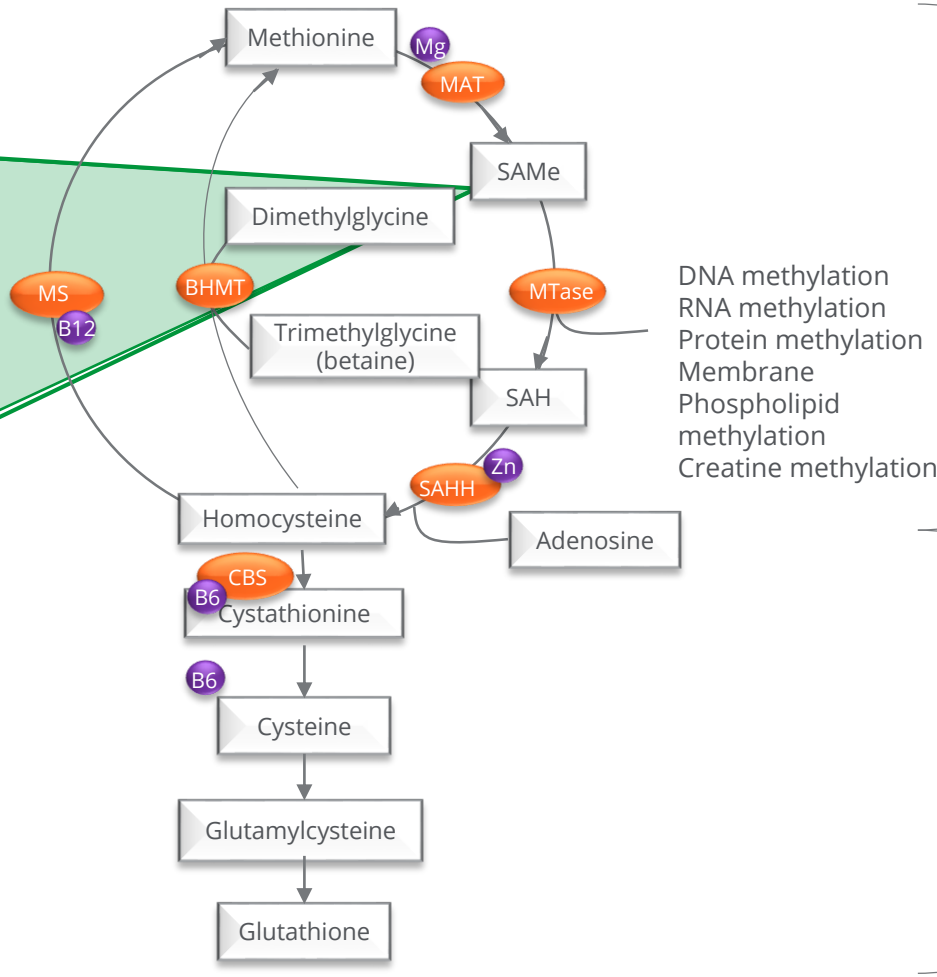
Methionine is an essential amino acid present in meat, eggs, and animal milk. Methionine is readily converted into s-adenosylmethionine (SAMe).



METHYLATION

1. METHIONINE CYCLE

SAMe is considered a universal methyl donor. It is the primary source of methyl groups for methylation of DNA, RNA, proteins, membranes, and creatine.

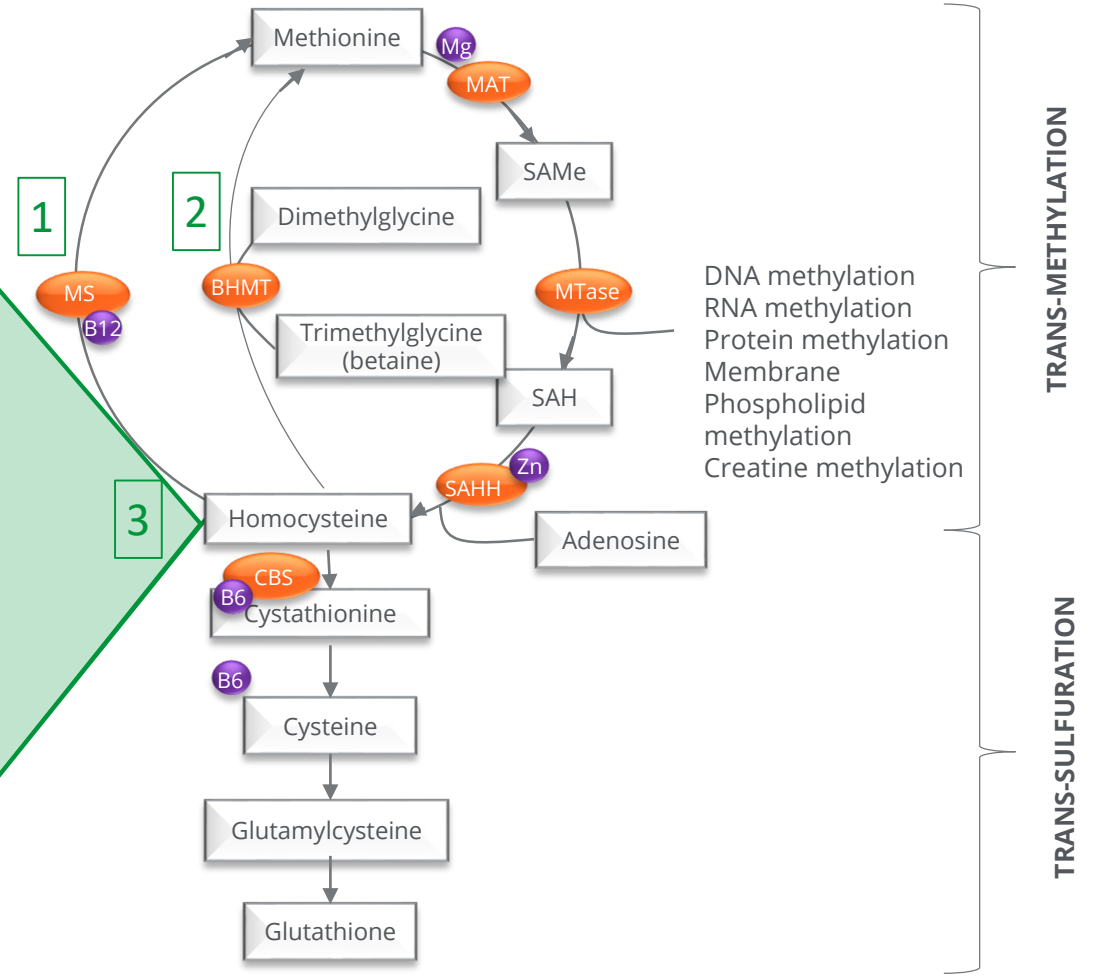


METHYLATION

1. METHIONINE CYCLE

Homocysteine is a critical component in the methionine cycle because it can be recycled in 3 different ways:

1. Transmethylation back into methionine via methionine synthase (MS) and Vit B12
2. Transmethylation back into methionine via betaine-homocysteine methyltransferase (BHMT)
3. Transulfuration into glutathione vie cystathionine beta synthase (CBS) and Vit B6



METHYLATION

1. METHIONINE CYCLE

High plasma levels of homocysteine, **hyperhomocysteinemia**, is associated with higher risk for[1,2]:

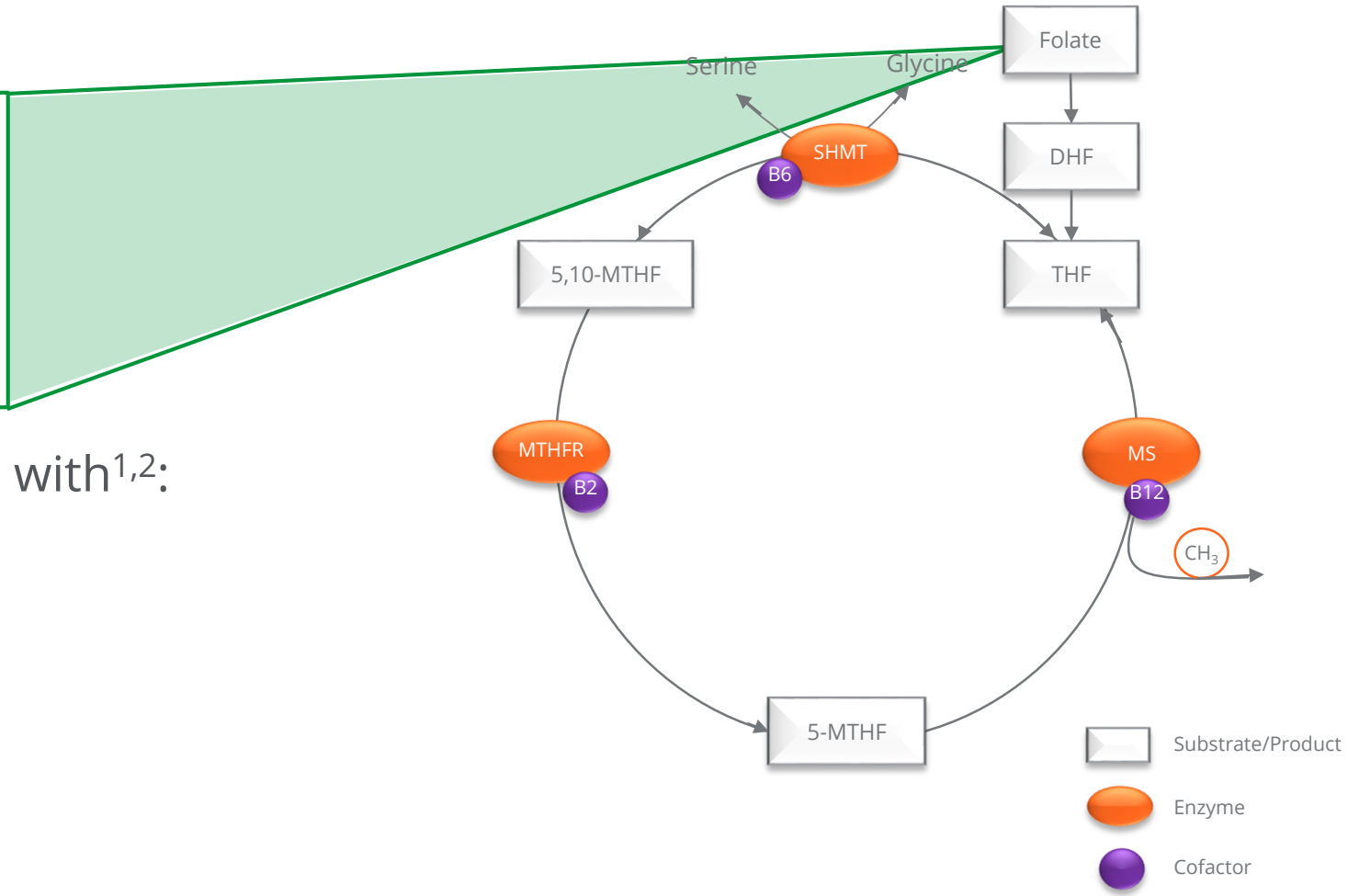
- Neural tube defects in offspring
- Depression
- Myocardial infarctions
- Cerebrovascular disease
- Peripheral vascular disease

Elevations in homocysteine levels are related, at least in part, to deficiencies in folate, vitamin B12, vitamin B6, and vitamin B2[1,3].

