



The Steroidogenic Pathway: Understanding What Influences Each Step

Ellen Antoine, DO, FACEP, ABIHM, IFMCP

June 22, 2016



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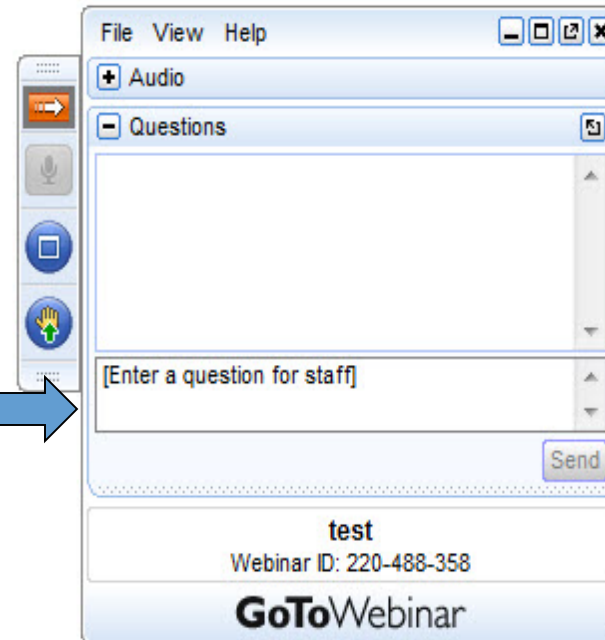
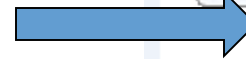
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Technical Issues & Clinical Questions

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.



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Objectives:

- Overview of the steroidogenic cascade
- Metabolic pathways (positive and negative influences)
- Case studies to apply hormone assessments in clinical practice



Disclaimer

- The suggestions in this webinar are just that....suggestions. They are for educational purposes only.
- They are based on my research as well as my anecdotal experience with patients.
- These are not necessarily recommended for all patients and caution should be used in those with abnormal liver or kidney function.
- Consider these a guideline and as such should not take the place of your clinical judgment nor be routine practice for all patients. Always practice personalized medicine and identify and address root causes of disease.
- Genova Diagnostics, and Ellen Antoine, DO, FACEP, ABIHM, IFMCP are not responsible for any adverse effects or consequences resulting from the use of any of these suggestions in this webinar.



A Few Basics

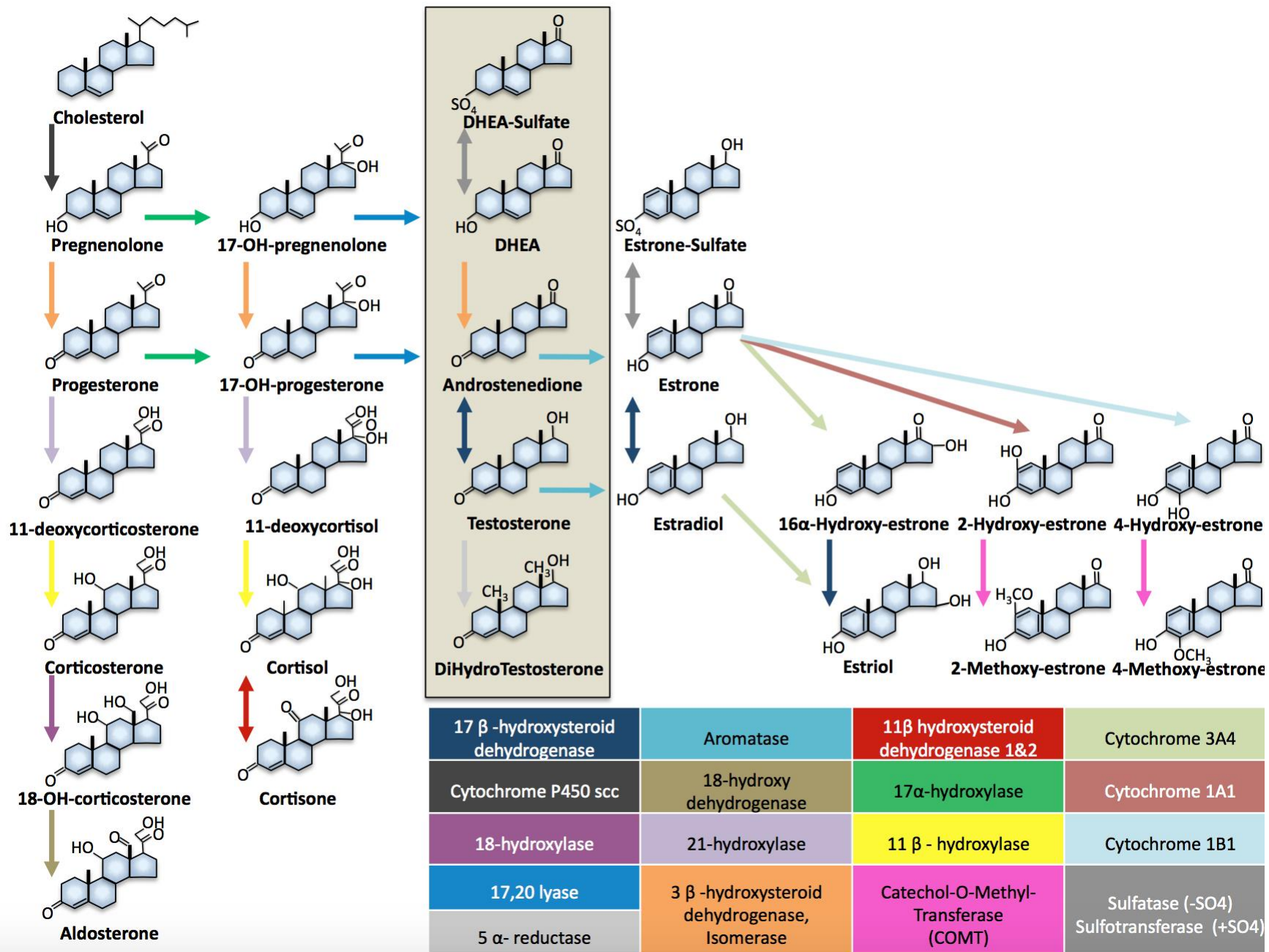
- No two patients are alike
 - Individualized evaluation leads to a more effective intervention
- Hormones do not function in isolation
 - Imbalances in one area will affect another
- The metabolic pathways taken by hormones will ultimately determine their effects

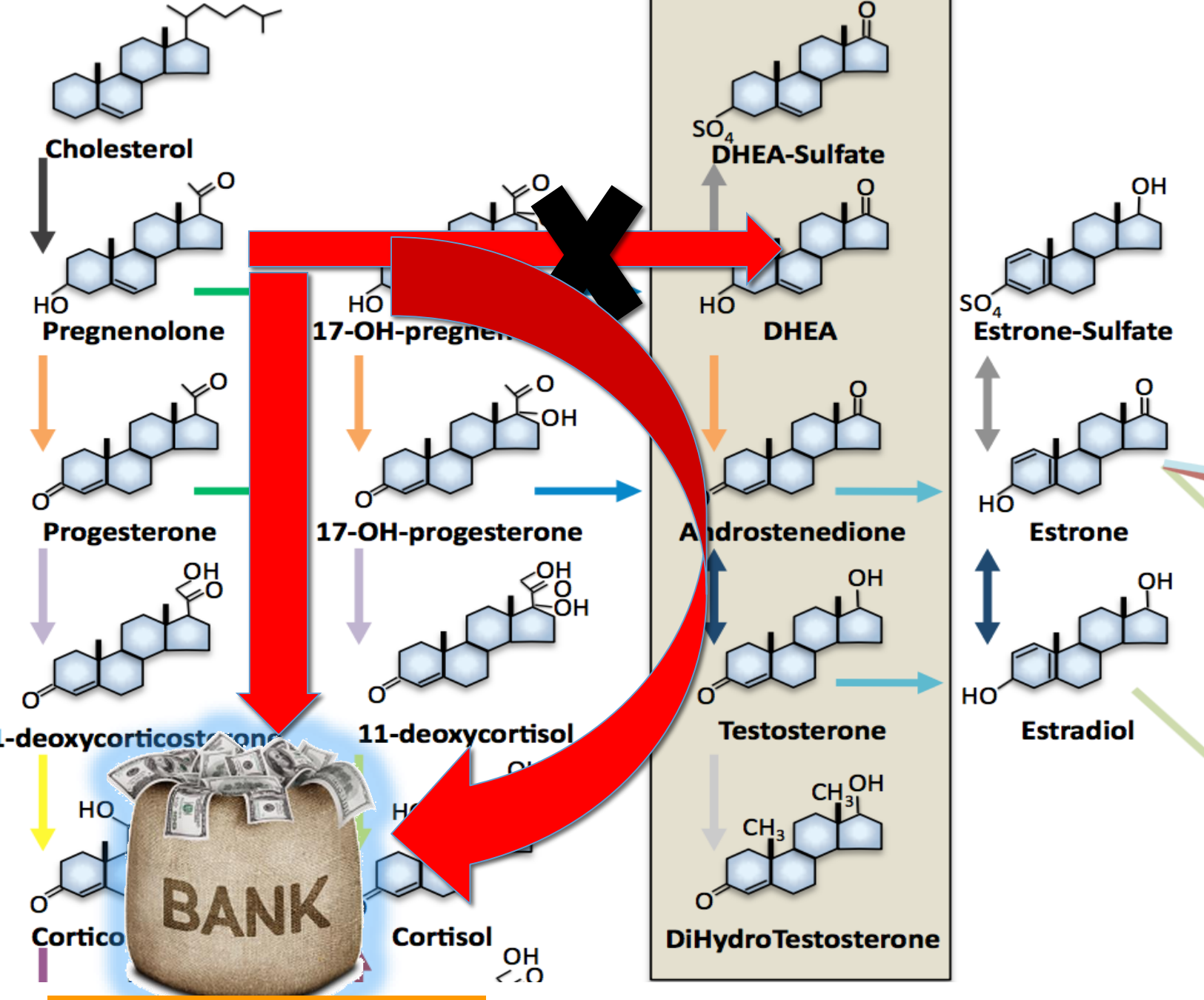
We need to understand this cascade in order to know how and when to intervene



Clinical Concerns

- Menopause
- Andropause
- Cognitive decline
- Fatigue
- Depression
- Heart disease
- Cancer
- Weight gain
- Osteoporosis
- Decreased libido/sexual dysfunction
- Insomnia
- Migraine headaches
- Mood swings/anxiety
- Hair loss/Hair in places it shouldn't be
- Irregular periods
- Erectile dysfunction





