Estrogen Metabolism

Tara Scott, MD. FACOG, FAAFM, ABOIM

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Webinar Technical Issues & Clinical Questions

- Please type any technical issue or clinical question into either the “Chat” or “Questions” boxes, making sure to send them to “Organizer” at any time during the webinar.
- We will be compiling your clinical questions and answering as many as we can the final 15 minutes of the webinar.

2

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WHO Am I?

- Tara Scott, MD
- Board certifications in: OB/GYN, Integrative Medicine, and Anti-Aging, Functional and Regenerative Medicine
- Lecture around the world teaching doctors a functional approach to women's health
- Medical Director of Integrative Medicine at Summa Health in Akron, OH

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Objectives

- Review the basics of estrogen metabolism
- Define SNPs and how they affect metabolism
- Discuss which SNPs affect the risk of breast cancer
- Review a case and demonstrate the information the DUTCH test provides

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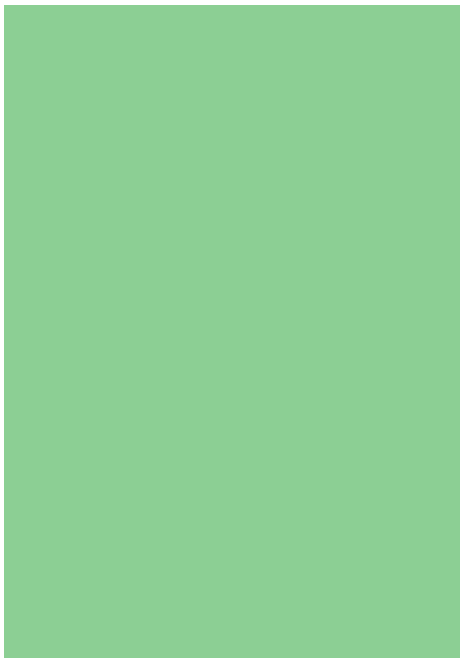
Why is it so important to check estrogen metabolism?

- Is it really possible to have a randomized placebo controlled trial with hormone therapy?
- You need to consider:
  - Weight, age, oophorectomy status
  - Pharmacokinetics- what the body does to the drug
  - Pharmacodynamics- what the drug does to the body



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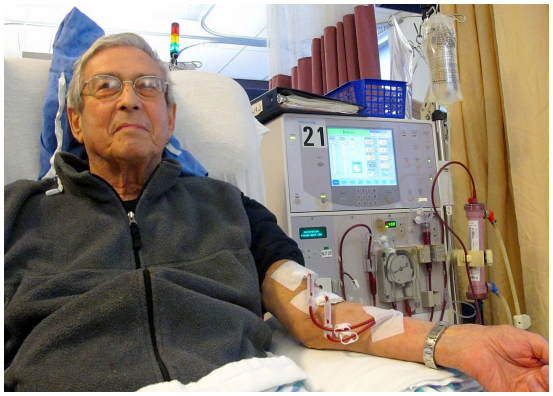
Suppose I tell all my patients to drink 2 liters of water

Marathon Runner in 80 degree weather

Dialysis Patient



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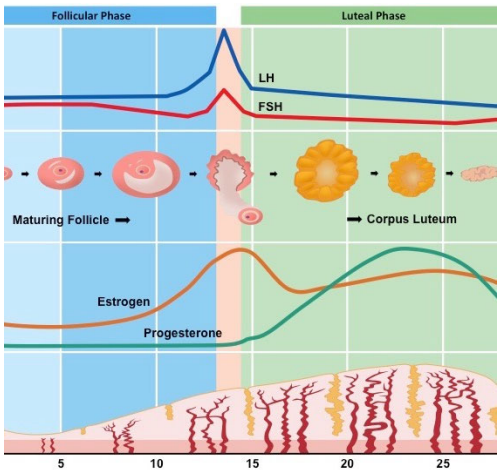
Menstrual Cycle

- Developing egg makes Estrogen- causes growth
- After its released, progesterone balances estrogen



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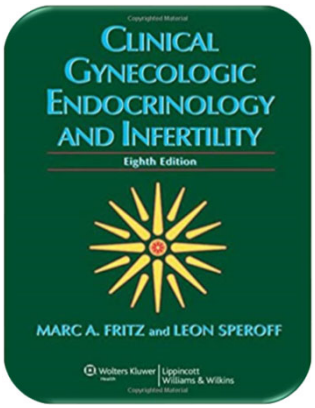
What do we Know



This was our Endocrinology Bible in residency!!

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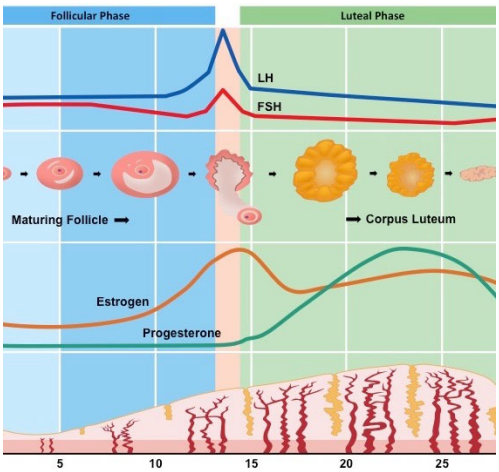
Menstrual Cycle

- Developing egg makes Estrogen- causes growth
- After its released, progesterone balances estrogen



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Estrogen causes proliferation

Page 126

Progesterone Inhibits proliferation, decline in DNA synthesis, interferes with the estrogen receptor

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Estrogen stimulates many oncogenes that mediate estrogen induced growth. Progesterone antagonizes this action- suppresses transcription of oncogene mRNA

Page 128

Pearls from Dr. Speroff

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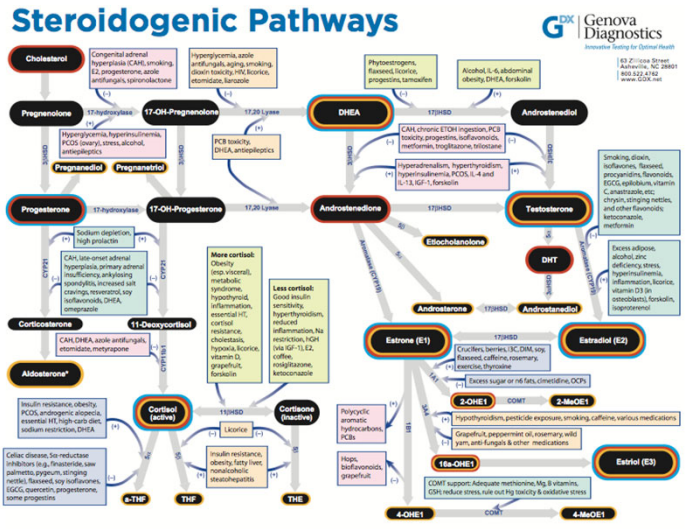
STEROIDOGENIC PATHWAY



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Estrogen- Functions

- Promotes growth
- Body development
- Slows bone loss
- Three main types
  - Estradiol- good for heart and bones
  - Estriol - good for skin
  - Estrone- goes to breast- sort of the bad one

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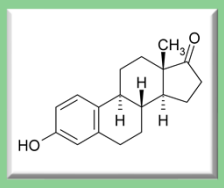

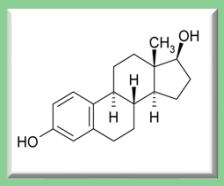

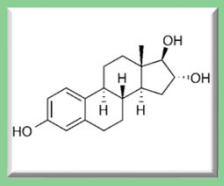

Samavat & Kurzer, 2015

Estrone (E1)

Predominant estrogen in **postmenopausal** women.