METHYLATION

2. FOLATE CYCLE

Folate is an essential water-soluble vitamin (Vit B9) found in dark green vegetables, legumes, beans, liver, citrus, fruit, and yeast.



Low folate levels are associated with[1,2]:

- Cardiovascular disease
- Cancers
- Neural tube defects
- Depression

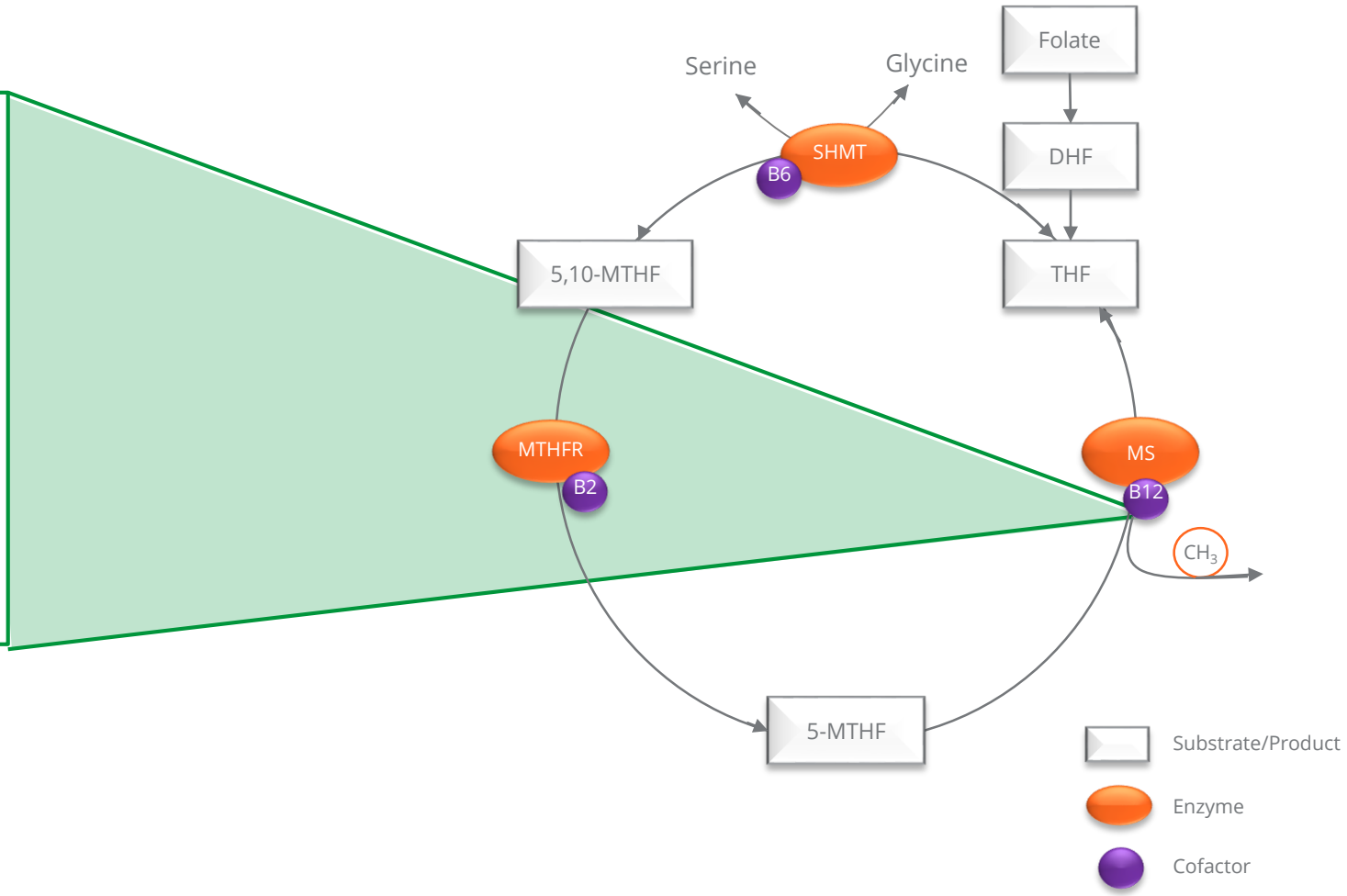
1. Crider, K.S., Yang, T.P., Berry, R.J., & Bailey, L.B. (2012). Folate and DNA methylation: A review of molecular mechanisms and the evidence for folate's role. *Advances in Nutrition: An International Review Journal, 3,* 21-28.
2. Miller, A.L. (2008). The methylation, neurotransmitter, and antioxidant connections between folate and depression. *Alternative Medicine Review, 13,* 216-226.

METHYLATION

2. FOLATE CYCLE

Vitamin B12 is a necessary and required cofactor for methionine synthase (MS).

In a large Canadian Health Measure Survey assessing 6000 people, there was a near 5-fold increase in persons deficient in B12 relative to folate[1].



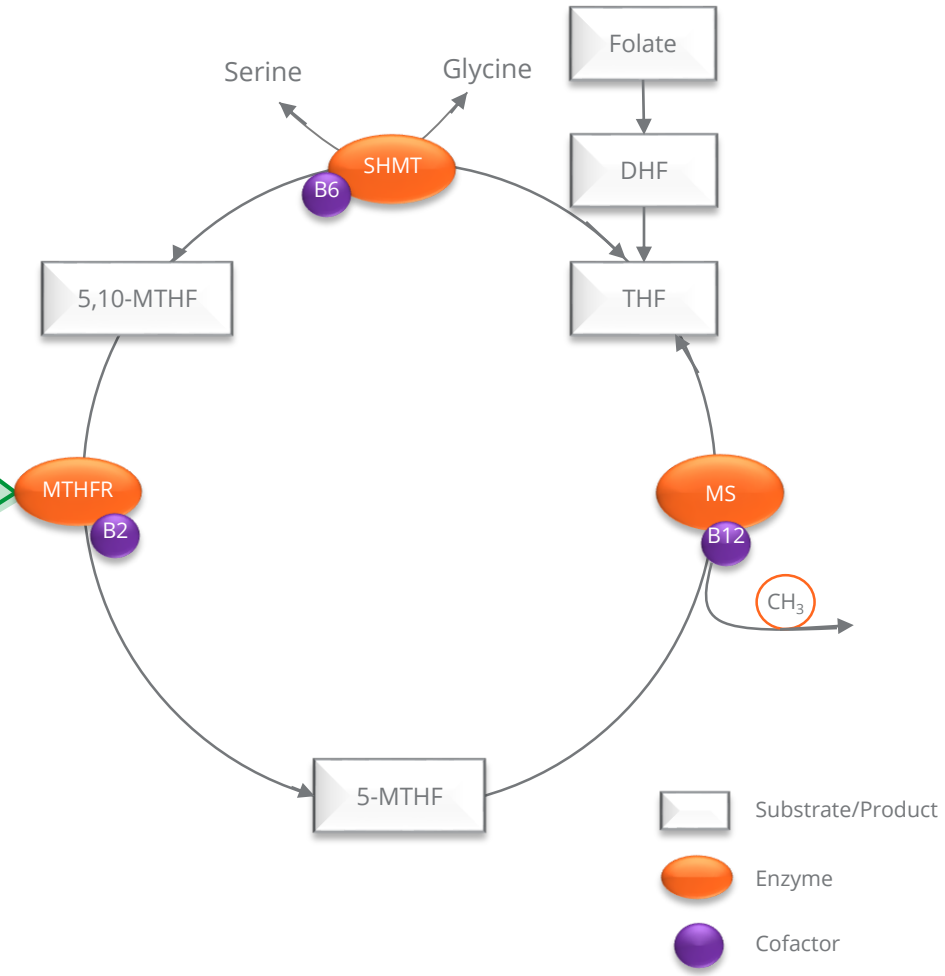
1. Glier, M., Green, T., & Devlin, A. (2013). Methyl nutrients, DNA methylation, and cardiovascular disease. *Molecular Nutrition & Food Research*, *58*(1), 172-182. doi: 10.1002/mnfr.201200636

METHYLATION

2. FOLATE CYCLE

Methylene-Tetrahydrofolate Reductase (MTHFR) is responsible for synthesizing folate's active metabolite, 5-methyltetrahydrofolate (5-MTHF).

5-MTHF acts as the methyl donor for remethylation of homocysteine. 5-MTHF can freely enter cells.



1. Glier, M., Green, T., & Devlin, A. (2013). Methyl nutrients, DNA methylation, and cardiovascular disease. *Molecular Nutrition & Food Research*, *58*(1), 172-182. doi: 10.1002/mnfr.201200636

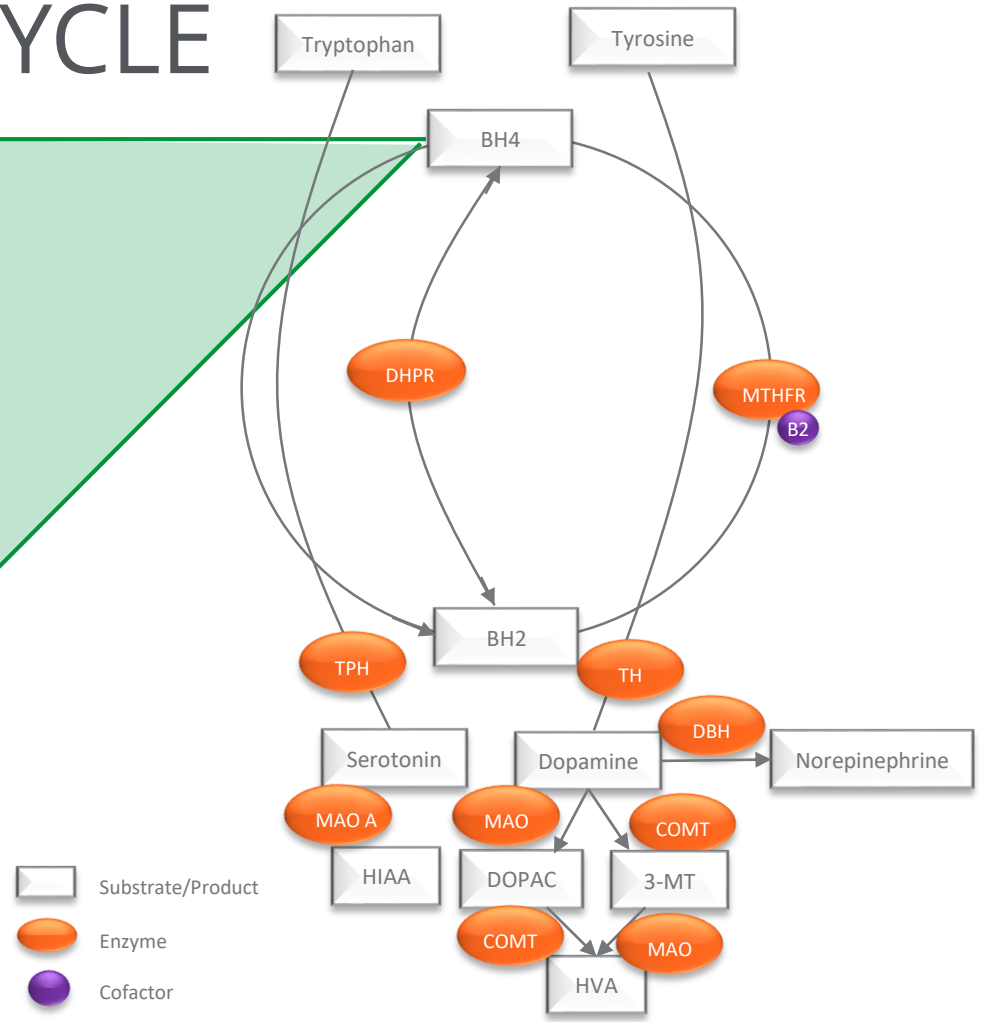
METHYLATION

3. NEUROTRANSMITTER (BH4) CYCLE

Tetrahydrobiopterin (BH4) is the rate-limiting nutrient cofactor essential in the synthesis of serotonin, dopamine, norepinephrine, and epinephrine.