Entertainment Money

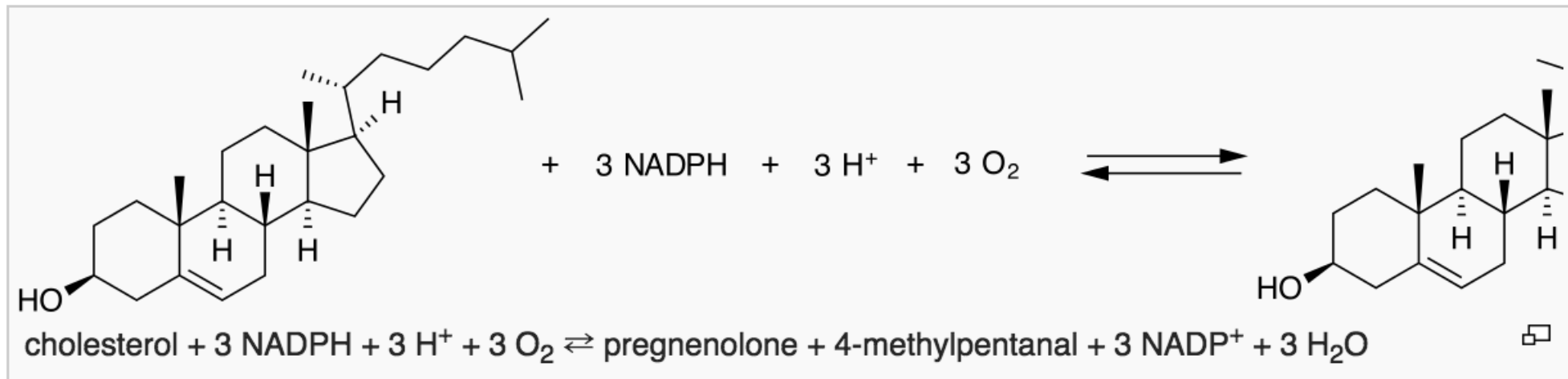
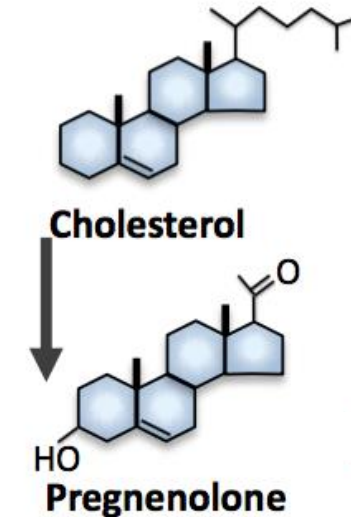
Pregnenolone Steal
Cortisol Steal
Progesterone Steal

SURVIVAL ACCOUNT



First and rate-limiting step in steroidogenesis is the conversion of cholesterol to pregnenolone by a single enzyme, P450scc (CYP11A1 gene)

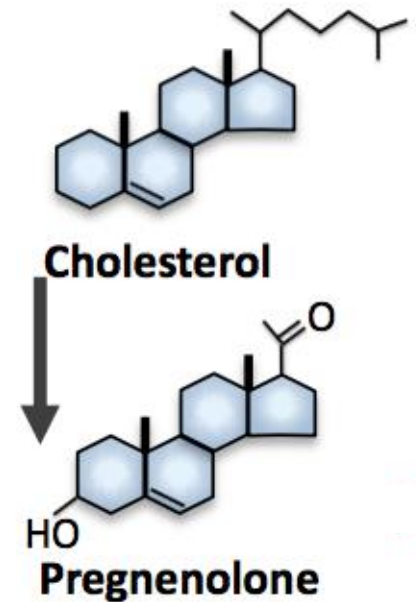
- Steroidogenic enzymes fall into 2 groups
 - **Cytochrome P450**
 - Type 1 – in the mitochondria
 - Type 2 – in the endoplasmic reticulum
 - **Hydroxysteroid dehydrogenase (HSDs)**
- Steroidogenic enzymes are modulated by cofactors

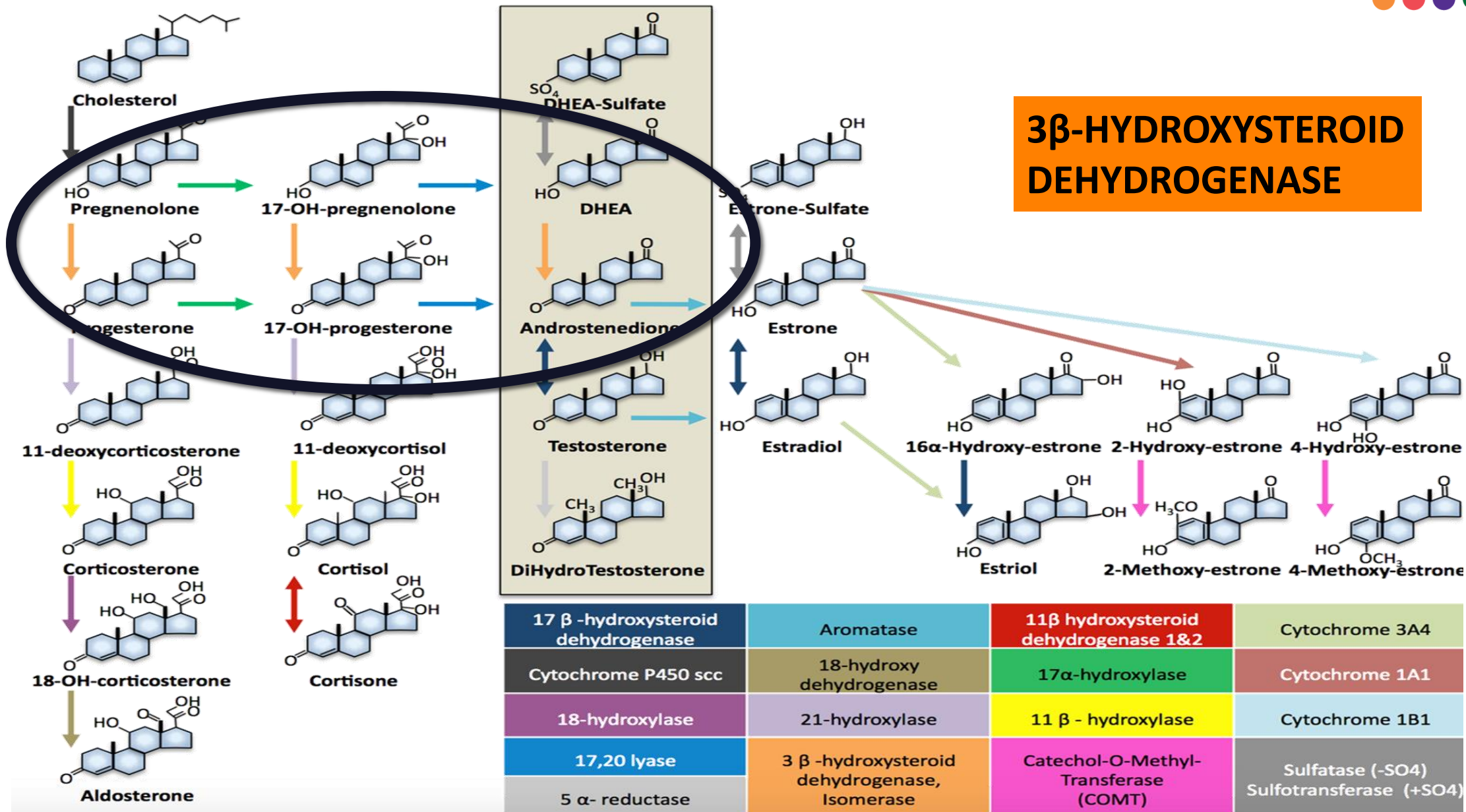




Cholesterol and Pregnenolone

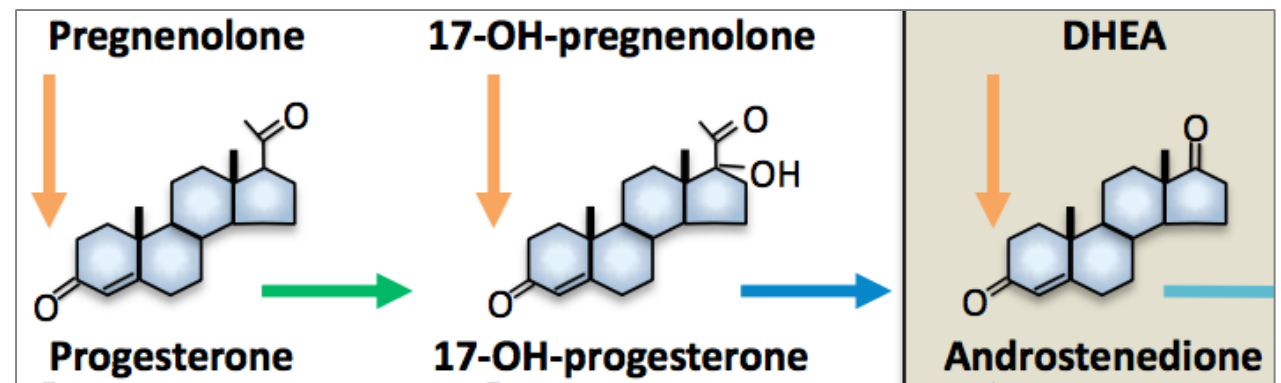
- Cholesterol
 - Building block of all the steroid hormones
 - Need healthy fats and an adequate cholesterol level to make hormones
 - Very low cholesterol levels contribute to poor hormone production
 - Statins, Red Yeast Rice, Binders, and genetically low cholesterol
 - Associated with increased risk for cancer, suicide, cancer, memory concerns
- Pregnenolone
 - Manufactured primarily in adrenal glands
 - Nearly all other steroid hormones are made from this precursor
 - In times of chronic adrenal stress, levels drop
 - Aging leads to a decrease – a biomarker of aging
 - Enhances memory and reduces stress-induced fatigue
 - Found in mice to be 100 x more effective for memory enhancement than other steroids
 - Other benefits include increased resistance to stress, reduced PMS, improved immunity, and repair of myelin sheaths





3 β -Hydroxysteroid Dehydrogenase (3 β -HSD)