Estradiol (E2)

Predominant estrogen in **premenopausal** women. Most biologically active estrogen in women

Estriol (E3)

Predominant estrogen in **pregnant** women. Most abundant estrogen in urine.

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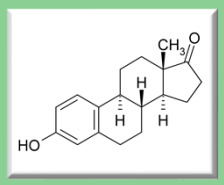
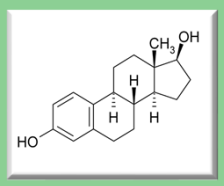


Estrone (E1)

Primarily synthesized from **androstenedione** by aromatase conversion in the ovaries.

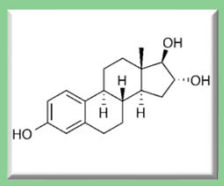
Reversibly converted into estradiol by enzyme, 17β-hydroxysteroid dehydrogenase Type II.



Estradiol (E2)

Primarily synthesized by **developing follicle** in the ovaries.

Reversibly converted into estrone by enzyme, 17β-hydroxysteroid dehydrogenase Type I.



Estriol (E3)

Synthesized from **estrone**, which can be converted from the hydroxylation of estradiol or 16-Hydroxyestrone.

Samavat & Kurzer, 2015

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I think of Estrogen
like three sisters

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Boothby, Lisa A., et Al. "Bio identical hormone therapy: a review" in *Menopause,* 2004, vol 11, No. 3, pp.356-367

	Estrogen Receptor- Alpha	Estrogen Receptor- Beta
17- Beta-estradiol	100	100
17- alpha-estradiol	58	11
Estriol	14	21
Estrone	60	37
4-OH-Estradiol	13	7
2-OH-Estrone	2	0.2
Tamoxifen	4	3
Raloxifene	69	16

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Other sources of Estrogens

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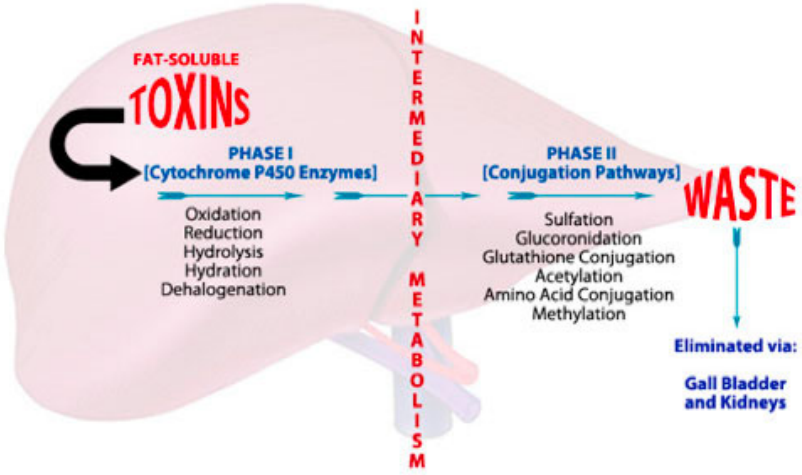
PHASES OF DETOXIFICATION



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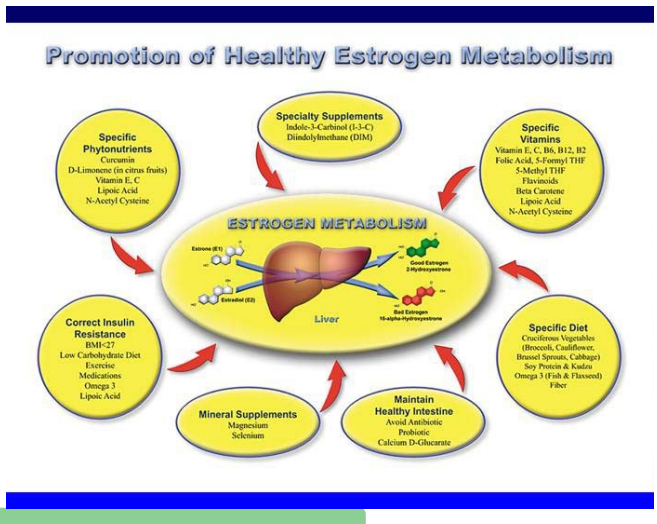
Healthy Estrogen Metabolism



- Specific Phytonutrients
- Specific Supplements
- Specific Vitamins
- Specific Diet
- Healthy Intestine
- Minerals
- Correct Insulin Resistance

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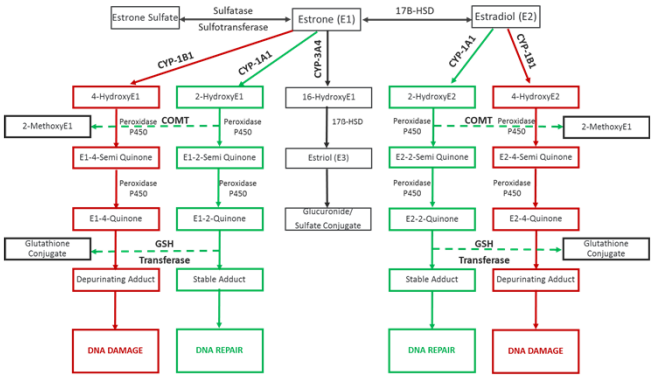
Estrogen Metabolism



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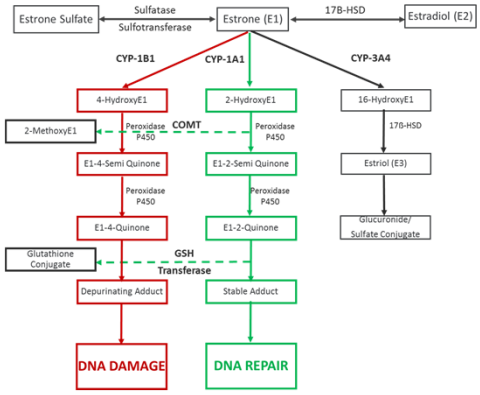
Estrone Metabolism



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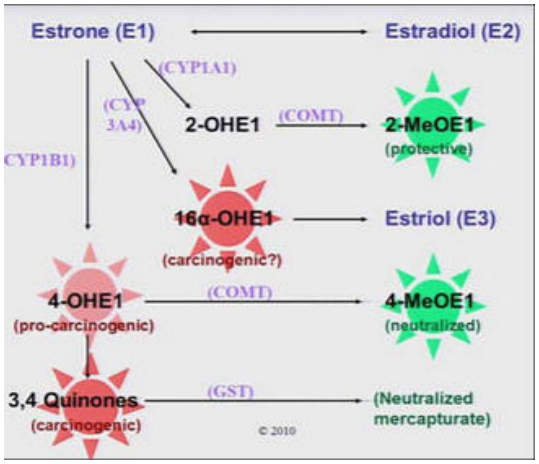
Estrogen Metabolism

More simplified . . .