Most of the body's endogenous source of BH4 is catalyzed by MTHFR, powered by the folate cycle.

The BH4-Folate relation if suspected to underlie the association between folate deficiency and depression[1,2].



1. Coppen, A., Swade, C., Jones, S.A., Armstrong, R.A., Blair, J.A., & Leeming, R.J. (1989). Depression and tetrahydrobiopterin: The folate connection. *Journal of Affective Disorders, 16,* 103-107.
2. Miller, A.L. (2008). The methylation, neurotransmitter, and antioxidant connections between folate and depression. *Alternative Medicine Review, 13,* 216-226.

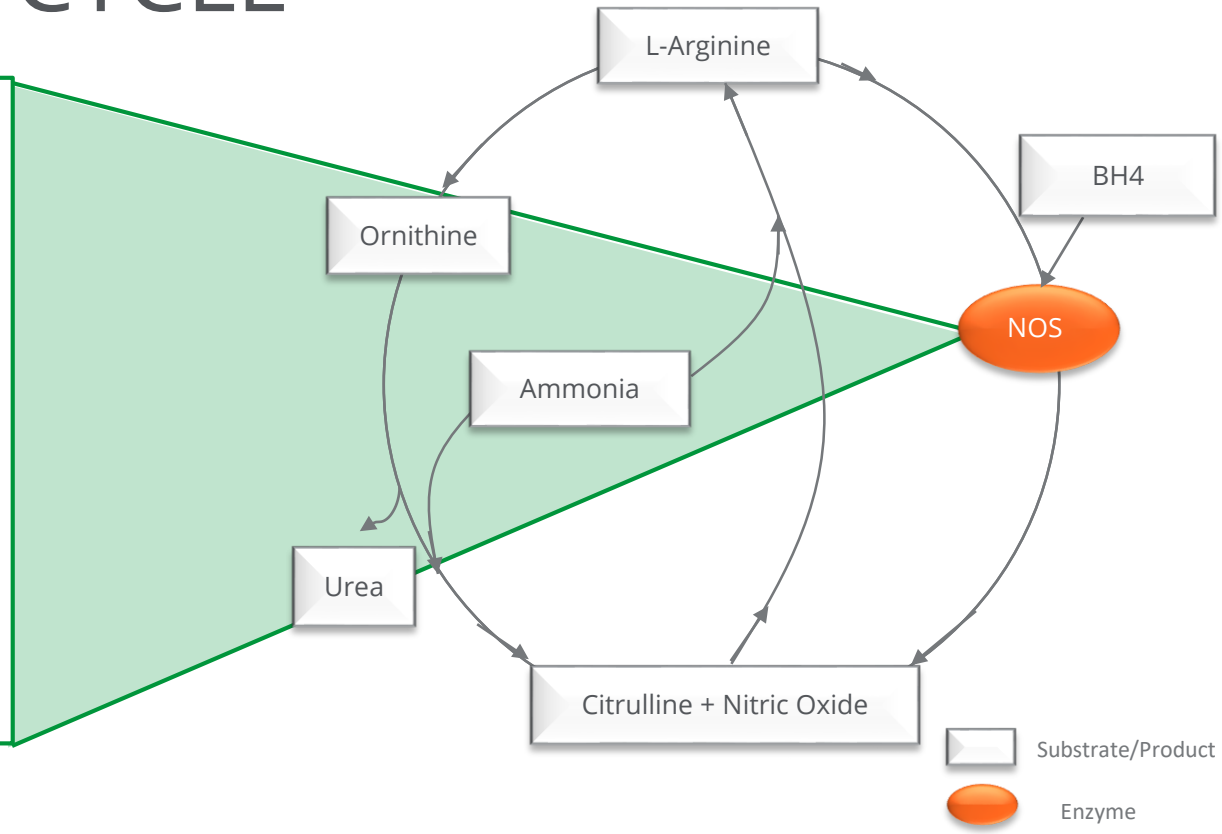
METHYLATION

4. NITRIC OXIDE (UREA) CYCLE

BH4 also serves as a cofactor in the synthesis of **Nitric Oxide (NO)**.

NO is an essential signaling molecule involved in neurotransmission, vasodilation, and immune responses[1].

BH4 also serves important implication is the metabolism and detoxification of ammonia.



1. Tejero, J. & Stuehr, D. (2013). Critical review: Tetrahydrobiopterin in nitric oxide synthase. *International Union of Biochemistry and Molecular Biology Inc., 65,* 358-365

GENETIC POLYMORPHISMS

Genetic Polymorphism

Two of more variations in genetic code that produces a different phenotype. Variations are considered equally acceptable alternatives.

Mutations

Variations in genetic code that are typically considered abnormal with aberrant functions. Mutation can range in size from a single DNA segment to a large segment of chromosome.

1. Tejero, J. & Stuehr, D. (2013). Critical review: Tetrahydrobiopterin in nitric oxide synthase. *International Union of Biochemistry and Molecular Biology Inc., 65,* 358-365

GENETIC POLYMORPHISMS

Single Nucleotide Polymorphism (SNP)

The single replacement of one nucleotide by another.
E.g., cytosine being replaced by thymine
E.g., arginine being replaced by guanine

1. Tejero, J. & Stuehr, D. (2013). Critical review: Tetrahydrobiopterin in nitric oxide synthase. *International Union of Biochemistry and Molecular Biology Inc., 65,* 358-365

GENETIC POLYMORPHISMS

Cystathionine Beta Synthase (CBS) C699T

- CBS is responsible for removing homocysteine from the methionine cycle.
- CBS C699T involves a base change from cytosine to thymine at base pair 699.
- CBS C699T kinetic effects are controversial. However most studies indicate enhanced CBS functioning by up to 10-fold.
- Enhanced CBS functioning results in accumulation of toxic ammonia and sulfite byproducts[1]. Accumulation of ammonia burdens nitric oxide cycle. BH4 is required for ammonia metabolism. As such, less BH4 is available for neurotransmitter synthesis.

1. Yasko, A. (2008). A guide to nutrigenomic testing.

GENETIC POLYMORPHISMS

Methylenetetrahydrofolate (MTHFR) C677T

- MTHFR is responsible for reducing folate into its active form.
- MTHFR C677T involves a base change from cytosine to thymine at base 677.
- MTHFR C677T is the most common SNP in the folate cycle[1,2].

1. Hiraoka, M. & Kagawa, Y. (2017). Genetic polymorphisms and folate status. *Congenital anomalies, 27*, 142-149.
2. Miller, A.L. (2008). The methylation, neurotransmitter, and antioxidant connections between folate and depression. *Alternative Medicine Review, 13,* 216-226.

GENETIC POLYMORPHISMS

Methylenetetrahydrofolate (MTHFR) C677T

- Heterozygous mutations (677CT) associated with 30% reduction in MTHFR activity[1,3].
- Homozygous mutation (677TT) associated with 60% reduction in MTHFR activity[1,3].
- Reduced MTHFR activity is associated with elevated homocysteine levels.
- This allele is present in approximately 10% of individuals worldwide[4].

1. Hiraoka, M. & Kagawa, Y. (2017). Genetic polymorphisms and folate status. *Congenital anomalies, 27*, 142-149.
2. Miller, A.L. (2008). The methylation, neurotransmitter, and antioxidant connections between folate and depression. *Alternative Medicine Review, 13,* 216-226.
3. Frosst, P., Blom, H.J., Milos R., et al. (1995). A candidate genetic risk factor for vascular disease: A common mutation in methylenetetrahydrofolate reductase. *Nat Genet, 10,* 111-113.
4. Wilcken B., Bamforth, F., Li, Z., et al. (2003). Geographical and ethnic variation of the 677C>T allele of 5,10 methylenetetrahydrofolate reductase (MTHFR): Findings from over 7000 newborns from 16 areas world wide. *Journal of Medical Genetics, 40,* 619-625.

GENETIC POLYMORPHISMS

MTHFR C677T Treatment

- MTHFR C677T can be enhanced by treatment with folate and/or vitamin B12.
  - E.g., In a study that assessed individuals with high dietary folate intake (>225 mcg/day), serum folate levels were significantly lower in individuals with 677TT that those with 677CC[1].
  - Authors recommended that individuals homozygous for 677TT consume approximately 1.4 times more folate to reach levels seen in individuals with 677CC of 677TC genotypes[1].

1. Nishio, K. Goto, Y., Kondo, T., Ito, S., Ishida, Y., Kawai, S., Naito, M., Wakai, K., & Hamajima, H. (2008). Serum folate and methylenetetrahydrofolate reductase (MTHFR) c677T polymorphism adjusted for folate intake.

GENETIC POLYMORPHISMS

Catechol-O-Methyl Transferase (COMT) V158M

- COMT is a responsible for the metabolism of monoamines and catechol estrogens.
- COMT V158M involves a base change from valine to methionine at base pair 158.
- COMT V158M results in reduced COMT activity.
- Reduced COMT activity is associated with higher dopamine and norepinephrine levels[1], lower pain tolerance[2], and catechol estrogen accumulation (DNA damage)[3]
    - E.g., Individuals with homozygous 158MM genotype administered significantly more morphine post-surgery[2].

1. Kotyuk, E., Duchek, J., Head, D., Szekely, A., Goate, A.M., & Balota, D.A. (2015). A genetic variant (COMT) coding dopaminergic activity predicts personality traits in healthy eldery. *Per Individ Dif, 1*, 61-66.
2. Tan, E.C., Lim, E.C., Ocampo, C.E., Allen, J.C., Sng, B.L., & Sia, A.T. (2015). Common variants of catechol-O-methyltransferase influence patient-controlled analgesia usage and postoperative pain in patients undergoing total hysterectomy. *Pharmacogenomics Journal, 16,* 186-192.
3. Ashton, K.A., Meldrum, C.J., McPhilips, M.L., Suchy, J., Kurzawski, G., Lubinski, J., & Scott, R.J. (2006). The association of the COMT V158M polymorphism with endometrial/ovarian cancer in HNPCC families adhering to the Amsterdam criteria. *Hereditary Cancer in Clinical Practice, 4,* 94-102.

METHYLATION

WHICH PATIENTS SHOULD BE EVALUATED FOR A METHYLATION ISSUE?

FATIGUE

- Regulatory genes involved in chronic fatigue syndrome (CFS) show hypomethylation within promotor regions[1].

MIGRAINES

- Individuals with MTHFR 677TT genotype have a significantly higher incidence of migraines (20.3%) relative to controls (9.6%)[2].

- Prevalence of MTHFR 677TT in patients with migraines with aura is significantly high (40.9%) [2].

1. Kotyuk, E., Duchek, J., Head, D., Szekely, A., Goate, A.M., & Balota, D.A. (2015). A genetic variant (COMT) coding dopaminergic activity predicts personality traits in healthy eldery. *Per Individ Dif, 1*, 61-66.
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WHICH PATIENTS SHOULD BE EVALUATED FOR A METHYLATION ISSUE?