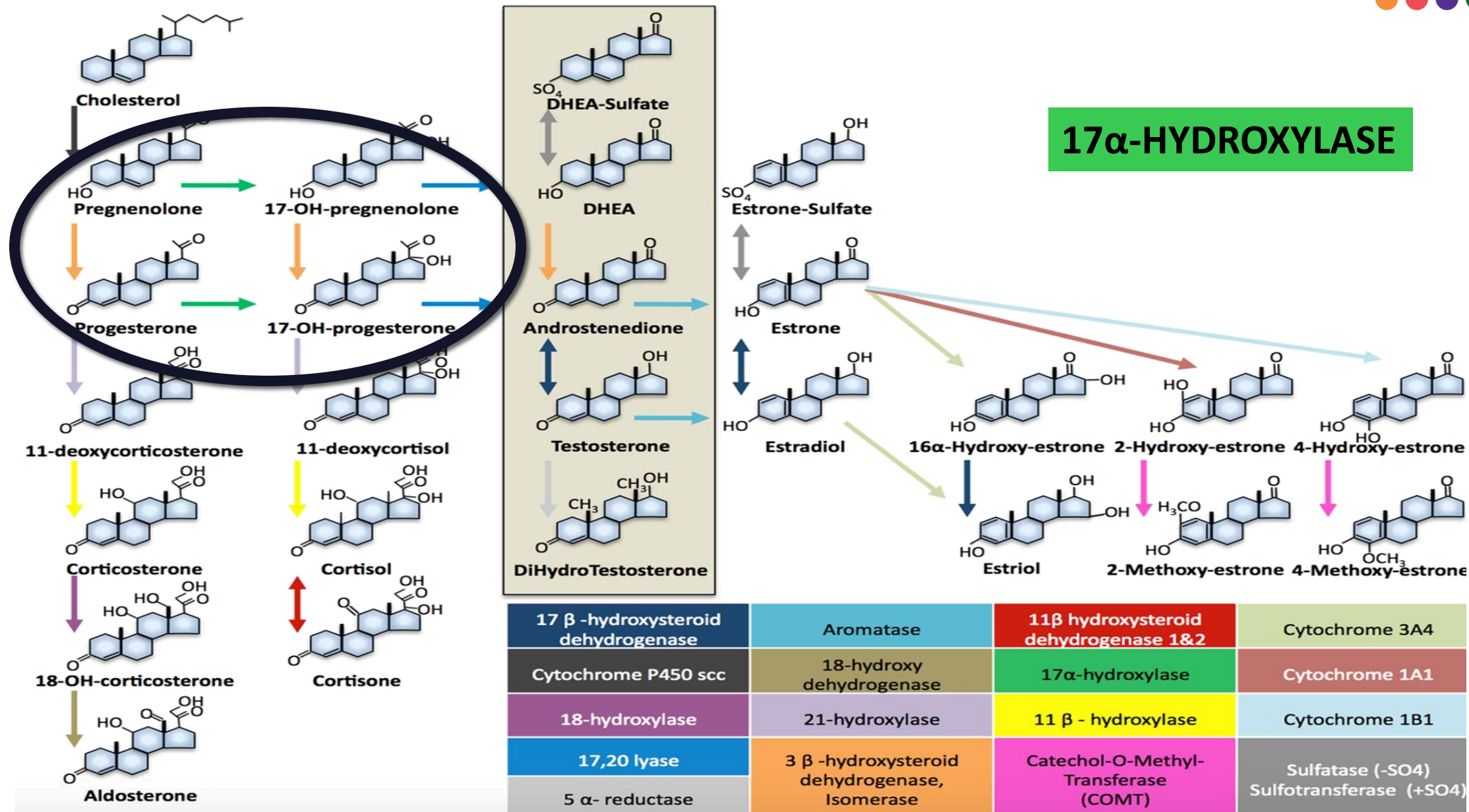
- Conversion of Pregnenolone to Progesterone
- Conversion of 17-OH Pregnenolone to 17-OH Progesterone
- Conversion of DHEA to Androstenedione
 - (also conversion of Androstenediol to Testosterone & 5 α -DHT to 5 α -Androstanediol)
- Only enzyme in adrenal pathway of corticosteroid synthesis that is NOT part of CYP450 enzymes
- Decreased activity:
 - Progestins
 - Metformin
 - Isoflavonoids (water soluble, plant pigments, legumes such as soy are the primary sources)
 - PCB toxicity
- Increased activity:
 - PCOS
 - High insulin
 - IL-4, IL-13 (associated with allergies)
 - Hyperthyroidism
 - Forskolin





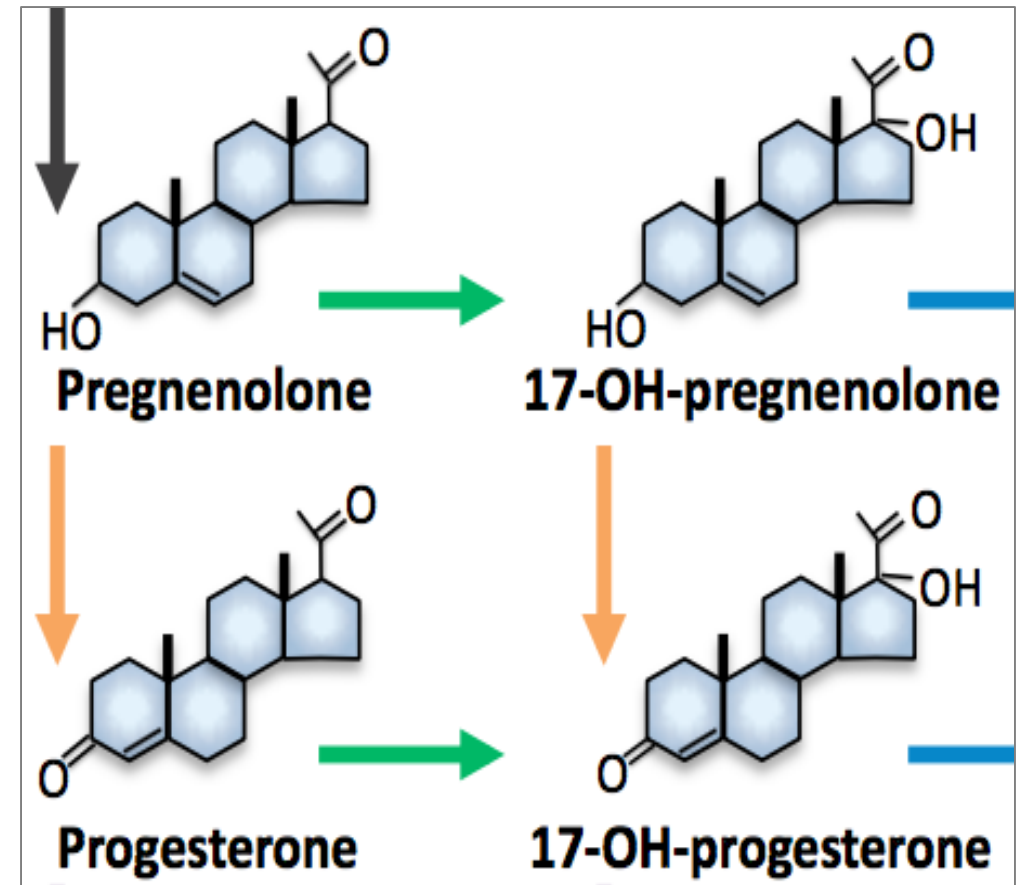
Progesterone

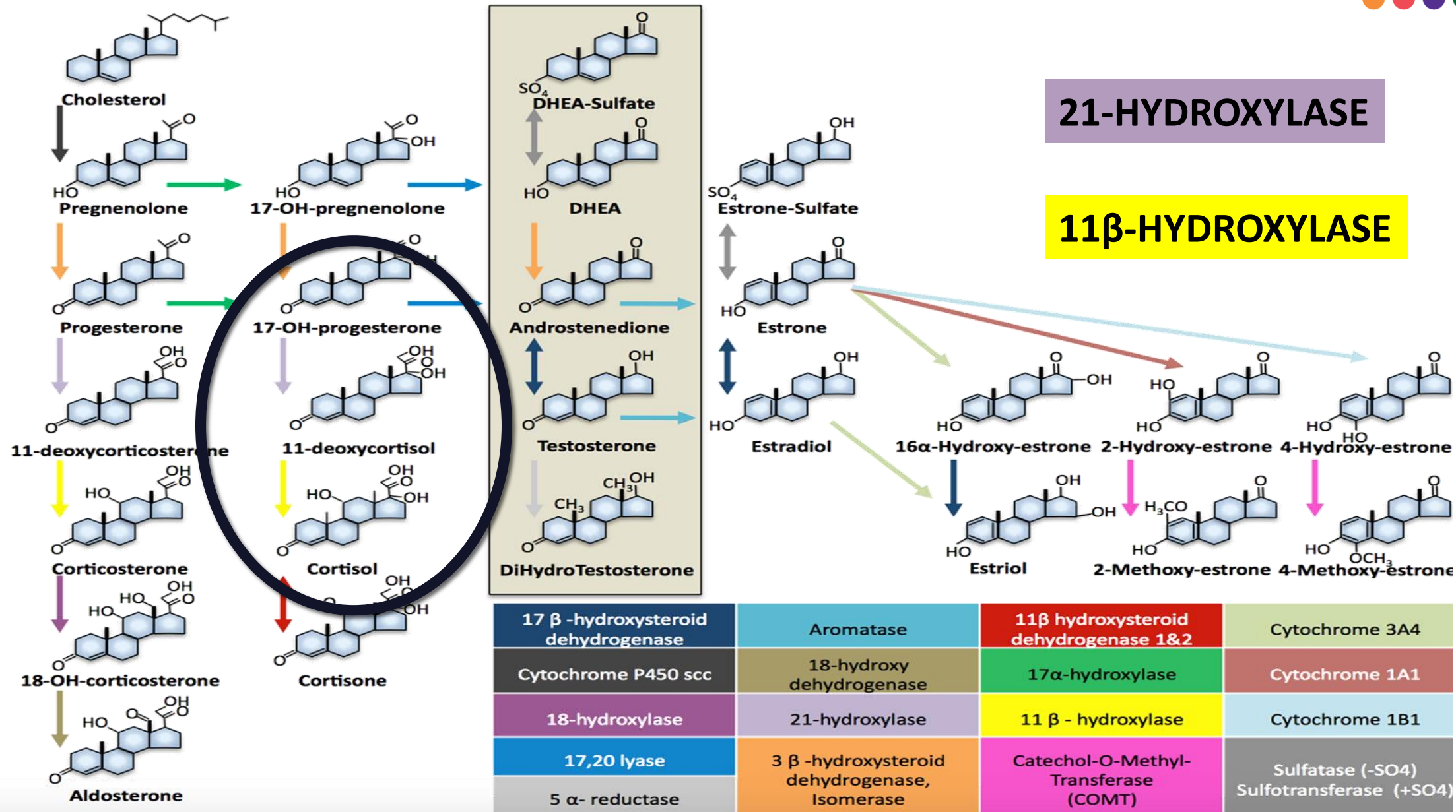
- Primarily made in ovaries (less in the adrenals)
- Increased progesterone:
 - Pregnancy
 - Pregnenolone administration (increased metabolites in urine but not actually increased blood progesterone levels)
 - Chaste Tree Berry (Vitex)
- Decreased progesterone:
 - Birth control pills
 - Stress
 - Increased insulin
 - Opioids
 - Luteal phase defect/anovulation
 - High prolactin
 - Underweight
 - Hypothyroidism
 - Hormonal IUD (Mirena – releases low levels of progestins)



17 α -Hydroxylase

- Converts Pregnenolone to 17-OH Pregnenolone
- Converts Progesterone to 17-OH Progesterone
- Downregulated activity:
 - Spironolactone
 - Azole antifungals
 - Congenital adrenal hyperplasia
- Upregulated activity:
 - High insulin
 - PCOS
 - Hyperglycemia
 - Stress
 - Alcohol