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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 & Kurzer, 2015
2. Gupta et al., 1998

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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 et al., 2003
2. Lakhani et al., 2003
3. Lottering et al., 1992

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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 et al., 1997
2. Cavalieri & Rogan, 2010
3. Liehr & Ricci

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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 et al., 1992
2. Castagnetta et al., 2002
3. Obi et al., 2011
4. Huang et al., 2012

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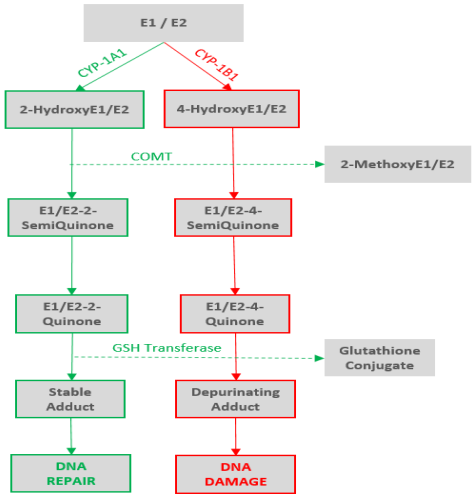
Preventing Negative Estrogen Burden

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. Cavalieri et al., 2001

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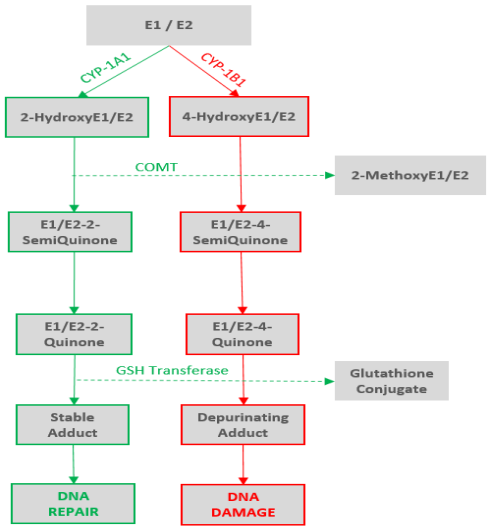
Preventing Negative Estrogen Burden

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 & Rogan, 2010
2. Zahid et al., 2008

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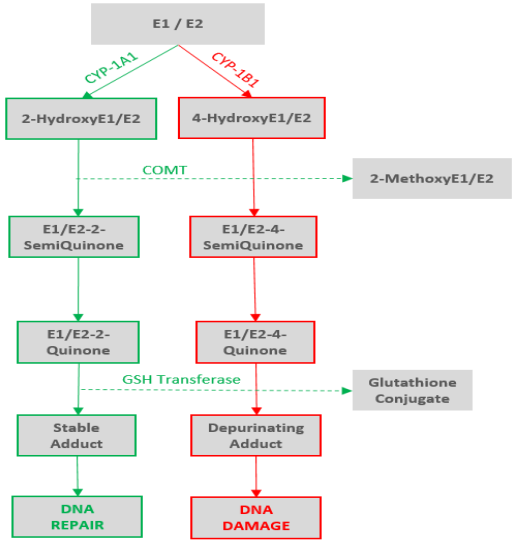
Preventing Negative Estrogen Burden

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 & Rogan, 2010
2. Zahid et al., 2008

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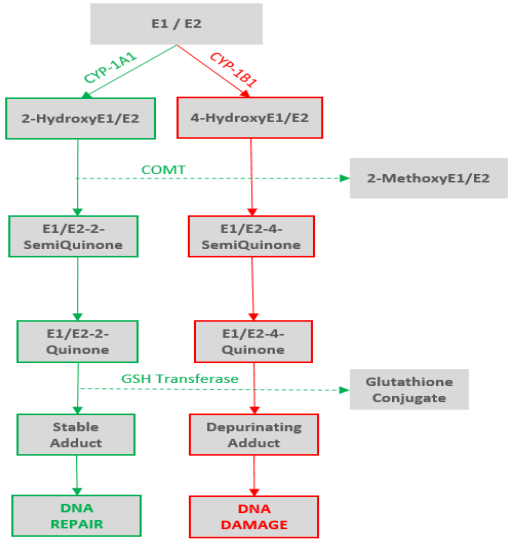
Preventing Negative Estrogen Burden

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 et al., 1996
2. Vassilopoulou-Sellin et al., 1999

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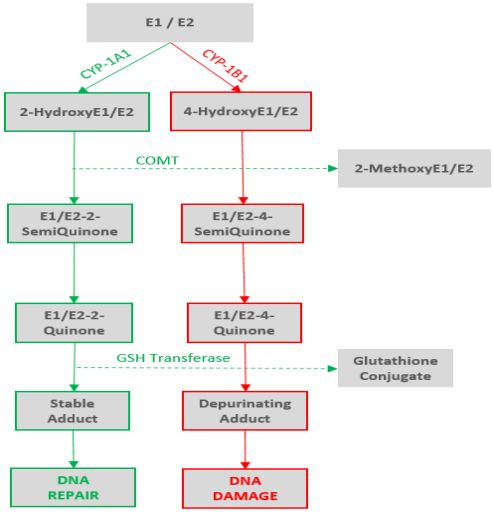
Preventing Negative Estrogen Burden

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. Eskinet al., 1995
2. Ghent et al., 1993
3. Conn et al., 2000
4. Smyth, 2003
5. Stoddard II et al., 2008

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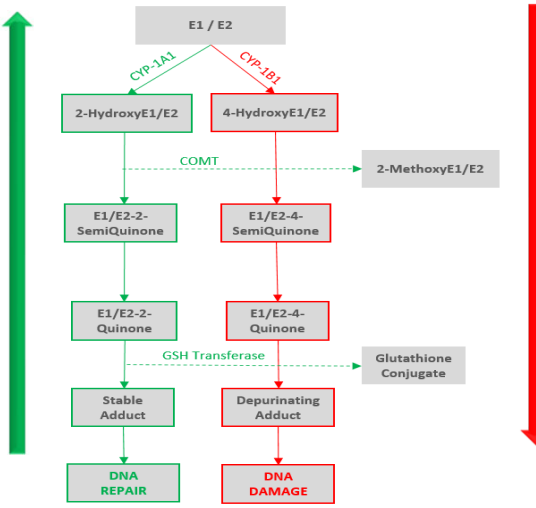
Preventing Negative Estrogen Burden