HIGH HOMOCYSTEINE IN SERUM

- Homocysteine recycling back into methionine requires remethylation and as such adequate sources of methyl groups.

BREAST CANCER

- There is an abundance of evidence supporting the association between disruptions in epigenetic methylation and the development of breast cancer[1].

- Methylation is also required for the metabolism of breast cancer promoting catechol estrogens[2,3].

1. Mahmood, N. & Rabbani, S.A. (2017). DNA methylation and breast cancer: Mechanistic and therapeutic applications. *Trends in Cancer Research, 12,* 1-18.
2. Raftogianis, R., Creveling, C., Weinshilboum, R., & Weisz, J. (2000). Chapter 6: Estrogen metabolism by conjugation. *Journal of the National Cancer Institute Monographs, 27,*
3. Shaik, M.M., Tan, H.L., Kamal, M.A., & Gan, S.H. (2014). Do folate, vitamins B6 and B12, play a role in the pathogenesis of migraine? The role of pharmacoepigenomics. *CNS & Neurological Disorders – Drug Targets, 13,* 828-835.

WHICH PATIENTS SHOULD BE EVALUATED FOR A METHYLATION ISSUE?

ENDOMETRIAL CANCER

- Several studies indicate a relation between the development of endometrial cancer and aberrations in methylation processes[1].

SENSITIVITIES TO SULFITE-CONTAINING FOOD

- Accumulation in endogenous sulfite synthesis caused by aberrant CBS functioning can result in sensitivities to sulfite-containing foods and may serve as an indirect indicator of impaired methyl processes.

1. Tao, M.H. & Freudenheim, J.L. (2010). DNA methylation in endometrial cancer. *Epigenetics, 5,* 491-498.

OUTLINE

HORMONE TESTING

- Serum
- Saliva
- Urine
- Blood spot

ESTROGEN METABOLISM

- Breast cancer
- Bad estrogens
- Good estrogens
- Preventing negative estrogen burden

CASE ASSESSMENT

METHYLATION

- Methionine cycle
- Folate cycle
- BH4 cycle
- Urea cycle
- Genetic SNPs

CASE ASSESSMENT (Continued)

CASE ASSESSMENT

CASE FOLLOW-UP – FEBRUARY 2015

Cecilia returns a few month later to review her methylation profile. Based on her methylation profile, are there any changes you would make to her nutraceutical treatment plan?

CASE ASSESSMENT

PLASMA METHYLATION

PLASMA METHYLATION PROFILE				
METABOLITES	**RESULT (02/15/2015)**	**PERCENTILE** 2.5th 16th 50th 84th 97.5th	**REFERENCE RANGE**	**UNIT**
Cysteine	29		20-38	µmol/dL
Methionine	1.6		1.6-3.6	µmol/dL
S-adenosylmethionine (SAM)	102		86-145	nmol/L
S-adenosylhomocysteine (SAH)	15.6		10-22	nmol/L
		68th 95th		
Cystathionine	0.01		< 0.05	µmol/dL
Homocysteine	8.2		< 11	µmol/L
SAM:SAH	6.5		> 4	

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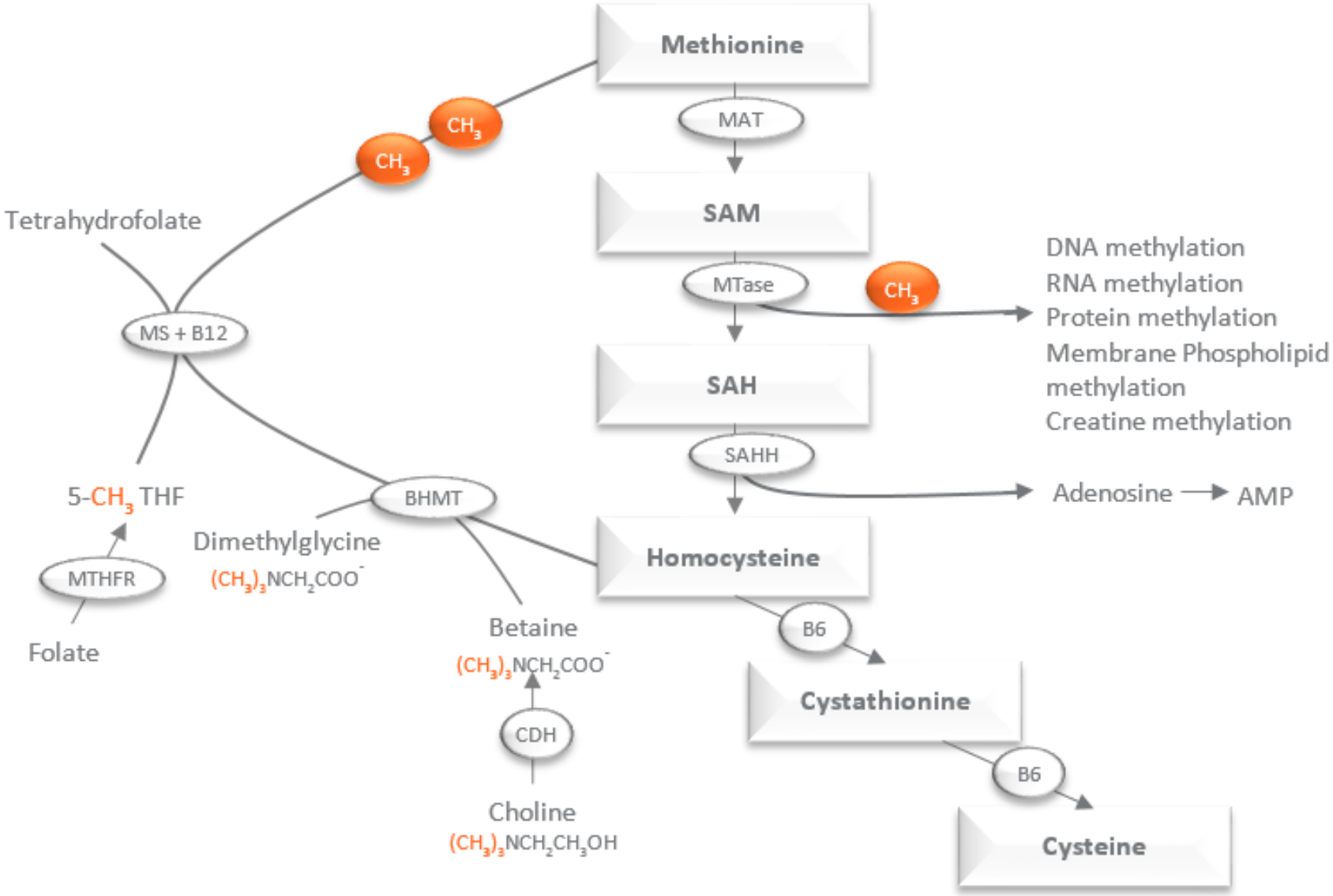
CASE ASSESSMENT



CASE FOLLOW-UP – JULY 2015

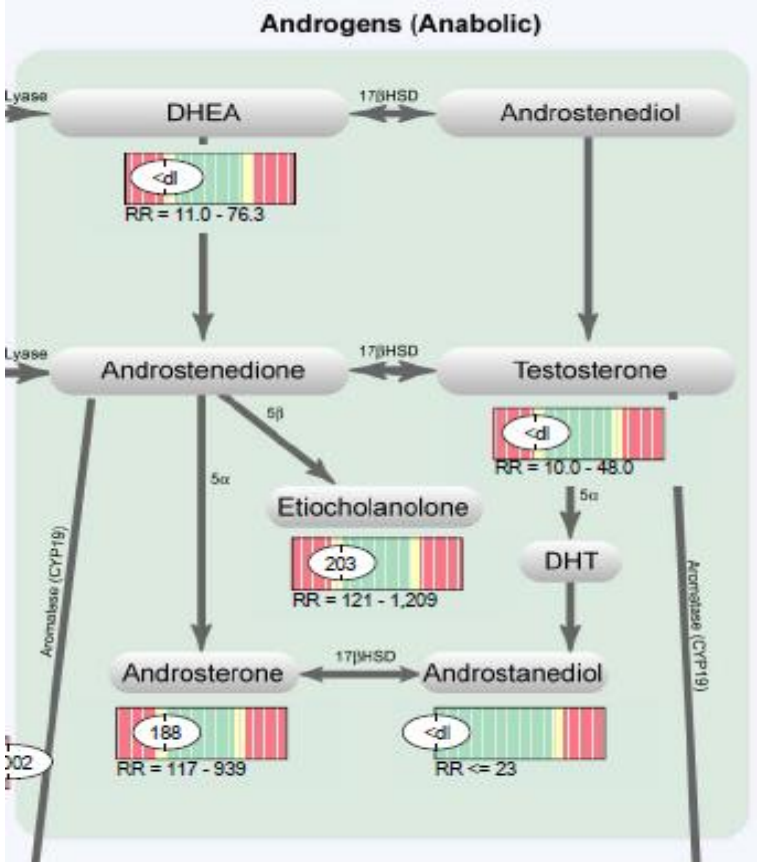
Cecilia returned later that year in the Summer to repeat a complete urinary hormone evaluation.

- **Cortisol levels remained high**
- Anabolic/catabolic ratio still favored **catabolic metabolism**.
- **4-Hydroxyestrone was still high**
- **Irregular bleeding**.
- Primary complaint is still **fatigue**
- **Sleep has improved**

CASE ASSESSMENT

URINARY HORMONE RESULTS

ANDROGENS (17-Ketosteroids)	
DHEA	<dl
Androsterone	188
Etiocholanolone	203
11-Keto-androsterone	9
11-Keto-etiocholanolone	77
11-Hydroxy-androsterone	76
11-Hydroxy-etiocholanolone	48
17-Ketosteroids, Total*	601
Testosterone	<dl
Androstanediol	<dl



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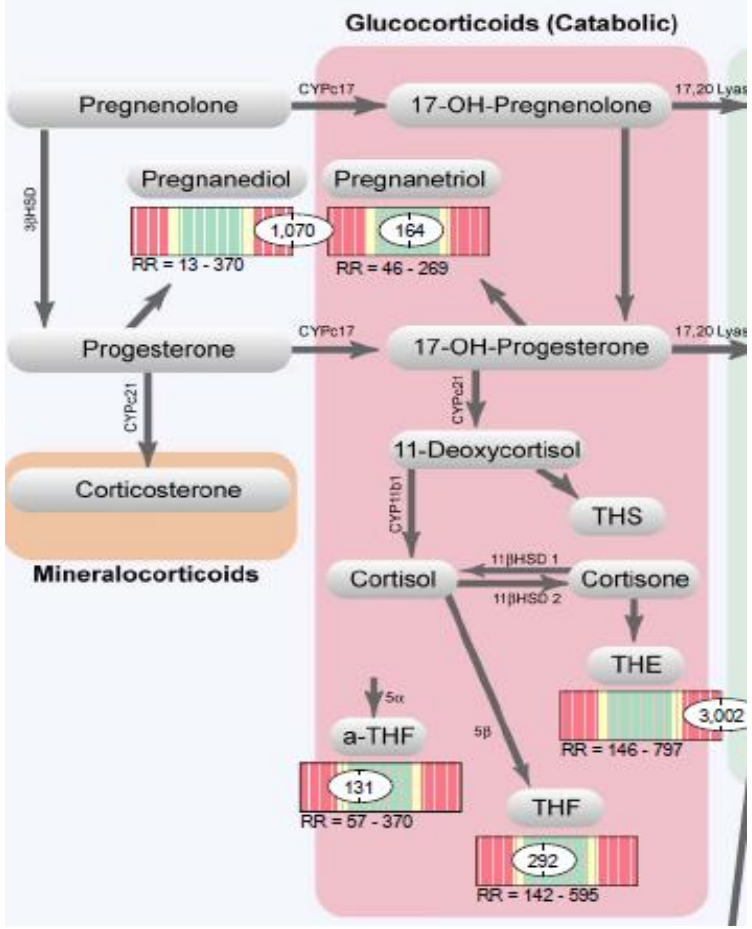
CASE ASSESSMENT