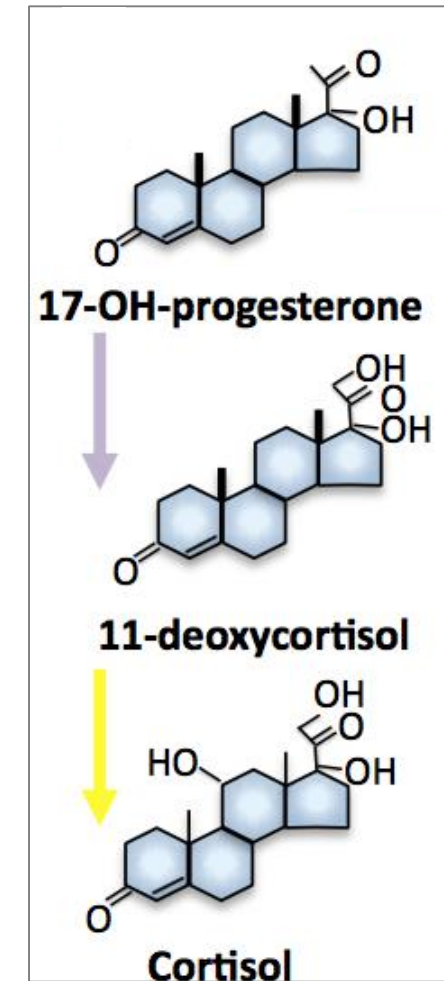
21-Hydroxylase

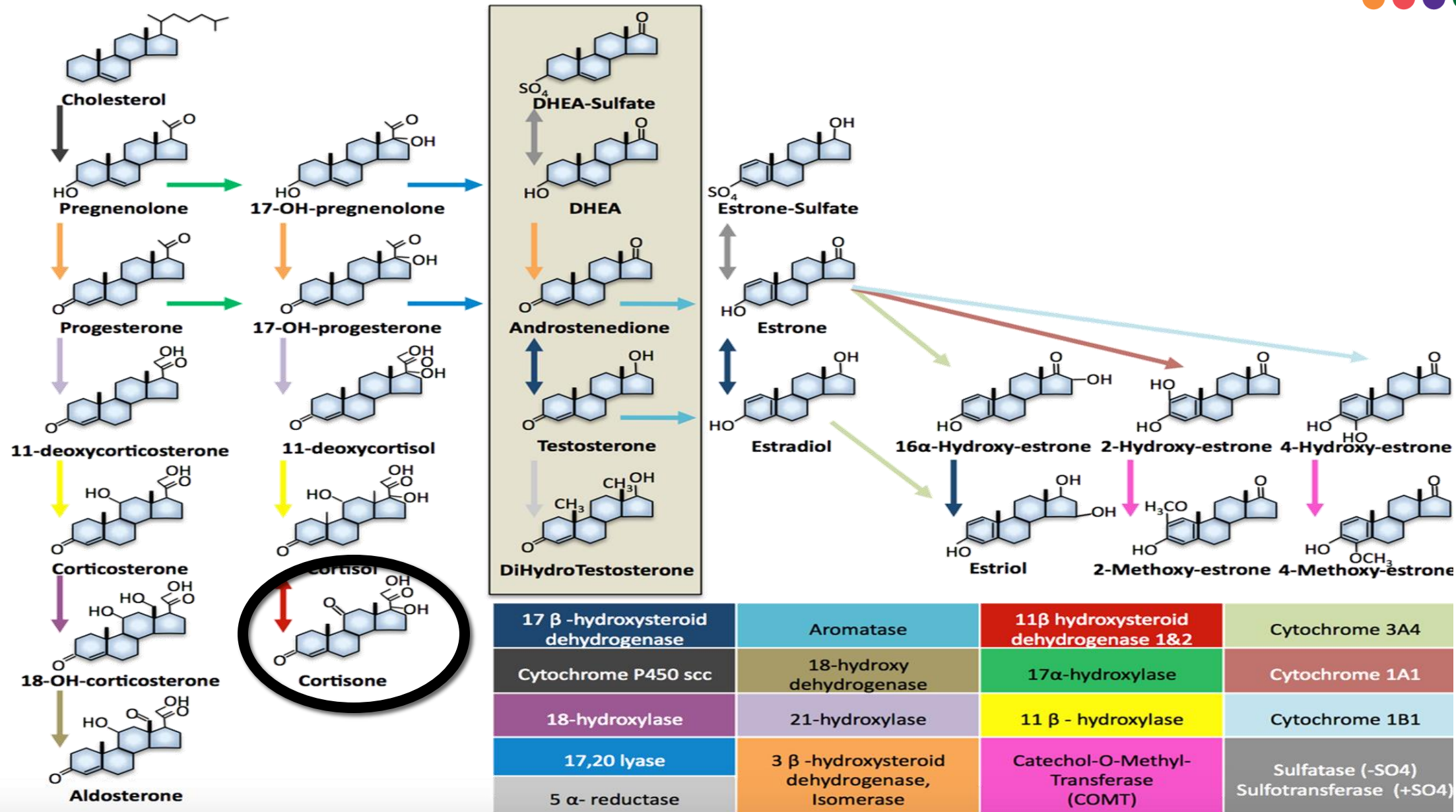
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11 β -Hydroxylase

Cortisol Production

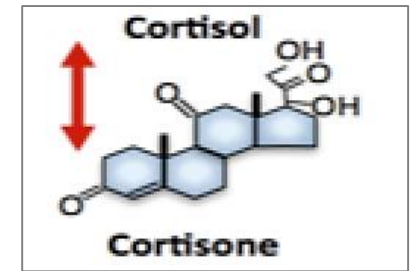
- Made in the adrenal glands
- Two enzyme reactions to convert from 17-OH-Progesterone
- Increased conversion to cortisol seen in:
 - Sodium depletion
 - High prolactin
 - Stress
 - Inflammation
 - Cushing's
 - Obesity
- Decreased cortisol:
 - Glucocorticoid use
 - Addison's Disease
 - Opioid use
 - Chronic marijuana use
 - Accutane