Increase **2-HydroxyE** Pathway Activity



Reduce **4-HydroxyE** Pathway Activity

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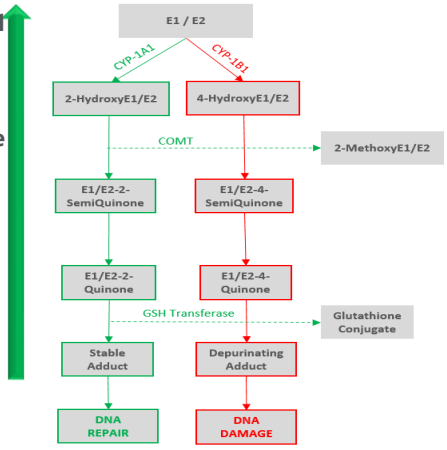
Preventing Negative Estrogen Burden

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



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

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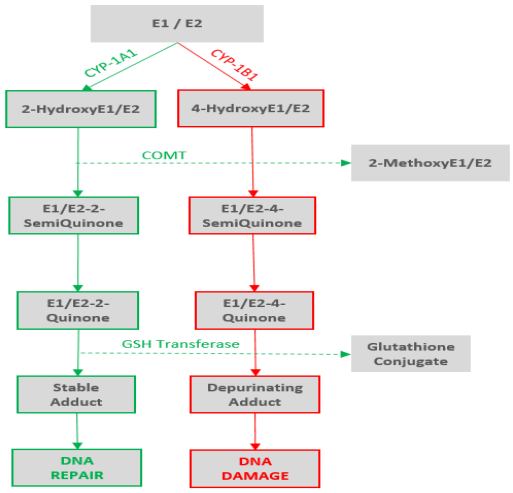
Preventing Negative Estrogen Burden

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. Bouvinck et al., 1996
2. Wolczanek et al., 1997

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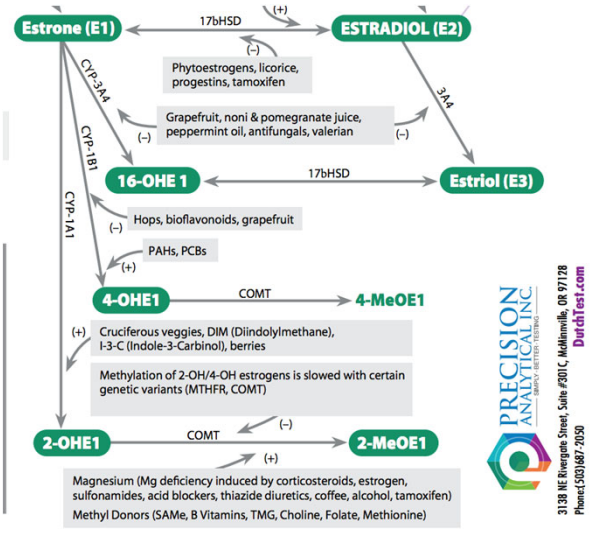
Urinary Hormone Results

Estrogens & Estrogen Metabolites



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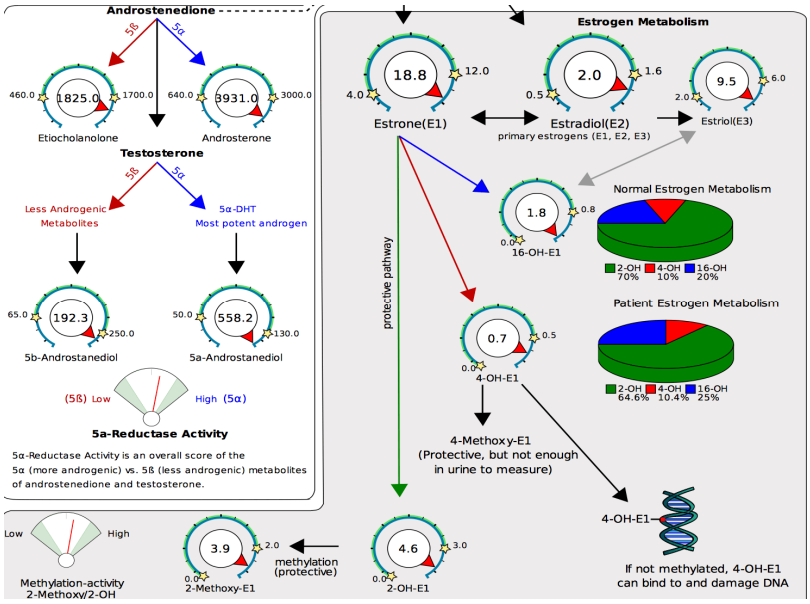
DUTCH sample report



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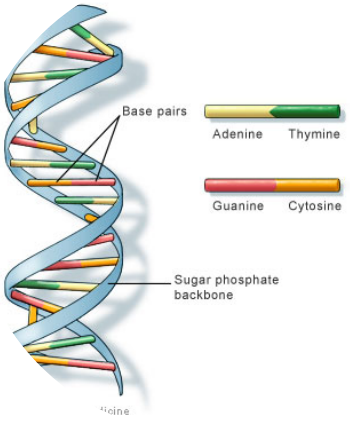

Genetics 101

What is DNA?

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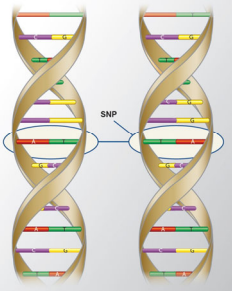
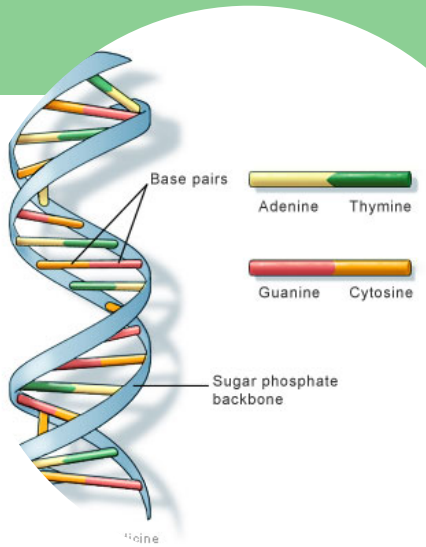
Genetics 101

What is a Single Nucleotide Polymorphism (SNP)?

A SNP (pronounced "snip") is a DNA sequence variation that occurs when a single nucleotide (A, T, C, or G) in the genome sequence is modified.