URINARY HORMONE RESULTS

GLUCOCORTICOIDS (17-Hydroxysteroids)	
Pregnanetriol	164
Allo-Tetrahydrocortisol, a-THF	131
Tetrahydrodeoxycortisol (THS)	
Tetrahydrocortisone (THE)	3,002
Tetrahydrocortisol (THF)	292
17-Hydroxysteroids, Total*	



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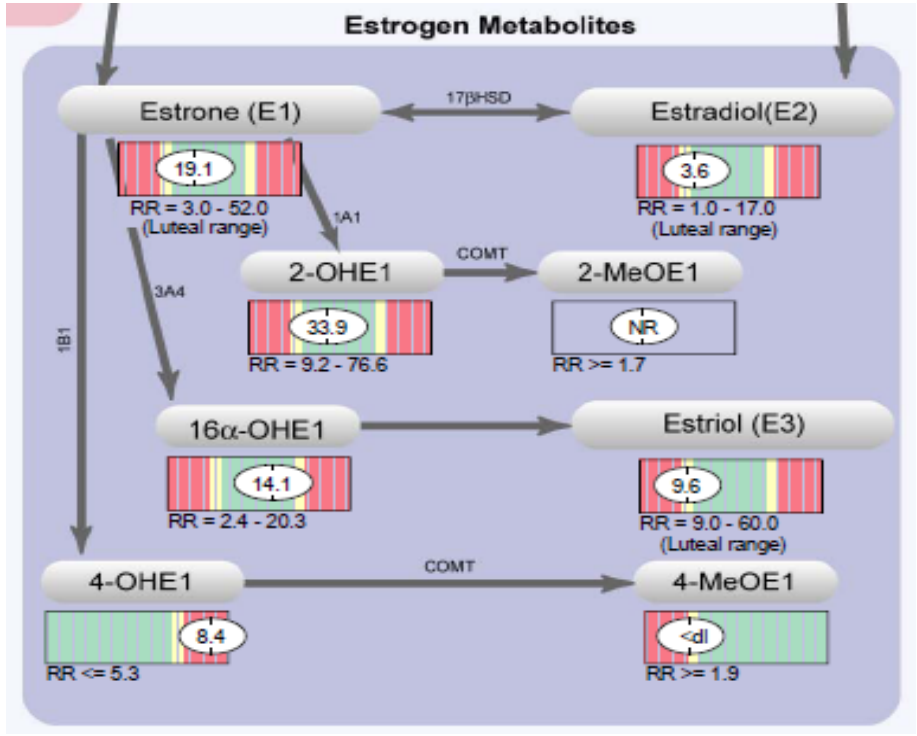
CASE ASSESSMENT

URINARY HORMONE RESULTS

ESTROGENS	
Estrone (E1)	
- Postmenopausal	19.1
Estradiol (E2)	
- Postmenopausal	3.6
Estriol (E3)	
- Postmenopausal	9.6
ESTROGEN METABOLITES	
2-Hydroxyestrone	23.9
16α-Hydroxyestrone	14.1
4-Hydroxyestrone	
2-Methoxyestrone	NR
4-Methoxyestrone	<dl



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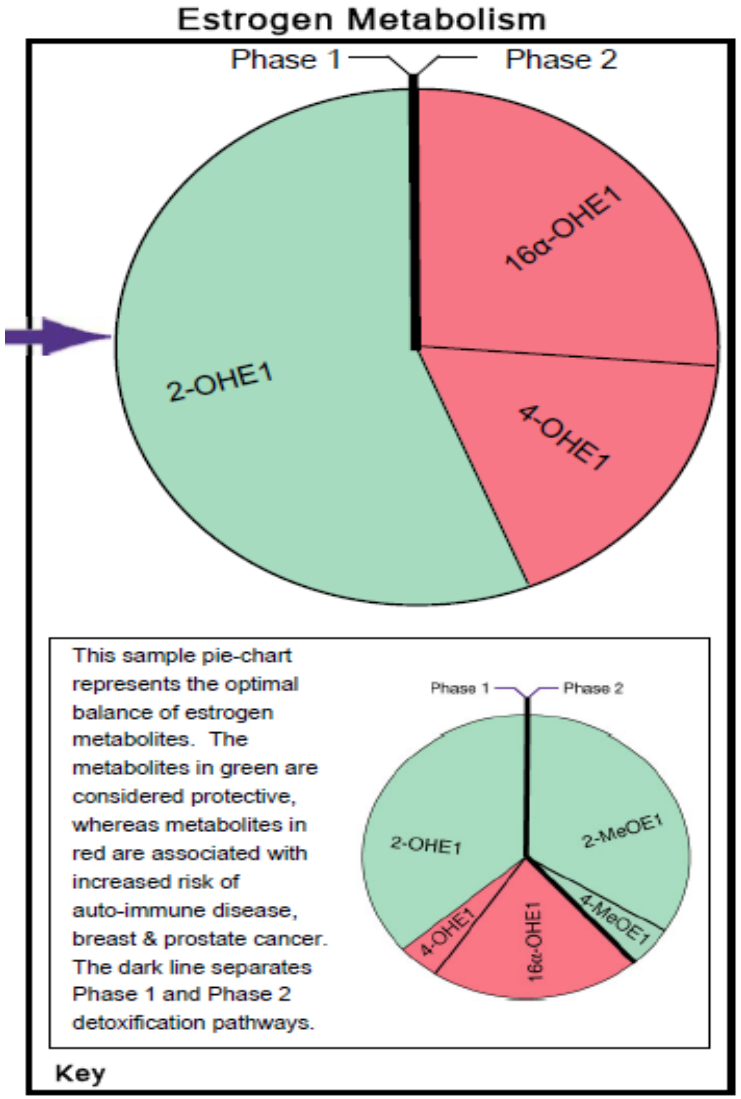
CASE ASSESSMENT

URINARY HORMONE RESULTS

RATIOS			
Anabolic (17-Ketosteroids)/ **Catabolic** (17-Hydroxysteroids) Balance	0.17 Catabolic	Anabolic	
Anabolic (17-Ketosteroids) (FMV urine)		601	
Catabolic (17-Hydroxysteroids) (FMV urine)			3,617
11β-HSD Index ((α-THF+THF)/THE)	0.14 Less cortisol		More cortisol
5α-Reductase Activity (Etiocholanolone/Androsterone)	More 5α-Reductase	1.08	Less 5α-Reductase
Estrogen Metabolism (2-Hydroxyestrone/16α-Hydroxyestrone)	16α-OHE1 (higher risk of breast cancer)	2.4	2-OHE1 (Lower risk of breast cancer)
Methylation Activity (2-Methoxyestrone/2-Hydroxyestrone)	Less Methylation	NR	More Methylation



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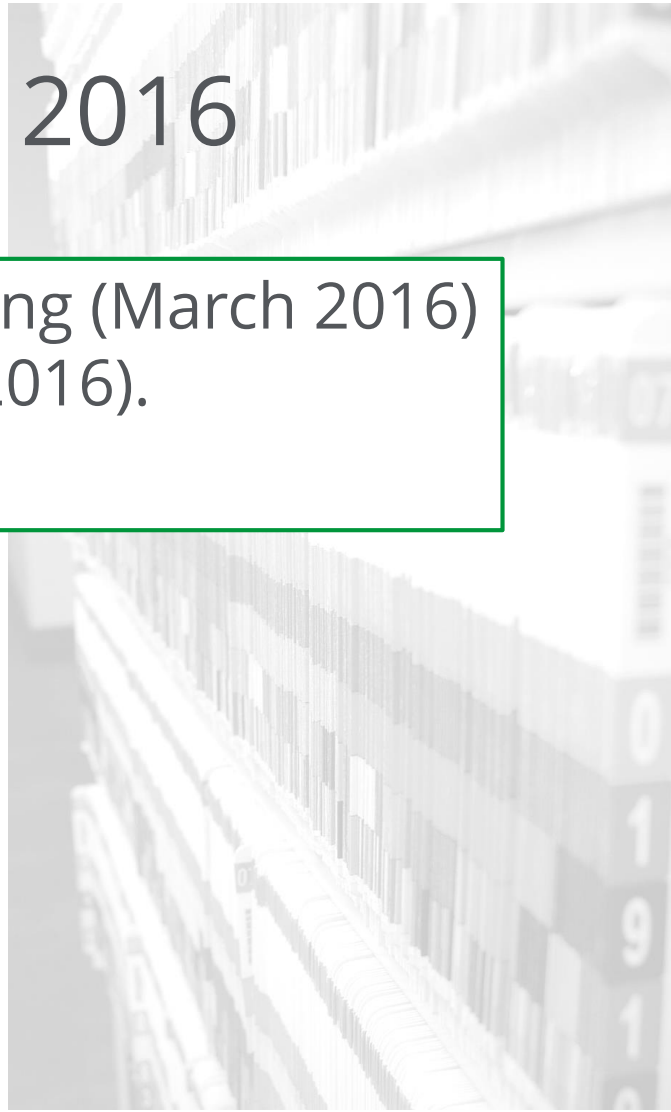
CASE ASSESSMENT

CASE FOLLOW-UP – MARCH 2016, JUNE 2016

In the subsequent year, Cecilia repeated methylation testing (March 2016) and was also prescribed genetic testing (June 2016).