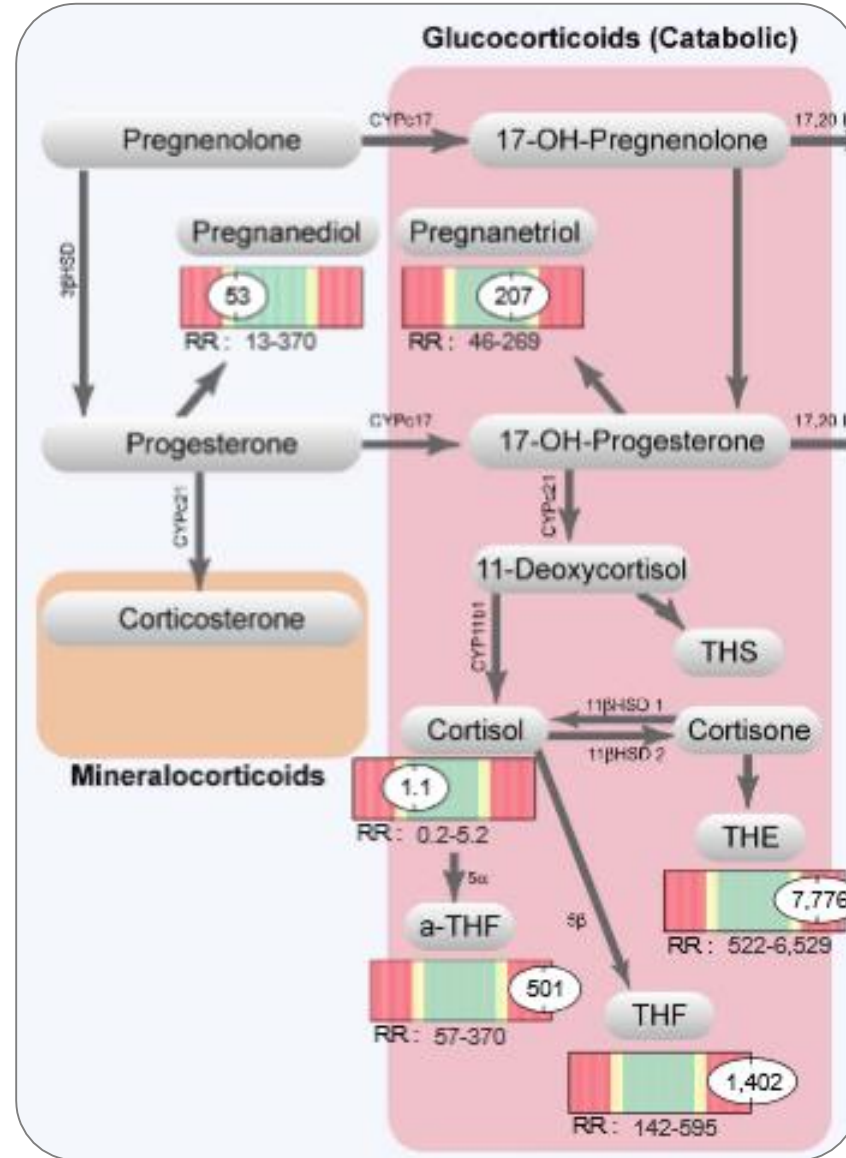


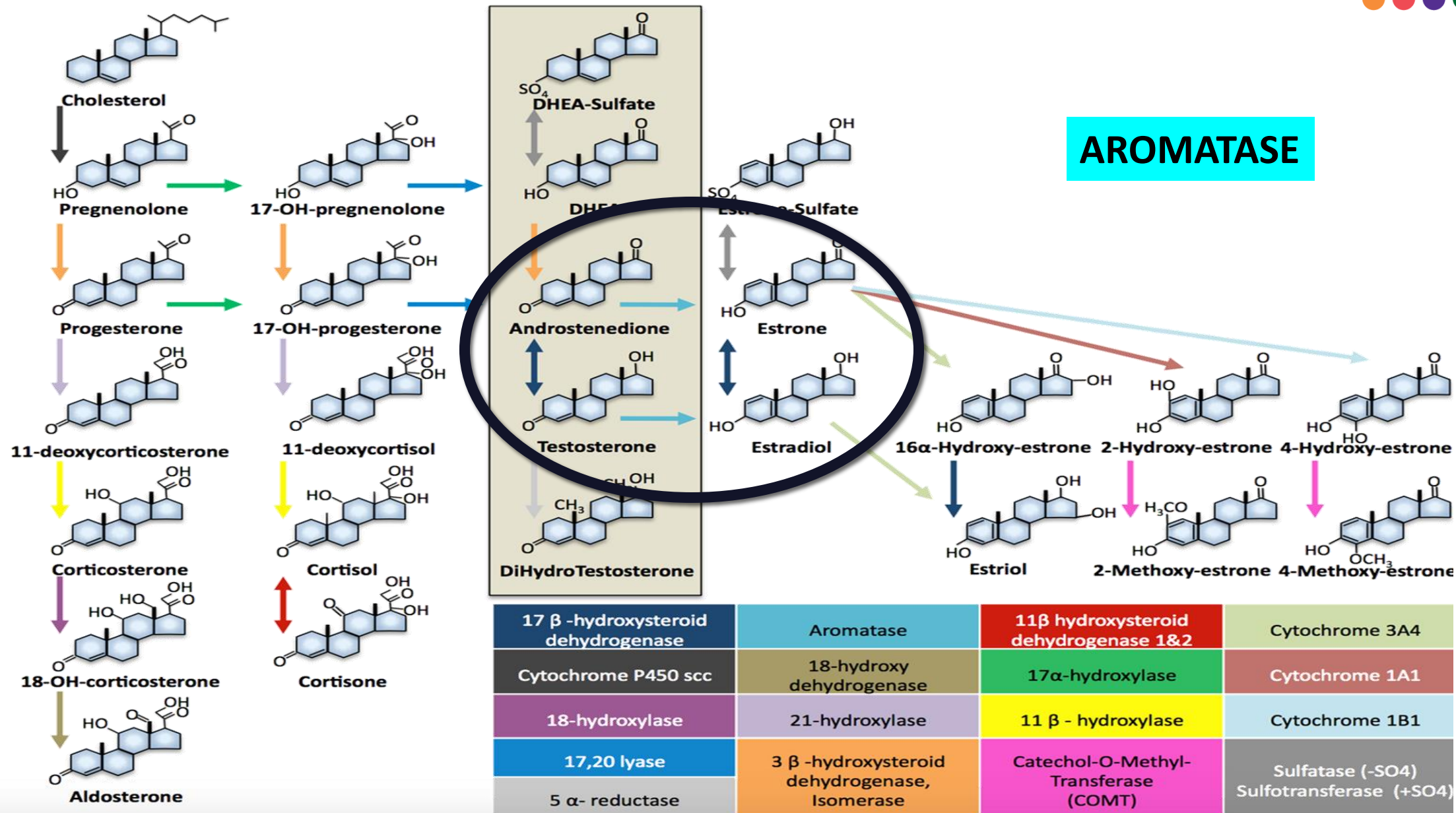


11 β – Hydroxysteroid Dehydrogenase 1 & 2

- Cortisol (active stress hormone) vs Cortisone (inactive form)
 - Via 11 β hydroxysteroid dehydrogenase 1&2
 - MORE CORTISOL
 - Stress, inflammation, Cushing's disease, obesity, hypothyroidism, licorice, grapefruit, high insulin, excess sodium, hypoxia, vitamin D, forskolin
 - MORE CORTISONE
 - Hyperthyroidism, estradiol, quality sleep, hGH (via IGF-1), good insulin sensitivity, reduced inflammation, Na restriction
- Cortisol is metabolized by: 5 α -Reductase and 5 β -Reductase (and 3 α -HSD) to a/b-THF & THE (cortisone metabolite) for excretion
 - Increased in:
 - Obesity
 - High insulin
 - Hyperthyroid
 - Decreased in:
 - Hypothyroidism
 - Anorexia
 - Poor liver function

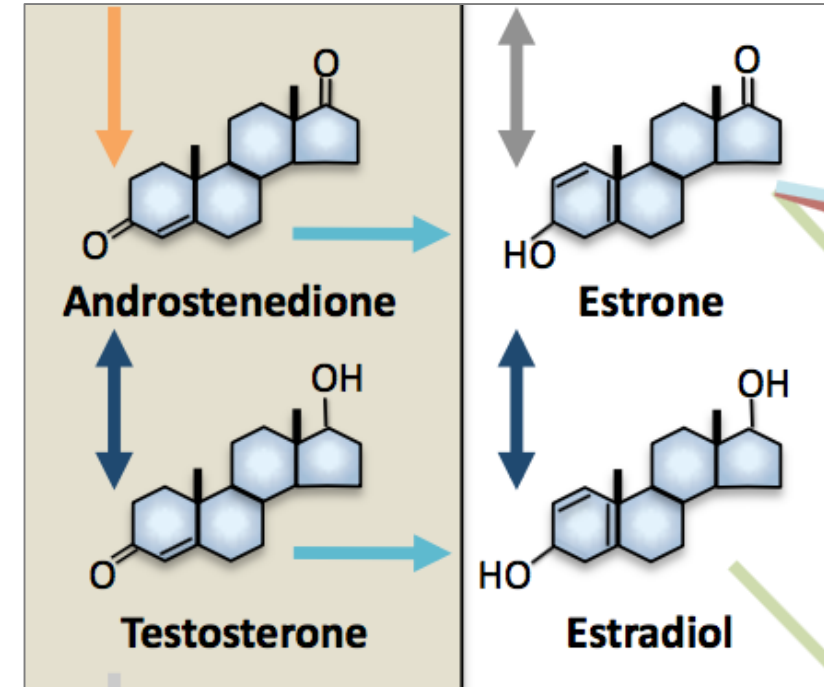






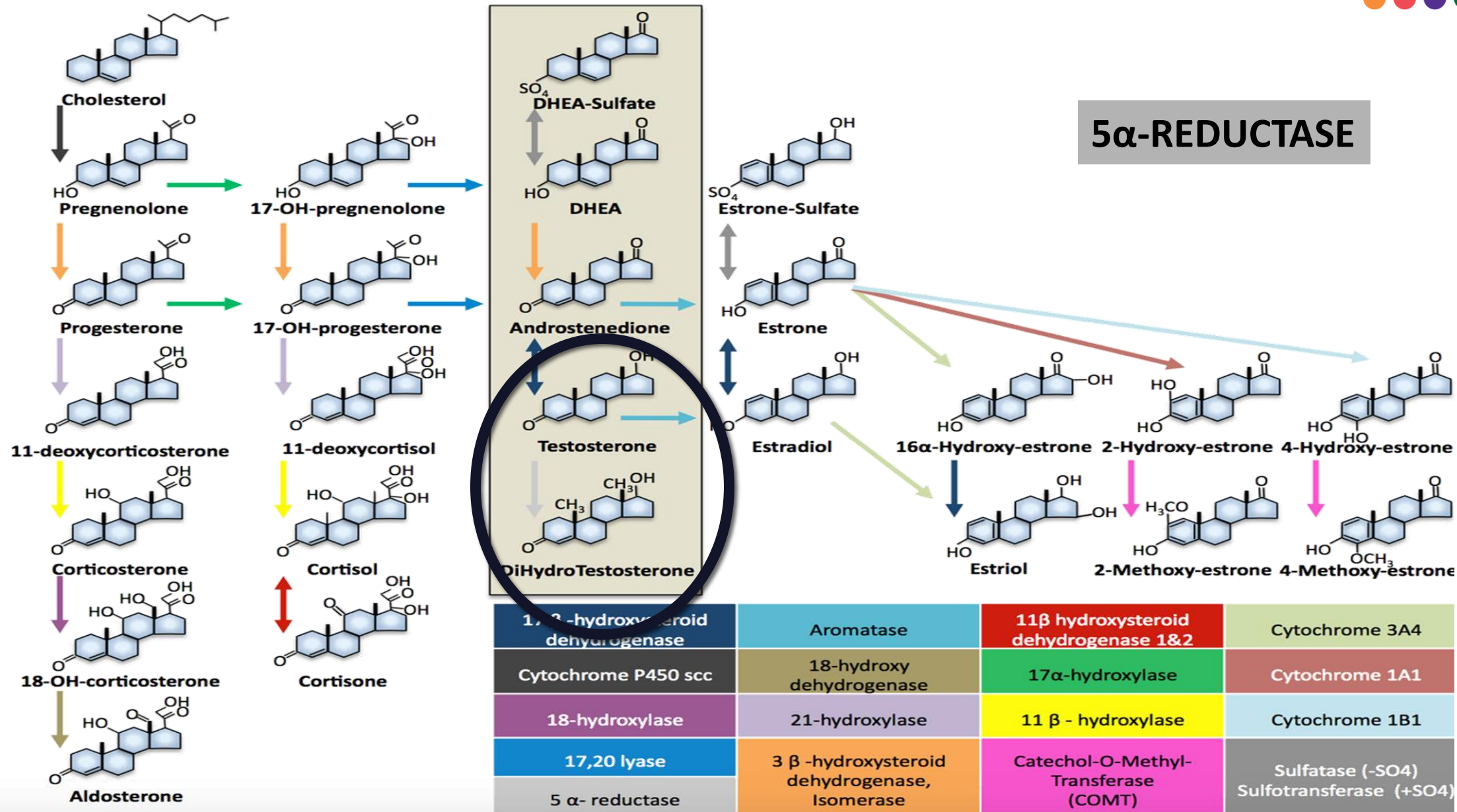
Aromatase

- Conversion of androstenedione to estrone (E1)
- Conversion of testosterone to estradiol (E2)
 - Decreased aromatase activity:
 - Chrysin
 - Zinc
 - Flaxseed
 - Nettles
 - EGCG (green tea extract)
 - Anastrozole
 - Increased aromatase activity:
 - Inflammation
 - Excess adipose
 - High insulin
 - Alcohol
 - Mold/biotoxin illness (CIRS)