SNPs do not necessarily cause disease, but they can help determine the likelihood that someone will develop a particular illness.





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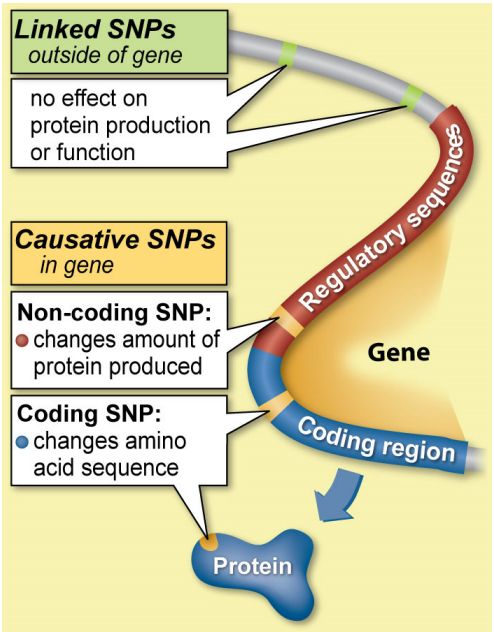
Not all SNPs are significant

It depends on where it is located.



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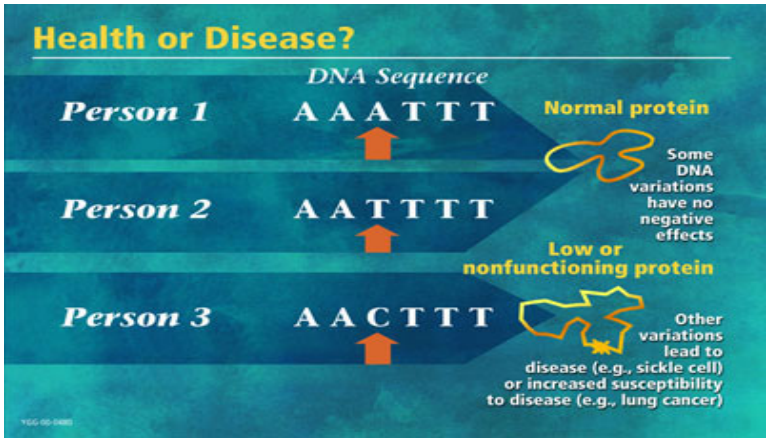
Genetics 101

Effects of SNPs on protein shape



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Genetics 101

Some SNPs change the meaning but not the function

Dr. Jay Scott

Dr. Joy Scott

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Genetics 101

Some SNPs are of no consequence

Are you coming too?

Are you two coming?

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Genetics 101

Some SNPs just denote ethnicity

Color
Personalize

Colour
Personalise

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Genetics 101

Some SNPs totally change the meaning

Cut

Cat

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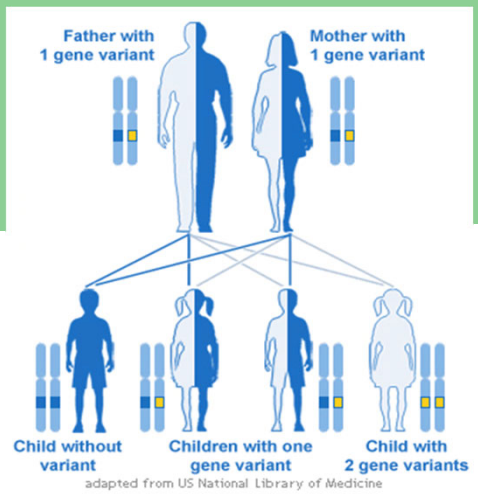
Genetics 101

Genetic Inheritance

- Heterozygous - one variation
- Homozygous - two variations



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Genetic Polymorphisms

MTHFR C677T

Methylenetetrahydrofolate

- 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 & Kagawa, 2017
2. Miller 2008

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Genetic Polymorphisms

MTHFR C677T

Treatment of MTHFR C677T

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 et al., 2008

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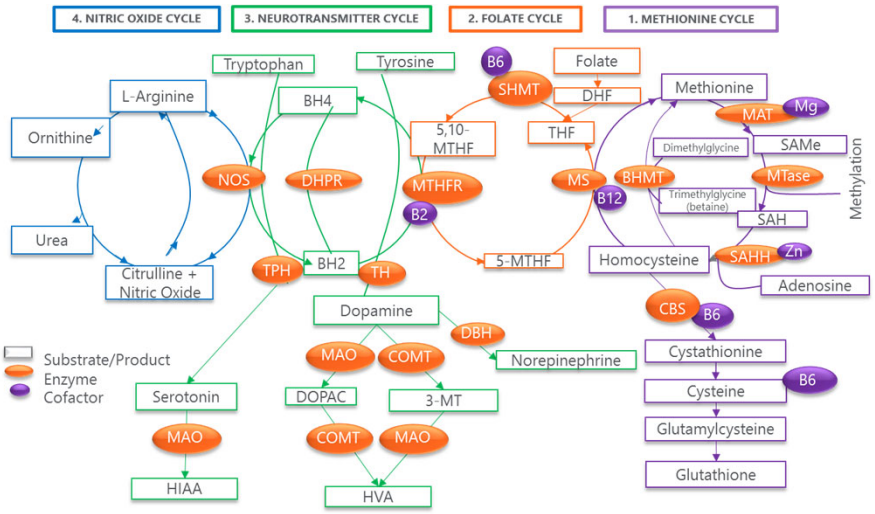

What is Methylation?

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Genetic Polymorphisms

COMT

Catechol-O-Methyl Transferase (COMT)

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 levels1, 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 et al., 2015
2. Tan et al., 2016
3. Ashton et al., 2006

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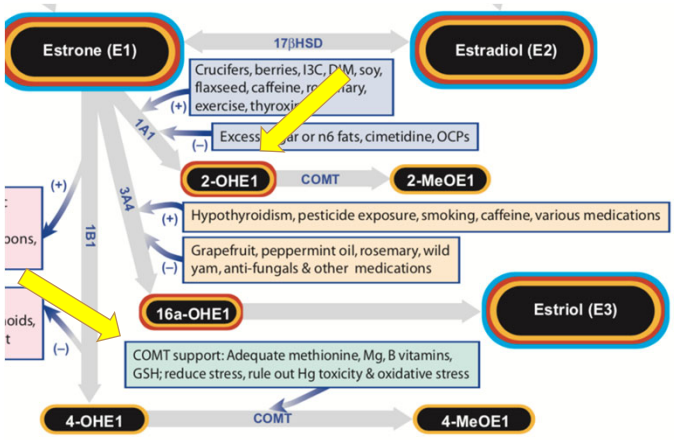
Genetic Polymorphisms