PLASMA METHYLATION

PLASMA METHYLATION PROFILE					
METABOLITES	RESULT (02/15/2015)	RESULT (03/10/2016)	PERCENTILE 2.5th 16th 50th 84th 97.5th	REFERENCE RANGE	UNIT
Cysteine	29	29		20-38	µmol/dL
Methionine	1.6	3.0		1.6-3.6	µmol/dL
S-adenosylmethionine (SAM)	102	111		86-145	nmol/L
S-adenosylhomocysteine (SAH)	15.6	12.6		10-22	nmol/L
			68th 95th		
Cystathionine	0.01	0.01		< 0.05	µmol/dL
Homocysteine	8.2	5.9		< 11	µmol/L
SAM:SAH	6.5	8.8		> 4	

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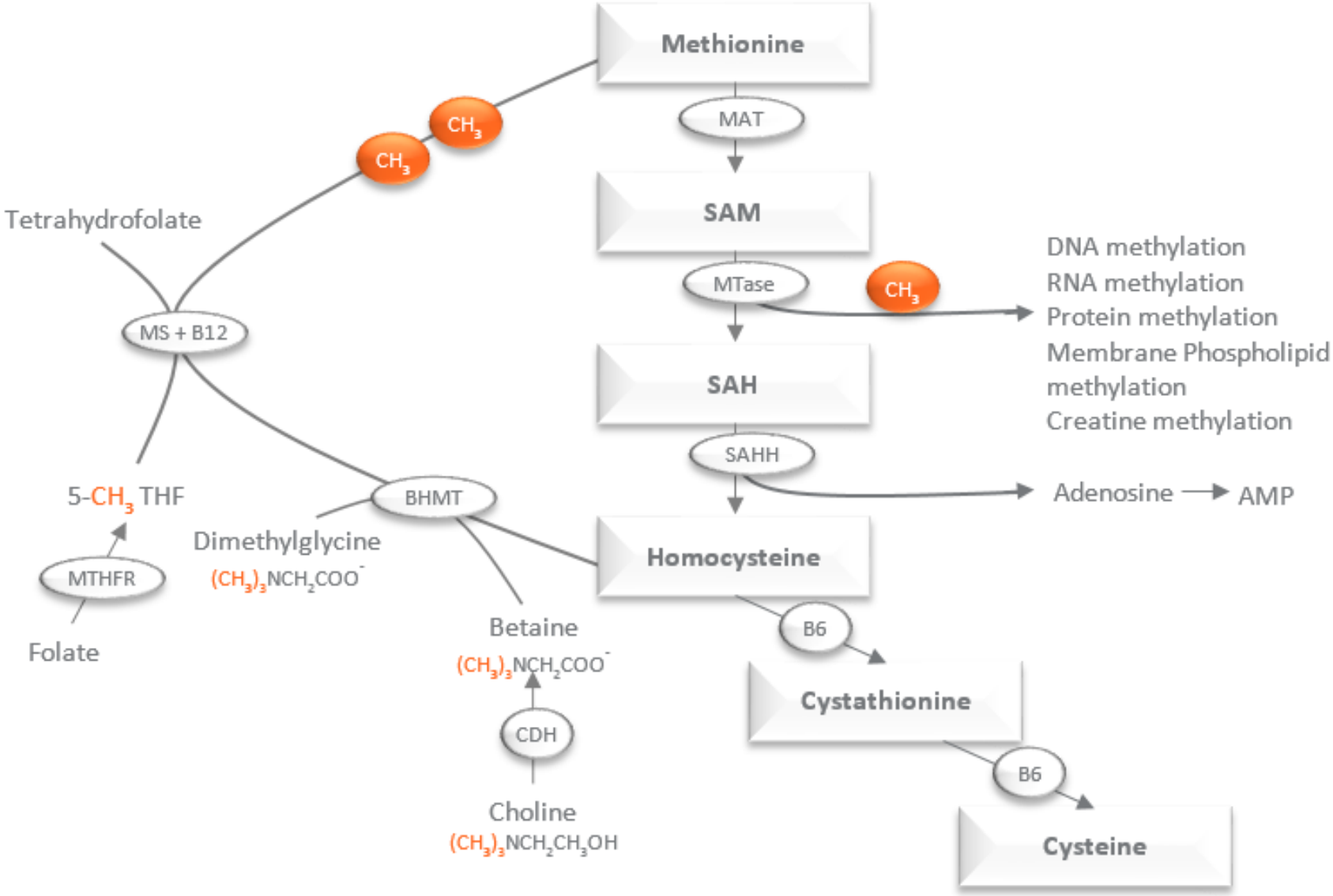
CASE ASSESSMENT



FLAGGED GENOTYPES

FLAGGED GENOTYPES			
GENE	**GENOTYPE**	**PHENOTYPE**	**ALLELES TESTED**
COMT	Val158Met AA	Low COMT activity	Val158Met
MTHFR	677C>T CT	Reduced MTHR activity	677C>T
SLC6A4	S/La	Decreased serotonin transporter expression	La, S, Lg

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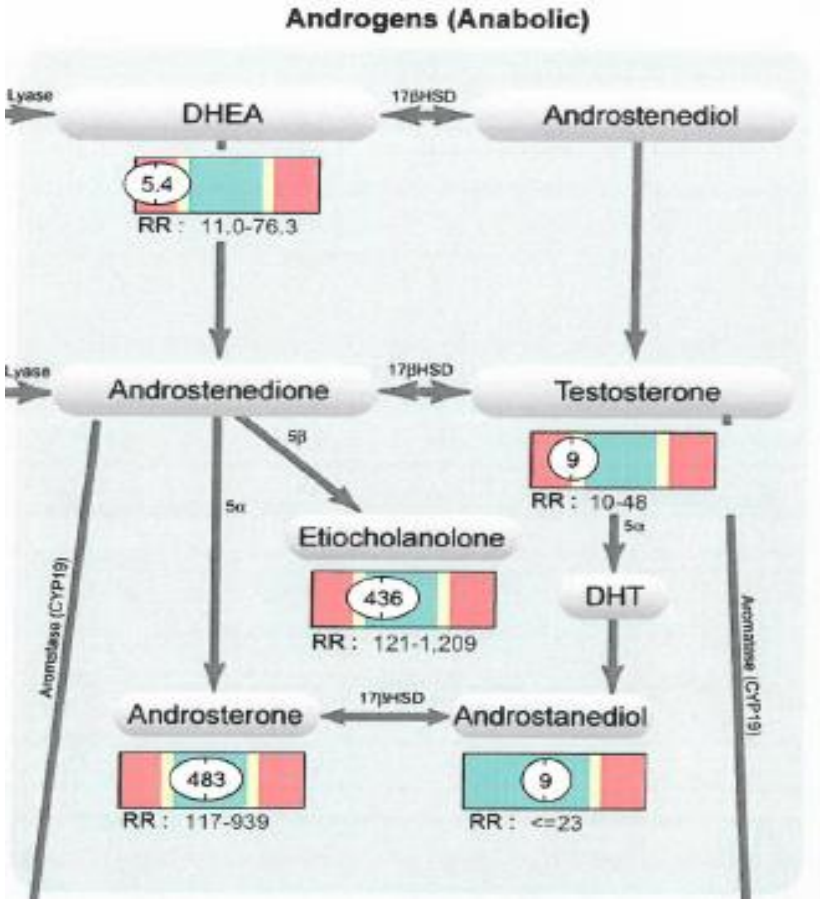
CASE ASSESSMENT

URINARY HORMONE RESULTS

ANDROGENS (17-Ketosteroids)	
DHEA	5.4
Androsterone	483
Etiocholanolone	436
11-Keto-androsterone	<dl
11-Keto-etiocholanolone	46
11-Hydroxy-androsterone	177
11-Hydroxy-etiocholanolone	72
17-Ketosteroids, Total*	1,224
	NR
Testosterone	9
Androstanediol	9



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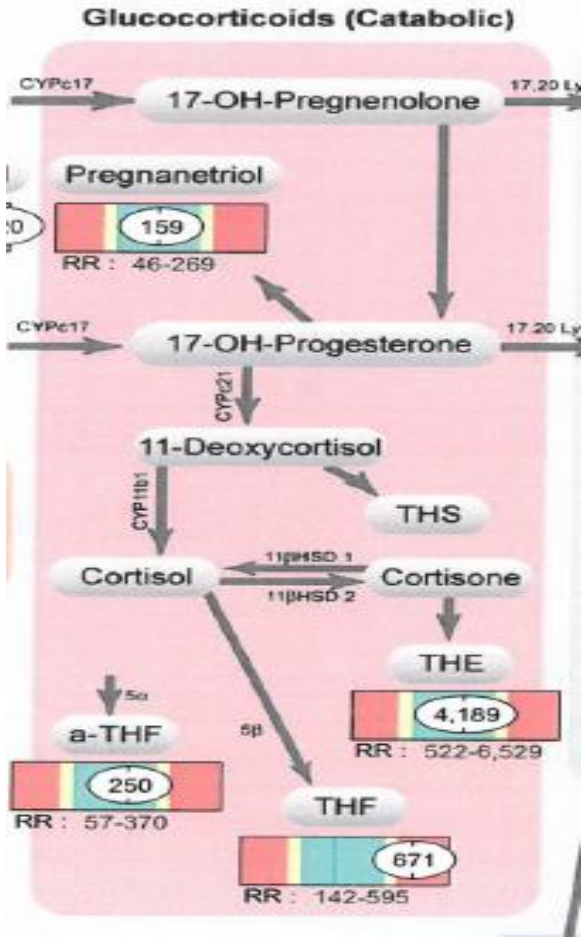
CASE ASSESSMENT

URINARY HORMONE RESULTS

GLUCOCORTICOIDS (17-Hydroxysteroids)	
Pregnanetriol	159
Allo-Tetrahydrocortisol, a-THF	250
Tetrahydrodeoxycortisol (THS)	54.2
Tetrahydrocortisone (THE)	4,189
Tetrahydrocortisol (THF)	671
17-Hydroxysteroids, Total*	5,323



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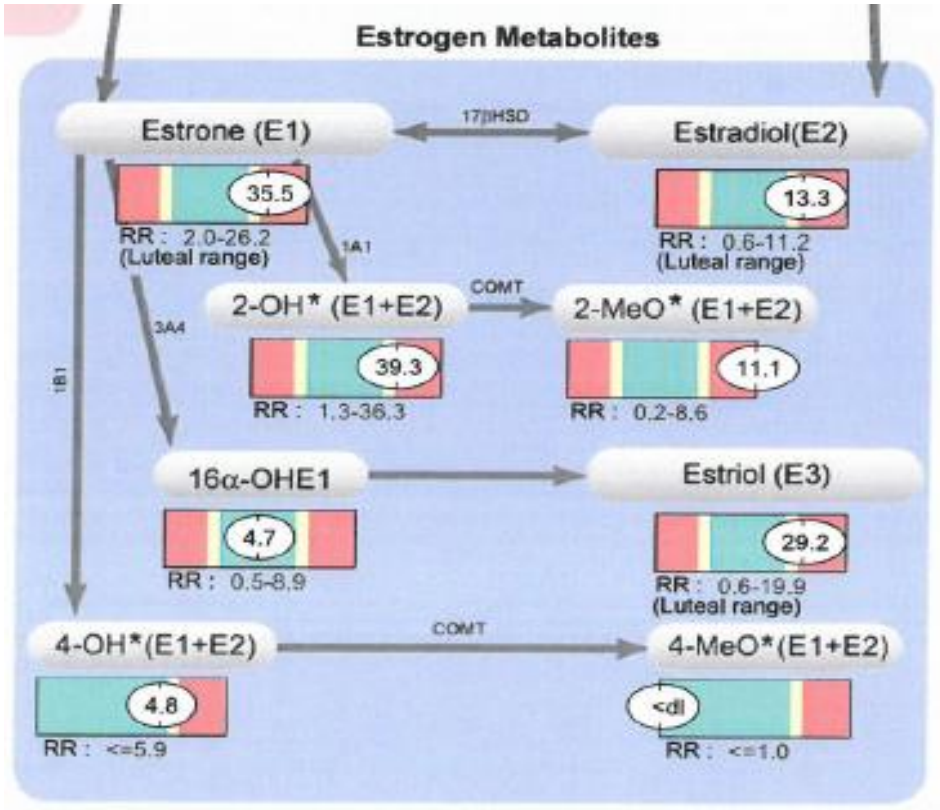
CASE ASSESSMENT

URINARY HORMONE RESULTS

ESTROGENS	
Estrone (E1)	
- Postmenopausal	
Estradiol (E2)	
- Postmenopausal	13.3
Estriol (E3)	
- Postmenopausal	29.2
ESTROGEN METABOLITES	
2-Hydroxyestrone + 2-Hydroxyestradiol	39.3
16α-Hydroxyestrone	4.7
4-Hydroxyestrone + 4-Hydroxyestradiol	4.8
2-Methoxyestrone + 2-Methoxyestradiol	11.1
4-Methoxyestrone + 4-Methoxyestradiol	<dl