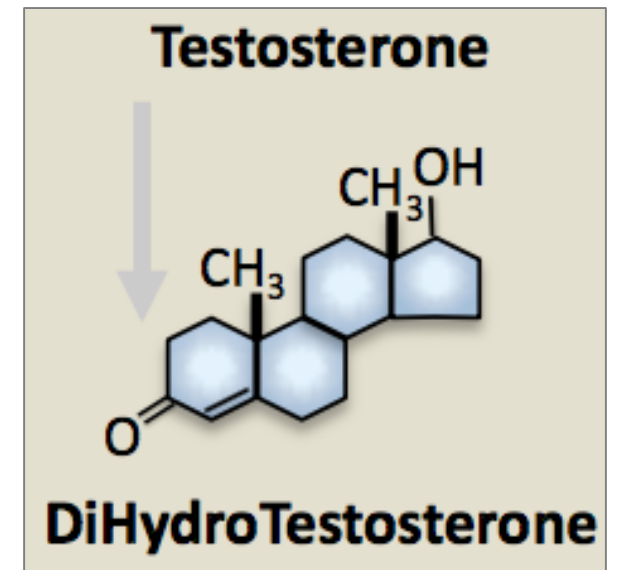


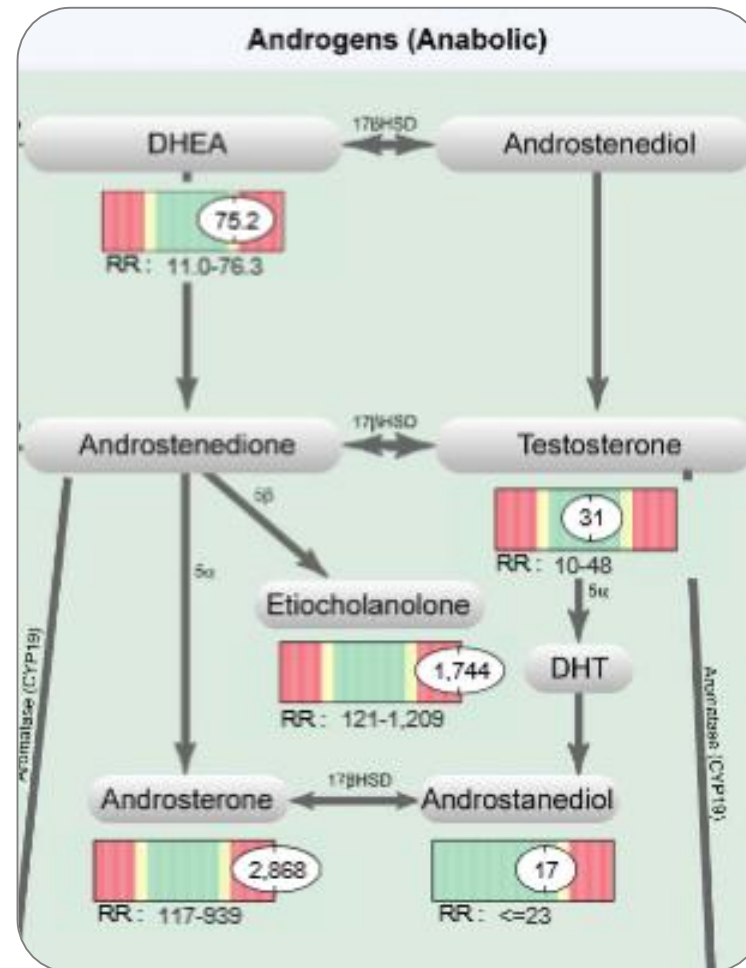
5 α -REDUCTASE

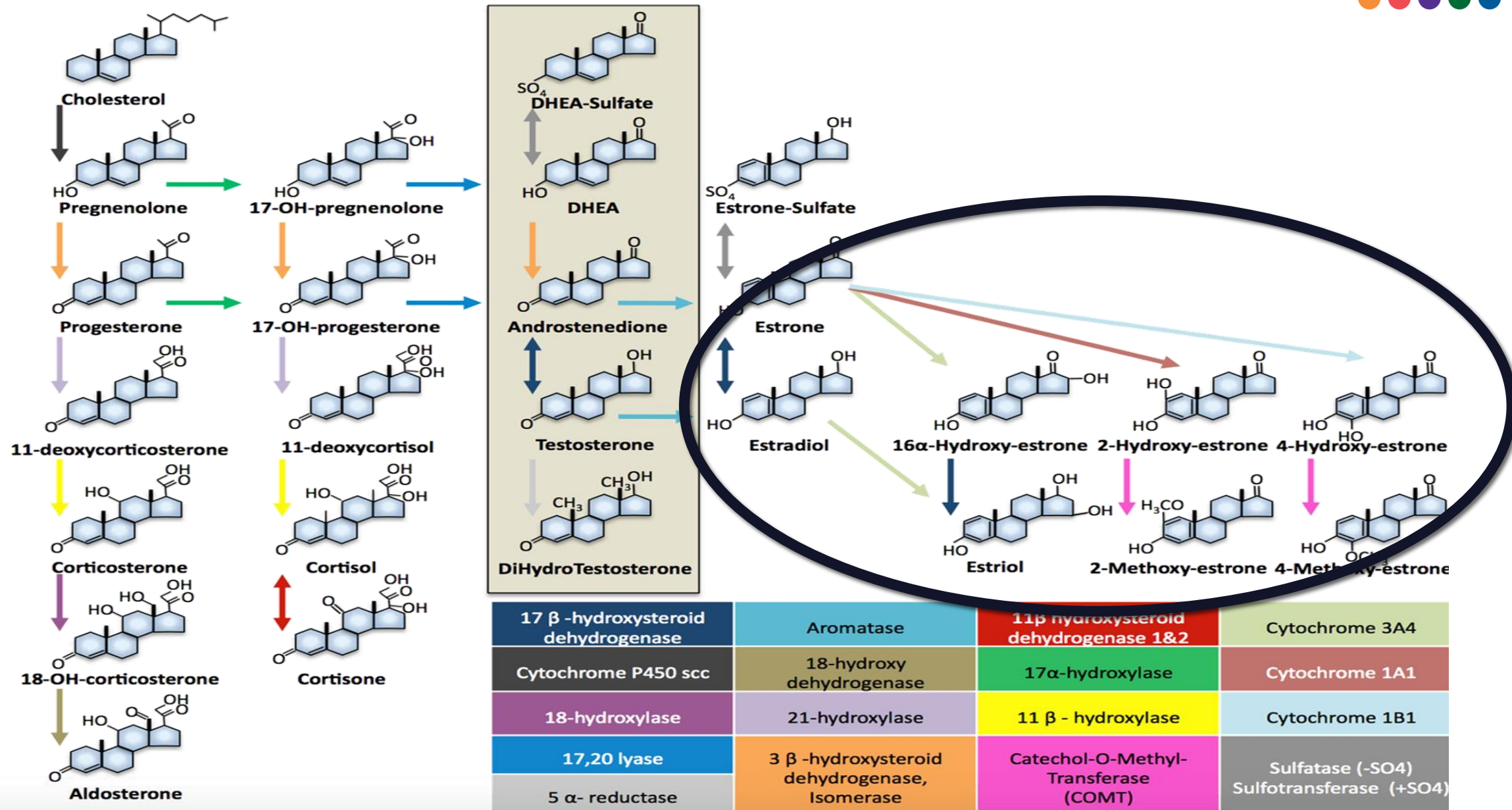


5 α -Reductase

- Best known because it makes androgens (testosterone) more potent
- Also responsible for:
 - Metabolizing progesterone into a-Pregnanediol
 - Metabolizing cortisol into a-THF (b-metabolites of both through 5 β activity)
- Upregulated leads to high androgen symptoms
 - Men (thinning hair, prostate issues)
 - Women (PCOS, thinning hair, acne, facial hair growth)
- Increased enzyme activity:
 - High insulin and obesity
- Decreased enzyme activity:
 - Saw palmetto, nettles, EGCG, progesterone, zinc, finasteride