COMT



1. Kotyuk et al., 2015
2. Tan et al., 2016
3. Ashton et al., 2006

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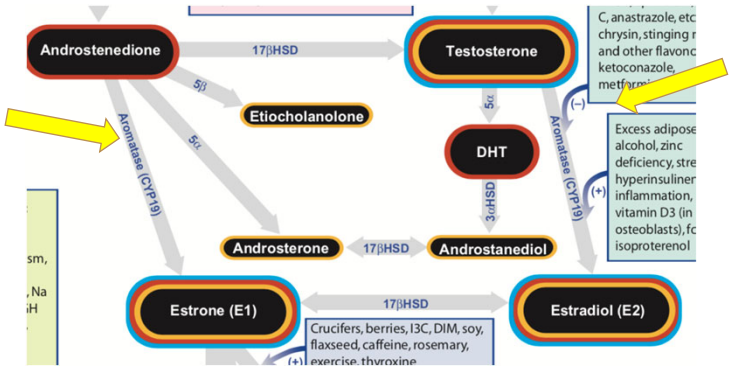
CYP 19A1

Converts Androgens (androstenedione and testosterone) into estrogens (estradiol and estrone)
If this is a fast version, it will make estrogen dominance worse



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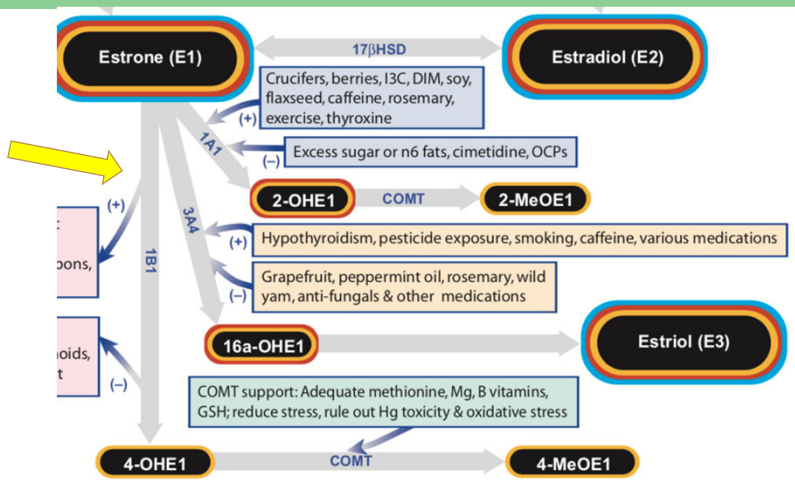
CYP 1B1

Metabolizes estrogen in 4 OH estrogens

If this is FAST, will increase the risk of estrogen dominance , especially if coupled with a slow COMT



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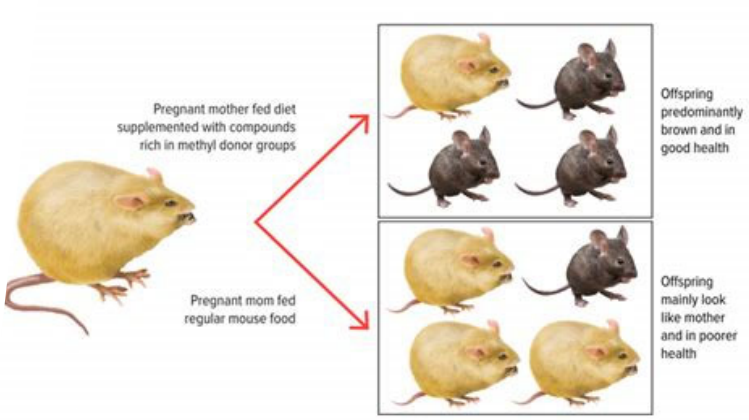
EPIGENETICS-Agouti Mice Experiment



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Case – Part 1

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Emma was a new patient, and her main complaint was severe PMS and anxiety. She has a lot of stress with 3 young children. The oldest was born prematurely at 28 weeks and has mild cerebral palsy.

Her main complaints were anxiety, poor sleep, and stress.

Medications: Vitamin D
Multivitamin

Family history: Thyroid disease- mother
Celiac disease- sister

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Case – Part 1

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- CORTISOL - PM: 6.8
- FERRITIN, SERUM: 40
- PROGESTERONE: 13.0
- TRIIODOTHYRONINE,FREE,SERUM: 2.8
- **DHEA-SULFATE: 361.1 High**
- **VITAMIN D, 25-HYDROXY: 21.3 Low**
- TSH: 2.080
- T4,FREE(DIRECT): 1.00
- REVERSE T3, SERUM: 13.8
- PREGNENOLONE, MS: 135
- **DIHYDROTESTOSTERONE: 3.2 Low**
- IRON BIND.CAP.(TIBC): 355
- UIBC: 272
- IRON, SERUM: 83
- IRON SATURATION: 23
- ENDOMYSIAL ANTIBODY IGA: NEGATIVE
- T-TRANSGLUTAMINASE (TTG) IGA: <2
- T-TRANSGLUTAMINASE (TTG) IGG: <2
- IMMUNOGLOBULIN A, QN, SERUM: 290

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Saliva Hormone Results 2015

Salivary Hormone Results

Estradiol ♦ pmol/L	7.0

	Reference Range
Follicular	2.8-8.8 pmol/L
Peak *	4.5-19.1 pmol/L
Luteal	2.8-8.2 pmol/L
Menopausal	3.7-9.4 pmol/L
Male	3.1-7.4 pmol/L
* Peak = Days 11 and 12	

Testosterone ♦ pmol/L	<30

	Reference Range
Premenopausal	34-148 pmol/L
Menopausal	34-148 pmol/L
Male	110-513 pmol/L

Estrone pmol/L	14.0

	Reference Range
Menopausal	4.7-18.9 pmol/L

Progesterone ♦ pmol/L	397

	Reference Range
Follicular	120-593 pmol/L
Peak *	328-1385 pmol/L
Luteal	145-797 pmol/L
Menopausal	163-669 pmol/L
Male	141-529 pmol/L
* Peak = Days 18 and 20	

Estriol pmol/L	80

	Reference Range
Menopausal	<= 133 pmol/L

P/E2 Ratio	57

	Reference Range
Follicular	23-159
Luteal	25-141
Menopausal	33-116

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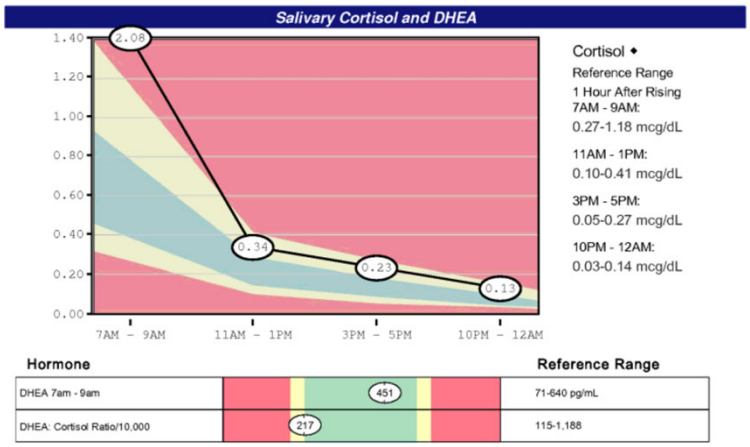
Saliva Hormone Results 2015



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Treatment Plan

Pt was treated with cyclic oral Progesterone 100mg days 14 until the next cycle begins

Vitamin D was replaced with D3 drops

Adaptogens were suggested for high cortisol

Patient information – Permission for use granted by T. Scott, MD, FACOG, FAAFM, ABOIM, NCMP
Laboratory Results – Adapted from Genova Diagnostics. Permission for use granted by A.L. Peace-Brewer, PhD, D(ABMLI), Lab Director at Genova Diagnostics. Genova Diagnostics is not involved in the teachings, opinions, or the diagnostic and treatment modalities discussed in this program.