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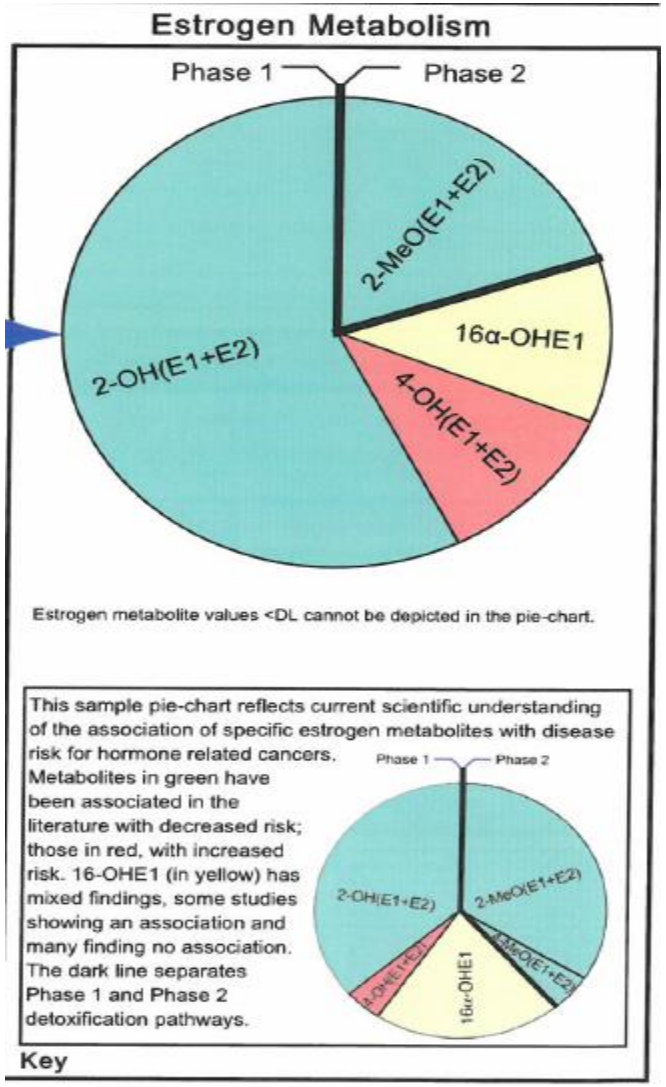
CASE ASSESSMENT

URINARY HORMONE RESULTS

RATIOS			
Anabolic (17-Ketosteroids)/ **Catabolic** (17-Hydroxysteroids) Balance	Catabolic	Anabolic 0.23	
Anabolic (17-Ketosteroids)		1,224	
Catabolic (17-Hydroxysteroids)		5,323	
5α-Reductase Activity (Etiocholanolone/Androsterone)	More 5α-Reductase	0.90	Less 5α-Reductase
Estrogen Metabolism (2-Hydroxyestrone/16α-Hydroxyestrone)	16α-OHE1 (higher risk of breast cancer)	8.4	2-OHE1 (Lower risk of breast cancer)
Methylation Activity (2-OH(E1+E2)/2-MeO(E1+E2))	Less Methylation	3.5	More Methylation



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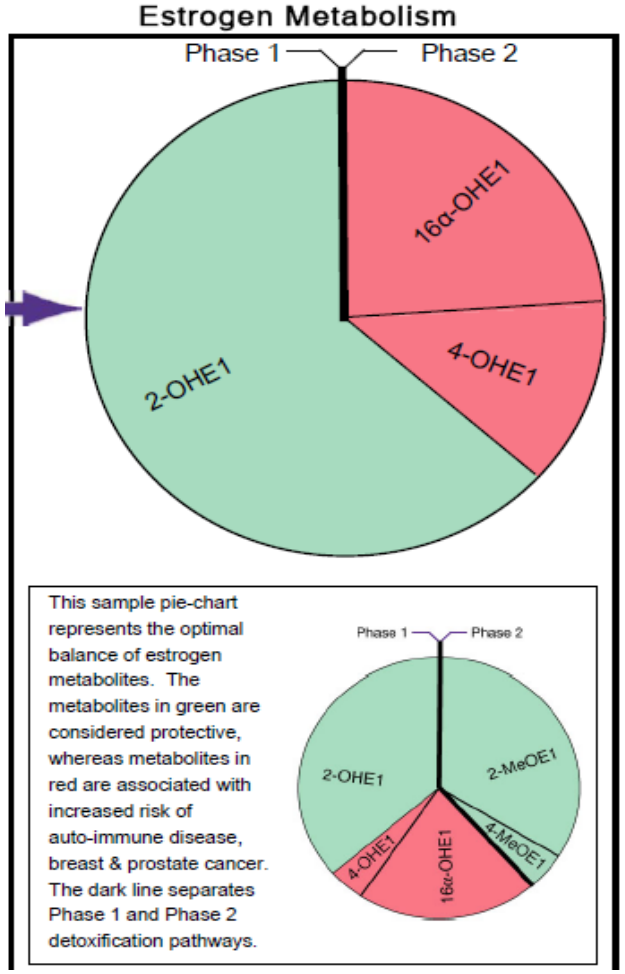
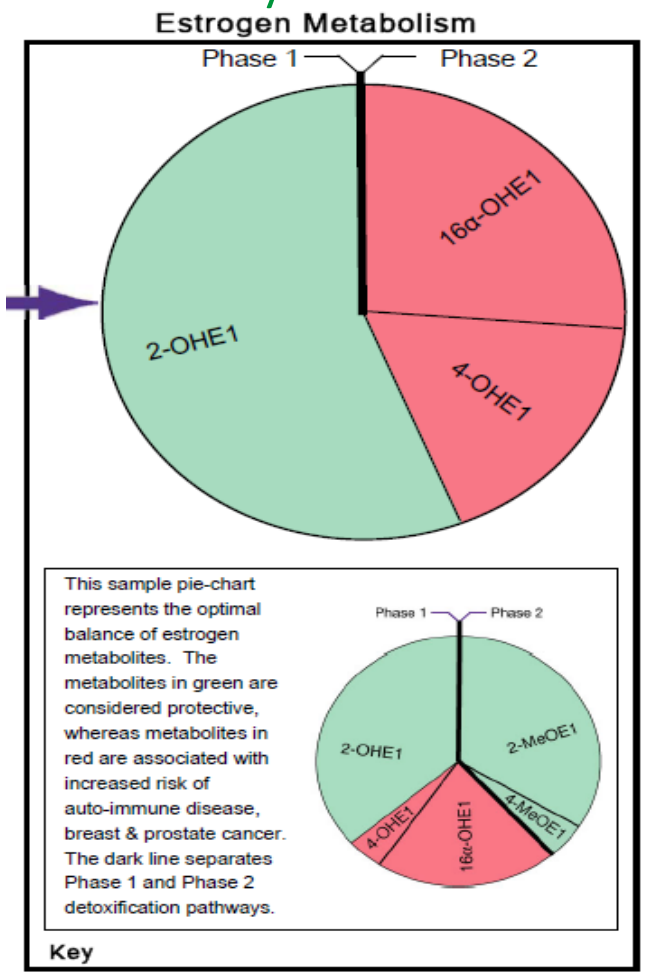
CASE ASSESSMENT