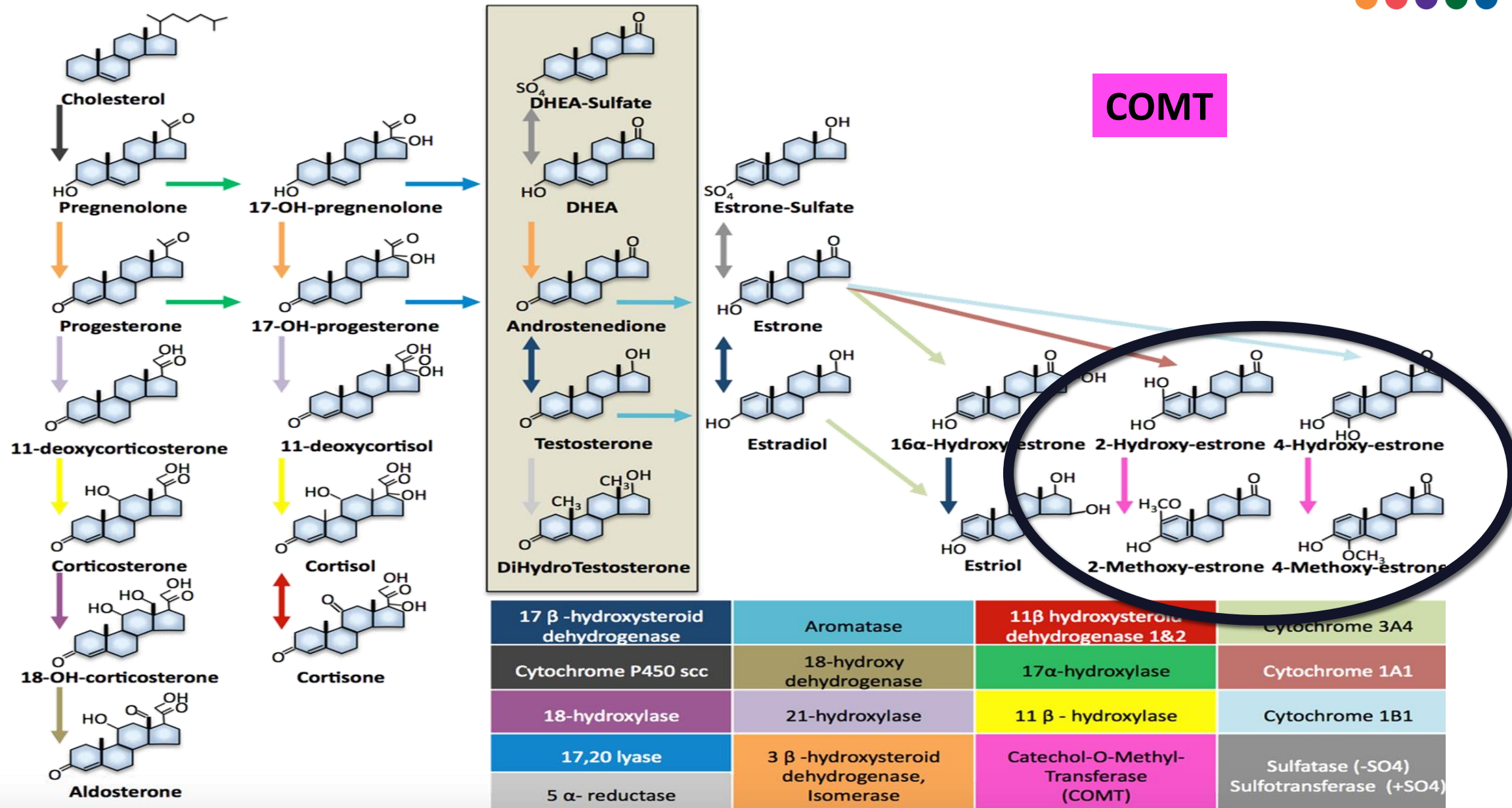






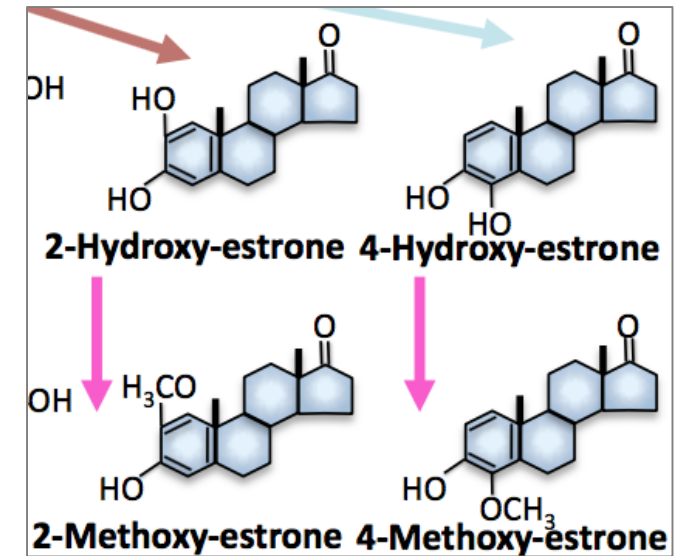
Estrogen Metabolism

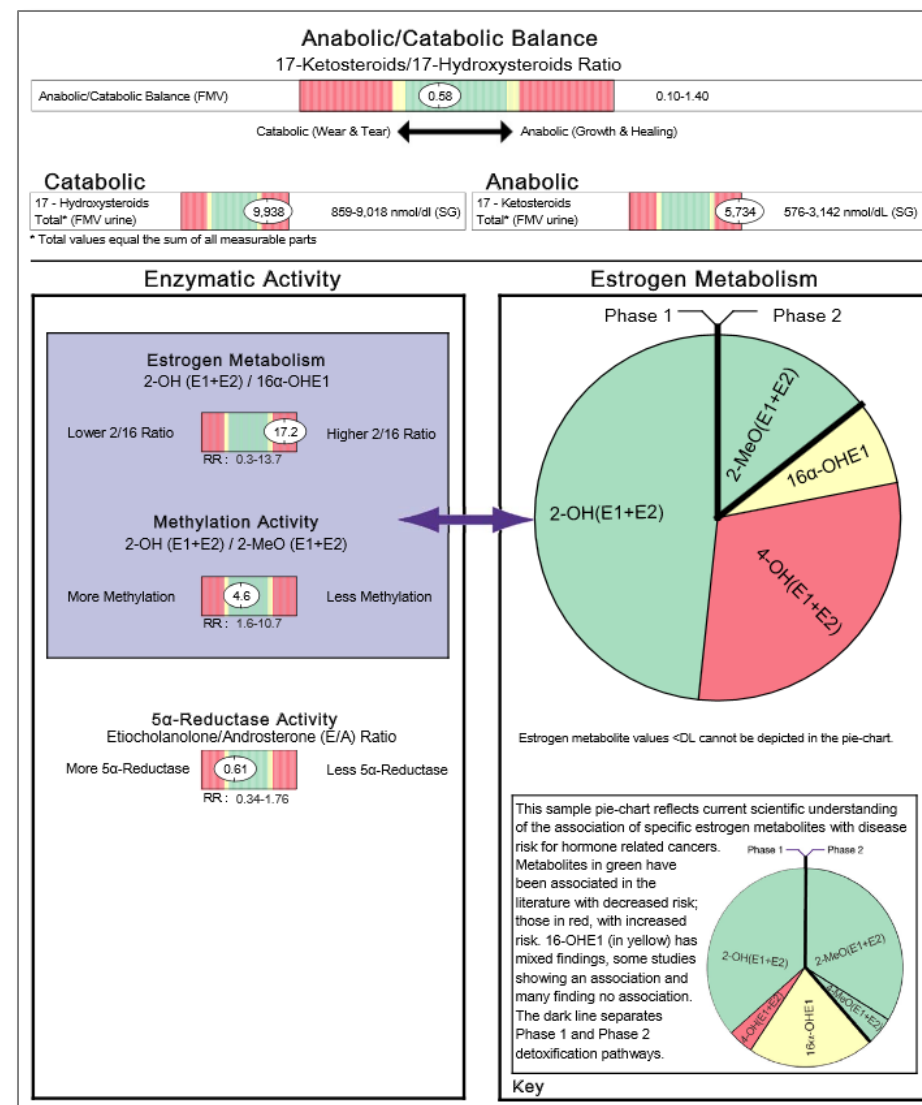
- E1 (Estrone) – main estrogen body makes post-menopausally. ↑ levels may ↑ breast ca
- E2 (Estradiol) – Over 400 functions in body, the most potent estrogen
- E3 (Estriol) – Least powerful but most beneficial
- Efficient metabolism results in predominance of 2-OH-E1 and 2-MeOE1
- Inefficient estrogen metabolism results in predominance of 16-OH-E1 and 4-OH-E1
 - Act negatively to allow oxidation
 - Damages DNA (4-OH-E1)
- Cytochrome P450 enzymes involved in metabolism
 - Healthy metabolism: Exercise, cruciferous veggies, pesticide free diet, weight loss, DIM/I3C, ↓ ETOH, soy, high protein diet, flax, Omega-3 fats, antibiotics (enterohepatic recirculation of estrogens)
 - Unhealthy metabolism: Pesticides, smoking, caffeine (conversion to more 16OHE1), hypothyroidism

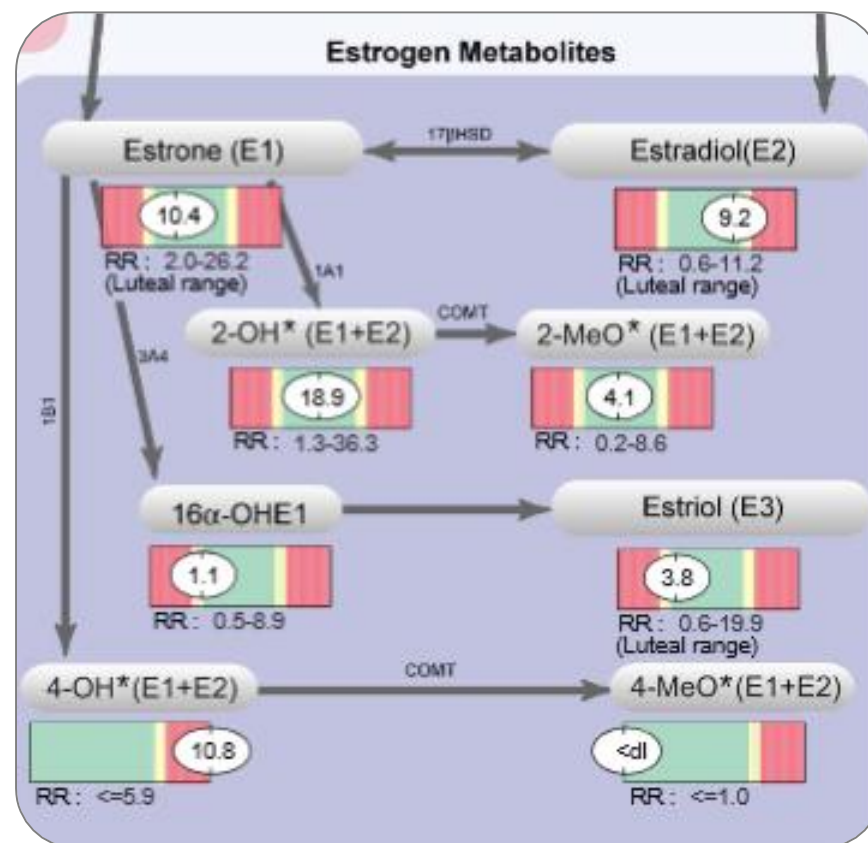


COMT – Catechol-O-Methyltransferase

- One of several enzymes that degrade catecholamines such as dopamine, epinephrine, and norepinephrine
- Principal enzyme in the conjugation pathway for hydroxylated estrogens
 - Carcinogenic 4-hydroxyestrogens
- Methylation of 2-OH/4-OH estrogens is slowed in:
 - Genetic variants (SNPs) in MTHFR and COMT
- COMT is upregulated by:
 - Methyl donors – S-AdoMet, B vitamins, TMG, choline, folate, and methionine









Integrative Assessment

CASE STUDIES



CASE PRESENTATION

34 year male physician – history of severe dizziness/vertigo, recently diagnosed with Lyme disease

- Complained of fatigue, decreased libido, difficulty sleeping (along with his other Lyme sx's), central weight gain
 - Wired but tired
 - Irritable
 - Impaired immunity



Continued...



CASE PRESENTATION

- Blood test results:
 - Cholesterol 162 (reference range < 200)
 - Estradiol 9.5 (reference range 7.6 – 42.6, optimal lower 1/3 of reference range)
 - Estrone 58 (reference range 12 -72, optimal lower 1/3 of reference range)
 - Progesterone 0.5 (reference range 0.3 – 1.5)
 - FSH 4.0 (reference range 1.5 – 12.4)
 - LH 3.4 (reference range 1.7 – 8.6)
 - Prolactin 5.2 (reference range 4 – 15.2)
 - Testosterone 316 (reference range 348 – 1197, optimal upper 1/3 of reference range)
 - Free Testosterone 3.6 (reference range 8.7 – 25.1)
 - DHEA-S 65.2 (reference range 102.6 – 416.3, optimal upper ½ reference range)
 - SHBG 43.9 (reference range 16.5 – 55.9)
 - Pregnenolone 28 (reference range < 150, optimal 70-100)
 - AM Cortisol , serum 30 (reference range 7 – 28, optimal 10 – 15 in the morning)
 - MTHFR – heterozygous C677T
 - COMT – no SNPs
- Thyroid, lipids, other labs test (except inflammatory markers, Lyme Western Blot, etc) otherwise unremarkable





Salivary Hormone Results

Estradiol ♦ pmol/L

<2.5

Testosterone ♦ pmol/L

148

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	

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

Estrone pmol/L

8.8

Reference Range	
Menopausal	4.7-18.9 pmol/L

Progesterone ♦ pmol/L

149

Reference Range	
Follicular	120-693 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

<70

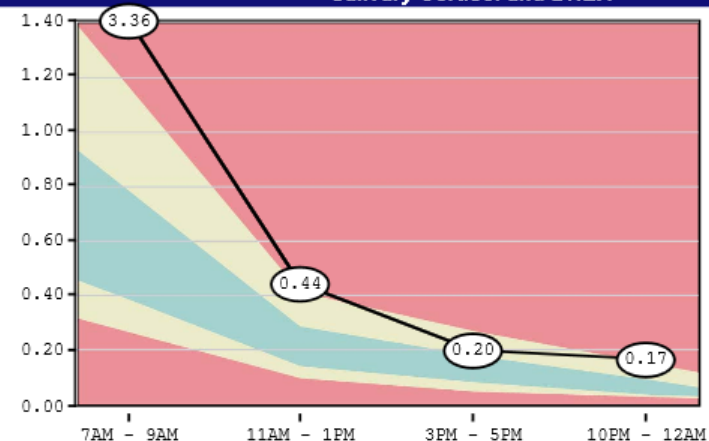
Reference Range	
Menopausal	<= 133 pmol/L

P/E2 Ratio

60

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

Salivary Cortisol and DHEA



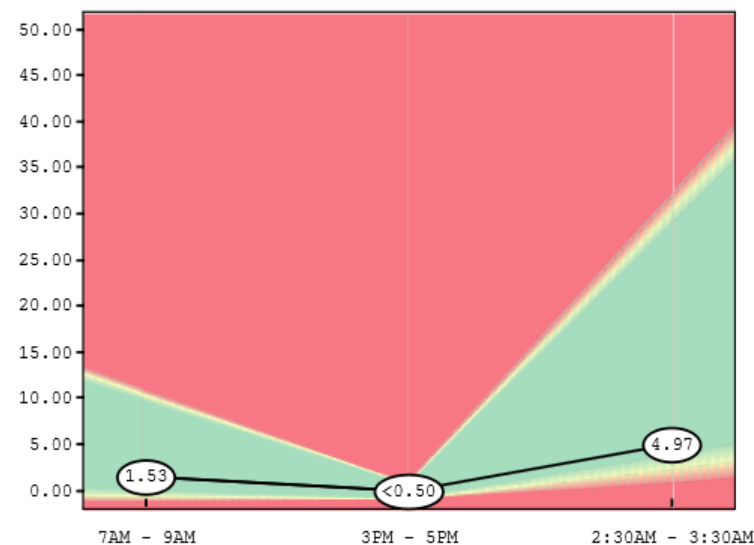
Cortisol ♦
Reference Range
1 Hour After Rising
7AM - 9AM:
0.27-1.18 mcg/dL
11AM - 1PM:
0.10-0.41 mcg/dL
3PM - 5PM:
0.05-0.27 mcg/dL
10PM - 12AM:
0.03-0.14 mcg/dL