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Genomics Results- 2016

COMT	Val158Met AG	Intermediate COMT Activity	Val158Met
CYP1A2	*1F/*1F	Normal Metabolizer - Higher Inducibility	*1C, *1D, *1E, *1F, *1J, *1K, *1L, *1V, *1W
CYP2B6	*1/*5	Unknown Phenotype	*2, *3, *5, *6, *9, *18, *28
CYP2C19	*1/*1	Normal Metabolizer	*2, *3, *4, *4B, *5, *6, *7, *8, *9, *10, *17
CYP2C9	*1/*2	Intermediate Metabolizer	*2, *3, *5, *6, *8, *11, *27
CYP2D6	*4/*4	Poor Metabolizer	*2, *3, *4, *4M, *6, *7, *8, *9, *10, *11, *12, *14A, *14B, *17, *29, *35, *41, *56A, *56B, *5 (gene deletion), XN (gene duplication)
CYP3A4	*1/*1	Normal Metabolizer	*2, *3, *12, *17, *22
CYP3A5	*3/*3	Poor Metabolizer	*1D, *3, *3C, *6, *7
DRD2	-241A>G T/T	Homozygous for rs1799978 T Allele	-241A>G, rs2283265
DRD2	rs2283265 C/C	Homozygous for rs2283265 C allele	-241A>G, rs2283265
Factor II	20210G>A GG	Normal Thrombosis Risk	20210G>A
Factor V Leiden	1691G>A GG	Normal Thrombosis Risk	1691G>A
MTHFR	1298A>C AA	Normal MTHFR Activity	1298A>C
MTHFR	677C>T CT	Reduced MTHFR Activity	677C>T

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CASE FOLLOW-UP

PT presented back to review serum labs- done mid luteal

Lab	Results	Normal Range
Estrone:	86	54-179
Estradiol:	122	43-211
DHEAS	312 H	57-297
Total Testosterone	20	8-48
Free Testosterone	2.6	0.0-4.2
Progesterone	11.0	1.8- 23.9

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CASE FOLLOW-UP

- Pt had previously been seen for stool results
- Digestive Issues
- Poor Diversity
- Decided to change to Progesterone troche for better aborption – 75mg

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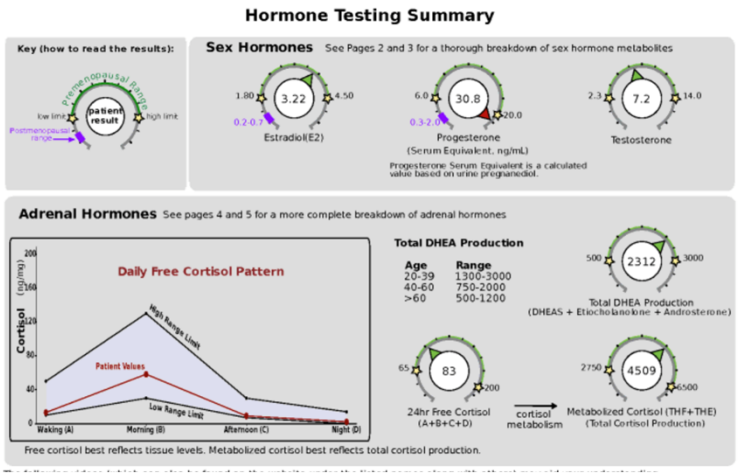
CASE Follow Up- DUTCH TESTING



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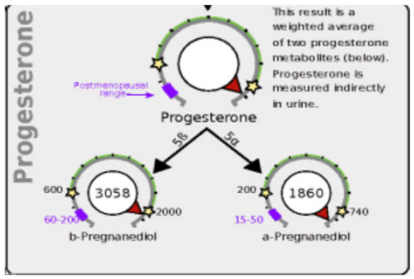
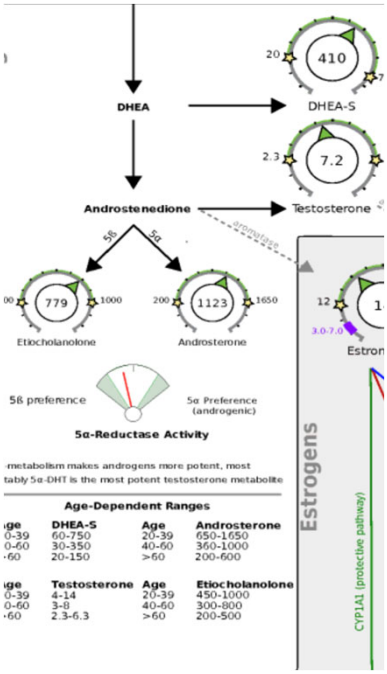
Androgens and Progesterone





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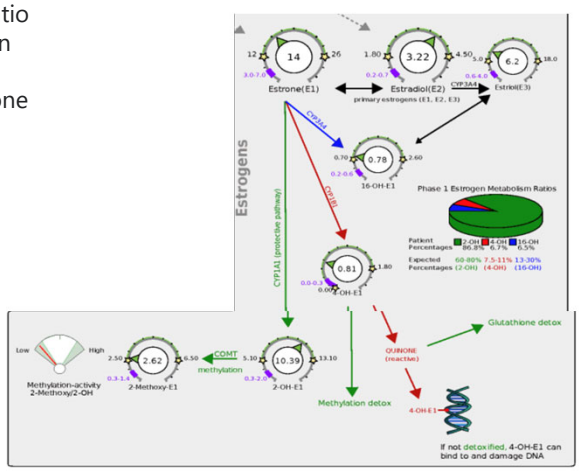
Estrogen Metabolism

- Important to assess the balance and ratio between the different types of estrogen
- Assess phase 1 and phase 2
- Pay attention to quantity of 4 OH Estrone