ESTROGEN METABOLISM OVER TIME

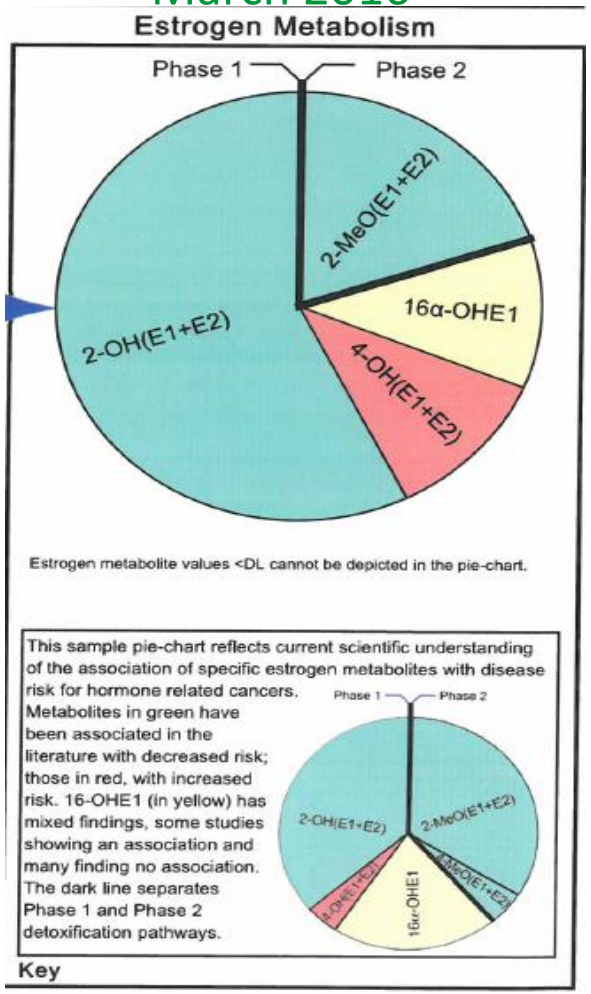
December 2014



July 2015

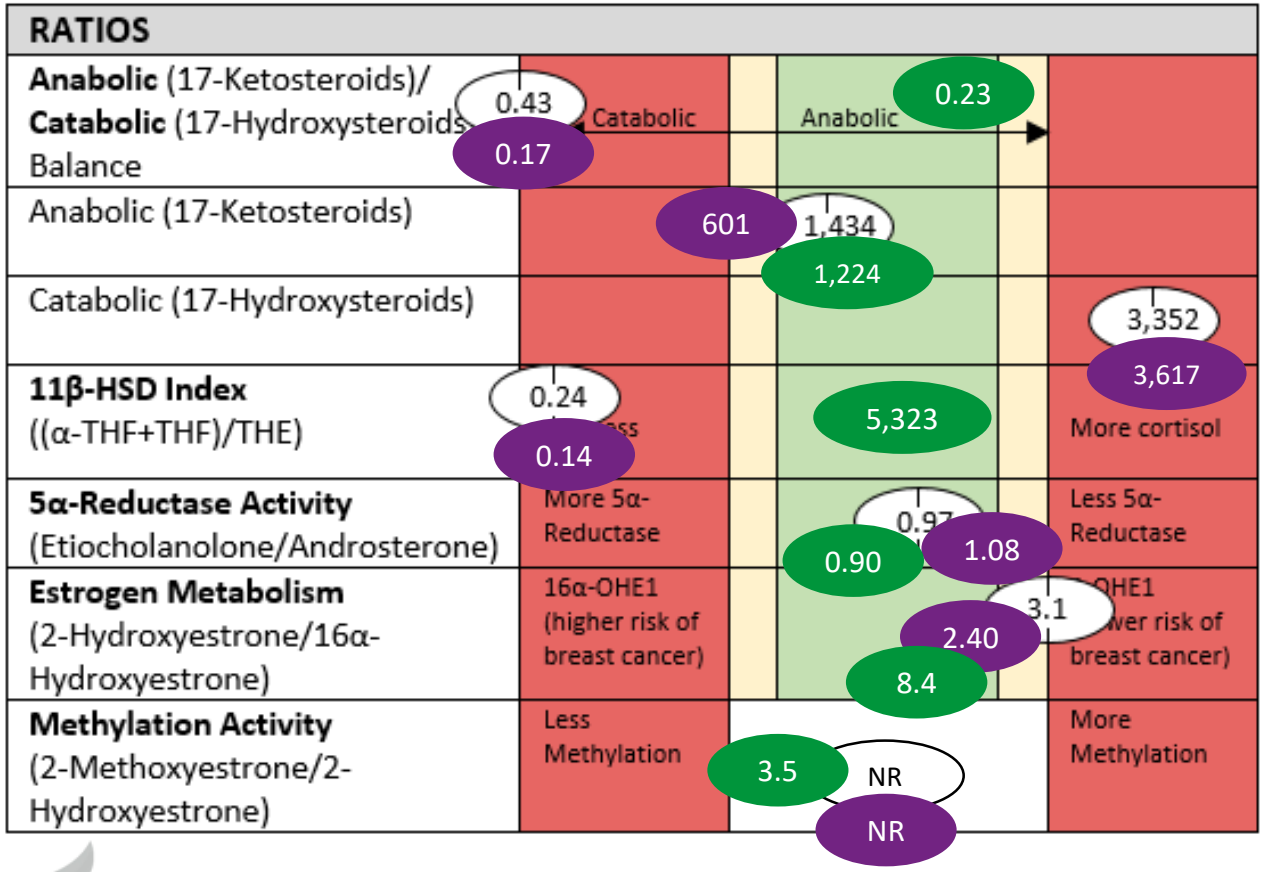


March 2016



CASE ASSESSMENT

ESTROGEN METABOLISM OVER TIME



- December 2014
- July 2015
- March 2016

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CASE ASSESSMENT

SALIVARY HORMONE RESULTS			
HORMONE	**RESULT**	**REFERENCE RANGE**	**UNIT**
Estrone (E1)	20.7	4.7-18.9	pmol/L
Estradiol (E2)	5.9	2.8-8.2	pmol/L
Estriol (E3)	177	≤133	pmol/L
Progesterone	2,153	145-797	pmol/L
P/E2 Ratio	365	25-141	-
Testosterone	<30	34-148	pmol/L
Cortisol			
• 7AM-9AM	0.331	0.097-0.337	mcg/dL
• 11AM-1PM	0.054	0.027-0.106	mcg/dL
• 3PM-5PM	0.050	0.013-0.068	mcg/dL
• 10PM-12AM	0.016	≤0.034	mcg/dL
DHEA (7AM-9AM)	43	71-640	pg/mL
DHEA: Cortisol Ratio / 10,000	130	115-1,188	-
Melatonin			
• 7AM-9AM	2.15	≤10.50	pg/mL
• 3PM-5PM	<0.50	≤0.88	pg/mL
• 2:30AM-3:30AM	13.48	2.53-30.67	pg/mL

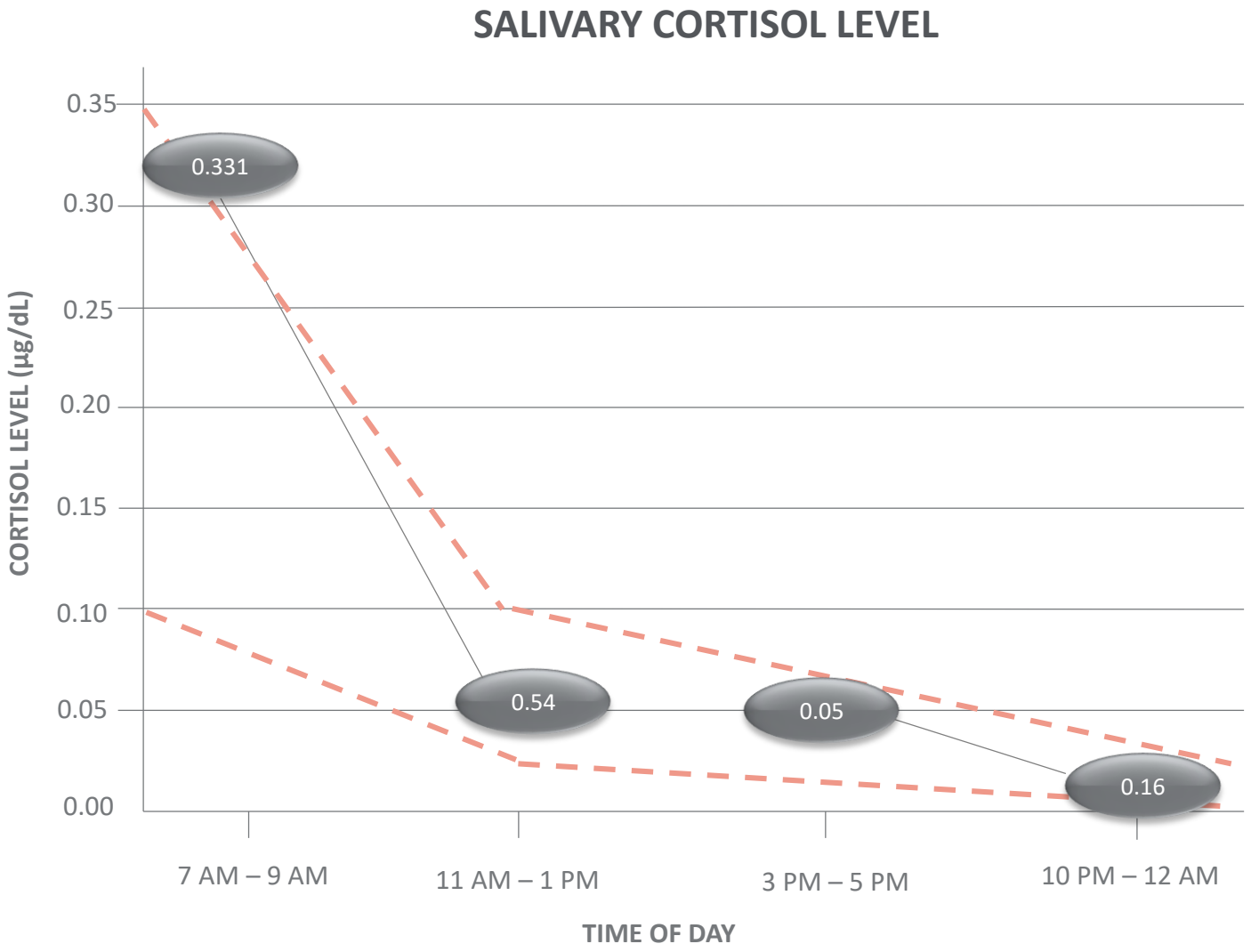
Key
Normal
Borderline
Abnormal

Patient was taking the following when these tests were conducted:

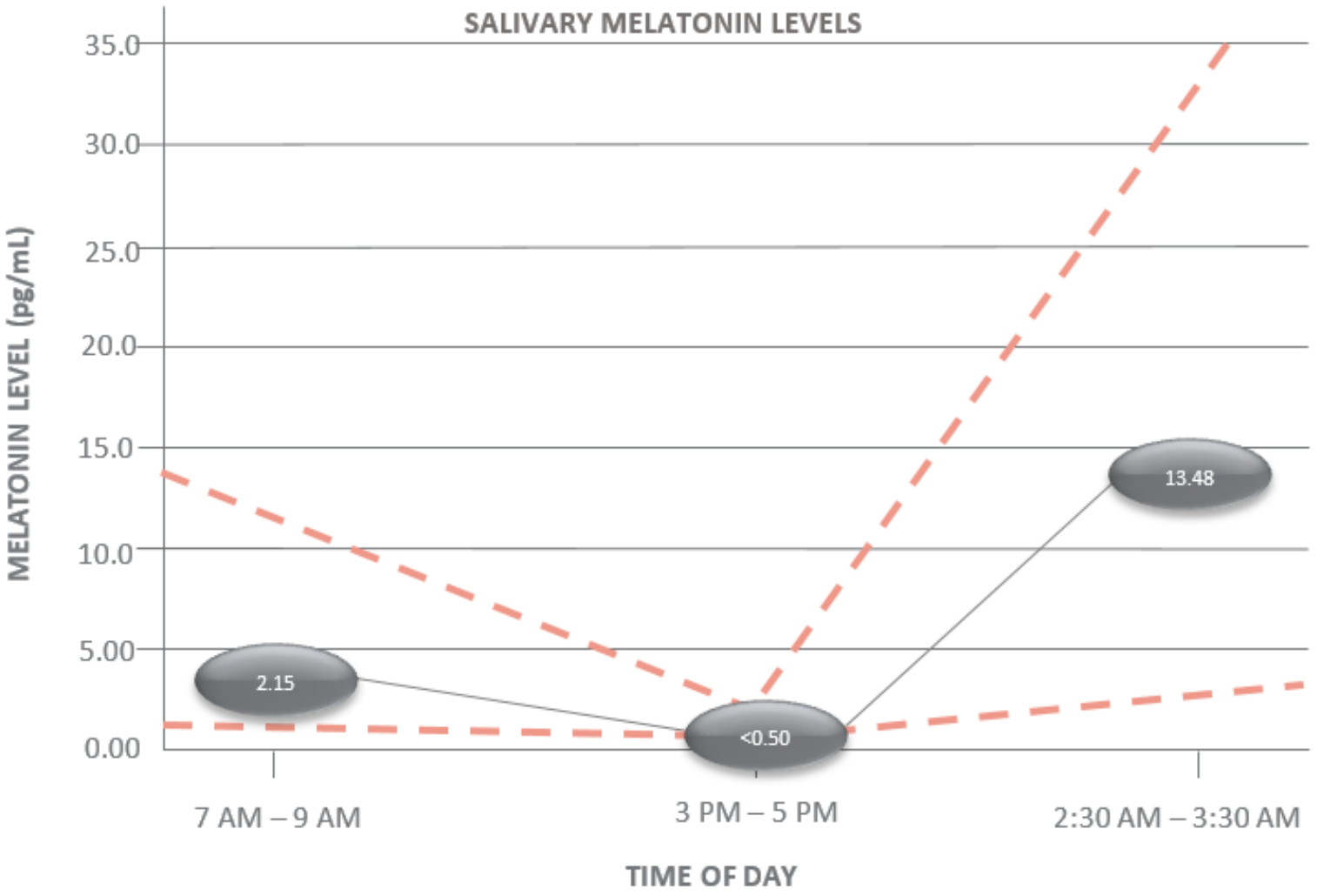
- Tamoxifen
- Resveratrol
- Alpha Lipoic Acid
- Adrenal Support

WCC 2018

CASE ASSESSMENT



CASE ASSESSMENT



CONCLUDING REMARKS

- Need to know the advantages and disadvantages of different types of hormone testing. What do the tests tell you?
- Estrogen metabolism has important implications in overall health and on how we prescribe HRT.
- Methylation processes, in part, determine estrogen metabolism profiles.
- As healthcare providers, **it's time we look outside the box** when treating hormone imbalances. We need to look at the whole picture.

THANK YOU FOR LISTENING

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Credits	1.5 CPE Hours = 0.15 CEUs	1.5 CPE Hours = 0.15 CEUs
Release Date	October 27th 2018	October 27th 2018
Expiration Date	October 27th 2019	October 27th 2019

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