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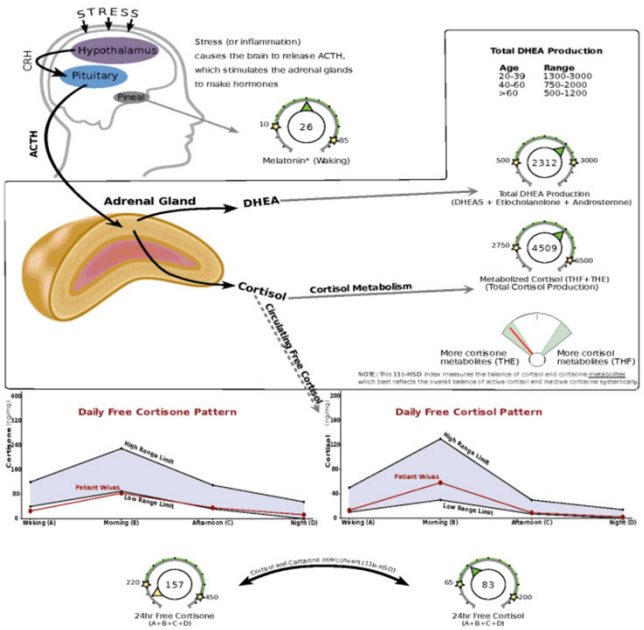

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Organic Acids

Category	Test		Result	Units	Normal Range
Nutritional Organic Acids					
Vitamin B12 Marker (may be deficient if high) - (Urine)					
	Methylmalonate (MMA)	Above range	2.4	ug/mg	0 - 2.2
Vitamin B6 Markers (may be deficient if high) - (Urine)					
	Xanthurenate	Within range	0.4	ug/mg	0 - 1.4
	Kynurenate	Within range	2.4	ug/mg	0 - 7.3
Glutathione Marker (may be deficient if low or high) - (Urine)					
	Pyroglutamate	Within range	45.7	ug/mg	32 - 60
Neurotransmitter Metabolites					
Dopamine Metabolite - (Urine)					
	Homovanillate (HVA)	Within range	6.4	ug/mg	4 - 13
Norepinephrine/Epinephrine Metabolite - (Urine)					
	Vanilmandelate (VMA)	Within range	4.9	ug/mg	2.4 - 6.4
Melatonin (*measured as 6-OH-Melatonin-Sulfate) - (Urine)					
	Melatonin* (Waking)	Within range	26.1	ng/mg	10 - 85
Oxidative Stress / DNA Damage, measured as 8-Hydroxy-2-deoxyguanosine (8-OHdG) - (Urine)					
	8-OHdG (Waking)	Within range	1.3	ng/mg	0 - 5.2

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Treatment options

HOW WOULD YOU CHANGE PROGESTERONE DOSE?

HOW WOULD YOU SUPPORT METHYLATION?

WHAT WOULD YOU GIVE FOR ADRENAL SUPPORT?

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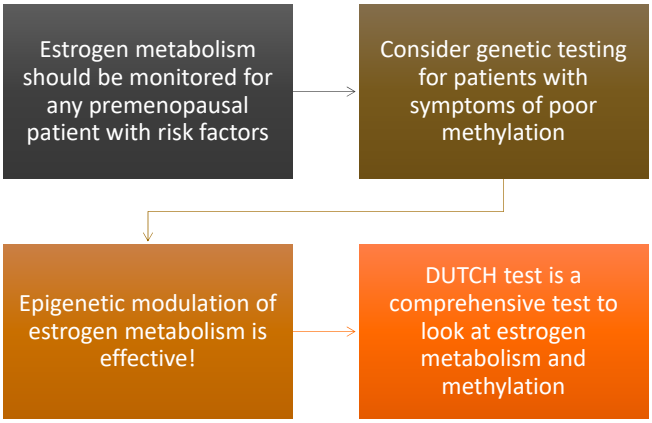
Conclusions



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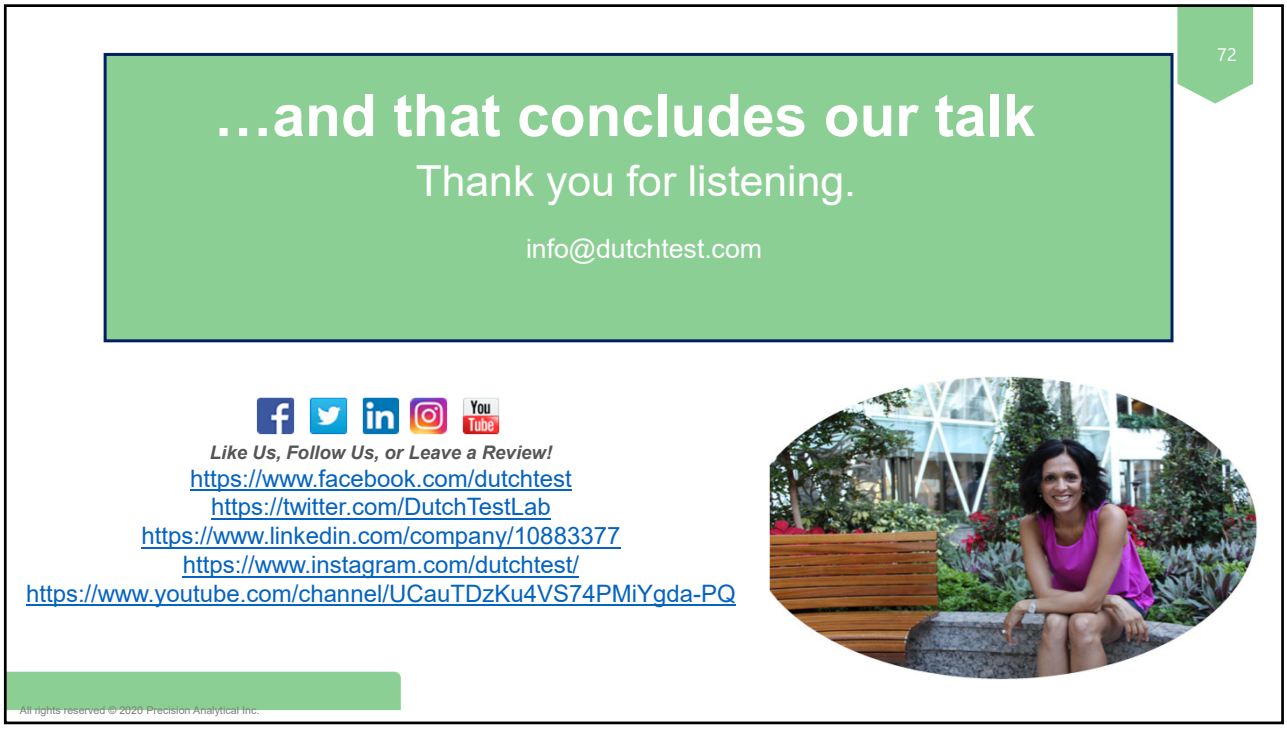
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