Hormone

Reference Range

DHEA 7am - 9am	14	71-640 pg/mL
DHEA: Cortisol Ratio/10,000	4	115-1,188

Salivary Melatonin

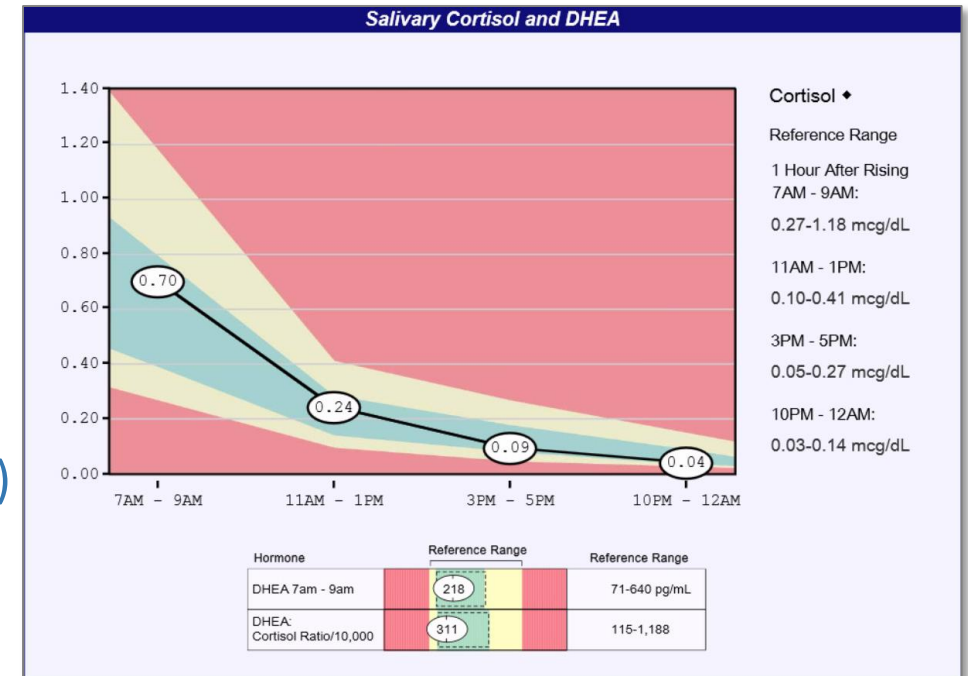


Reference Range
7AM - 9AM:
<=10.50 pg/mL
3PM - 5PM:
<=0.88 pg/mL
2:30AM - 3:30AM:
2.53-30.67 pg/mL



Recommendations

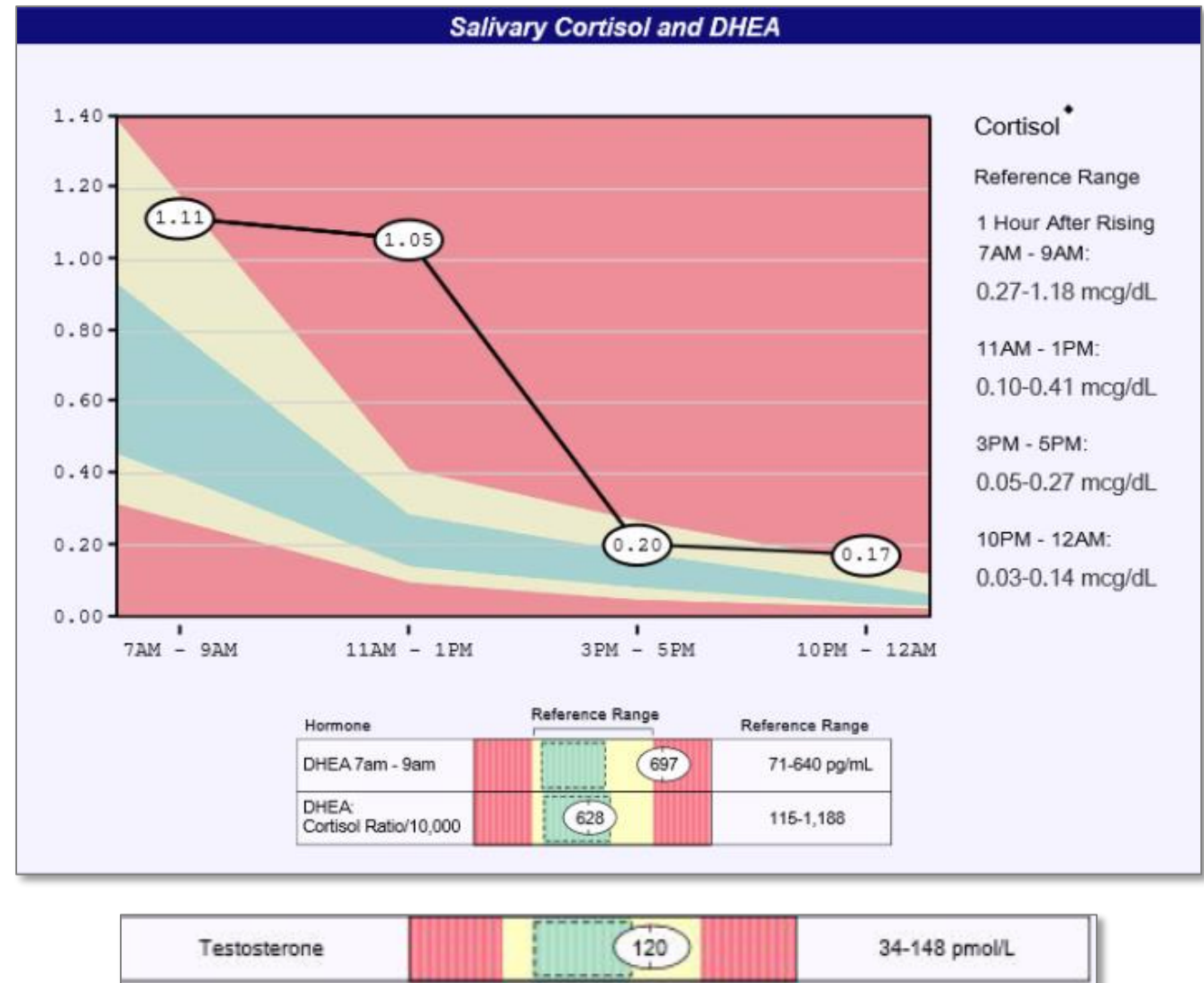
- Stress reduction
 - Emotional/Mental – breathing exercises, prayer, meditation, yoga, etc
 - Infection – antimicrobials/antifungals
 - Inflammation – dietary (low sugar/high protein) and anti-inflammatories (omega-3 fatty acids, curcumin, etc)
- Hormone support
 - Pregnenolone 100 mg
 - DHEA 25 mg
 - HCG 500 IU SQ twice weekly x 8 weeks (ultimately 20 mg testosterone/15 mg Chrysin)
 - Aromatase
 - Green tea, zinc, flaxseed
 - Adaptogenic herbs – Panax Ginseng, Rhodiola, Ashwaganda
 - Methylation support - Methylated folic acid, Methyl-B12, TMG, B2, B6





24 Year-Old Female

- With:
 - Irregular periods
 - Facial hair
 - Obesity
 - High carb diet
- Diagnosis:
 - PCOS
- Treatment:
 - Stress reduction
 - Diet – ↓carb↑prot
 - Mental/emotional
 - Inflammatory
 - Infectious
 - Oxidative
 - Other Recommendations
 - Metformin
 - Adaptogens
 - Spironolactone (maybe)
 - Zinc



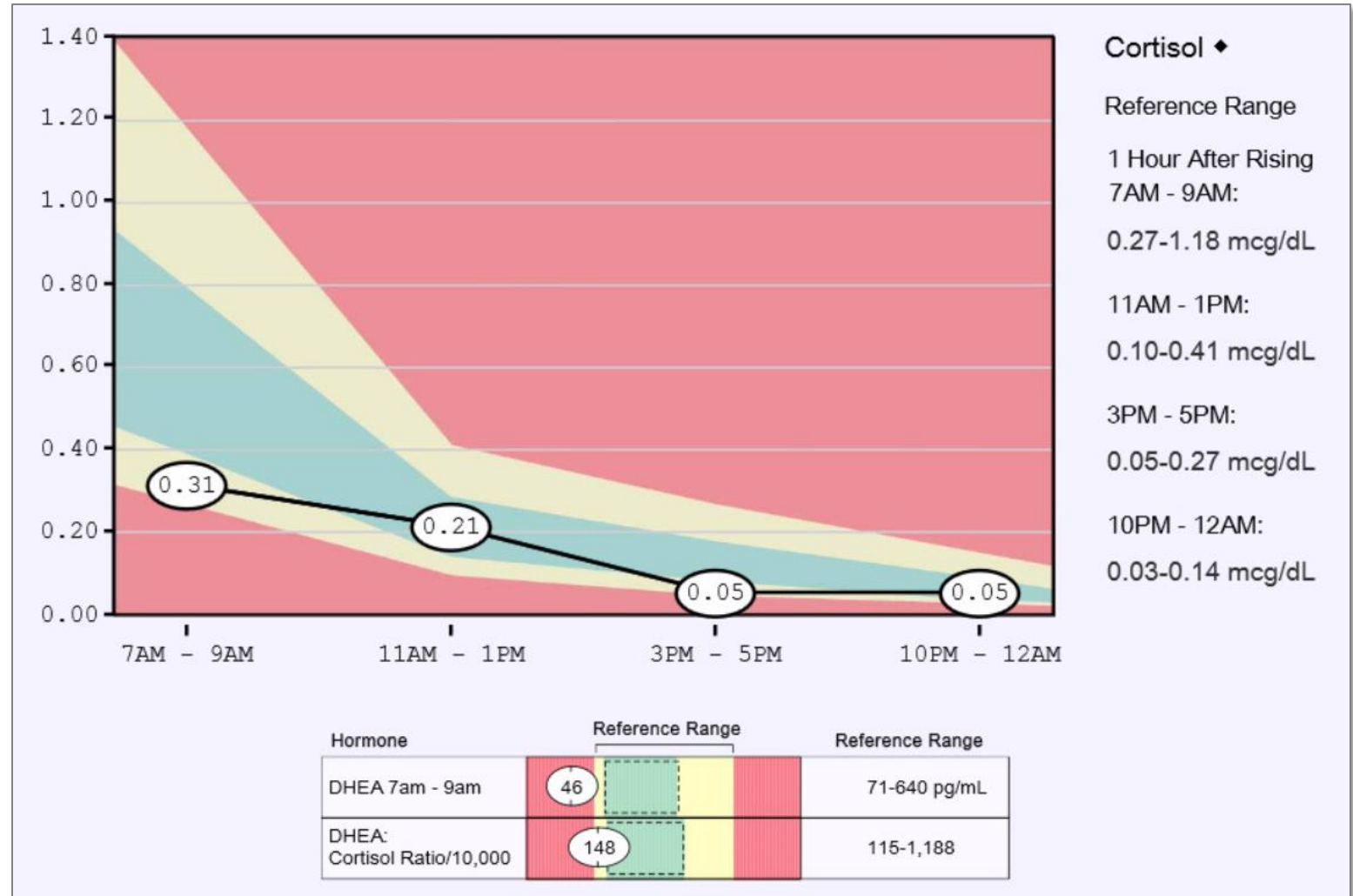


28 Year-Old Male w/IBD

- With:
 - Significant diarrhea
 - Weight loss
 - BRAT diet/low fat
- Lab Findings:
 - Cholesterol 118

Recommendations:

- Treat the gut
 - Probiotics
 - Glutamine
 - Omega-3 fats
 - Anti-inflammatory diet
 - Adequate fat intake
 - Licorice root
 - Pregnenolone
 - DHEA





Moderator:
Christine Stubbe, ND



Presenter:
Ellen Antoine, DO, FACEP, ABIHM, IFMCP

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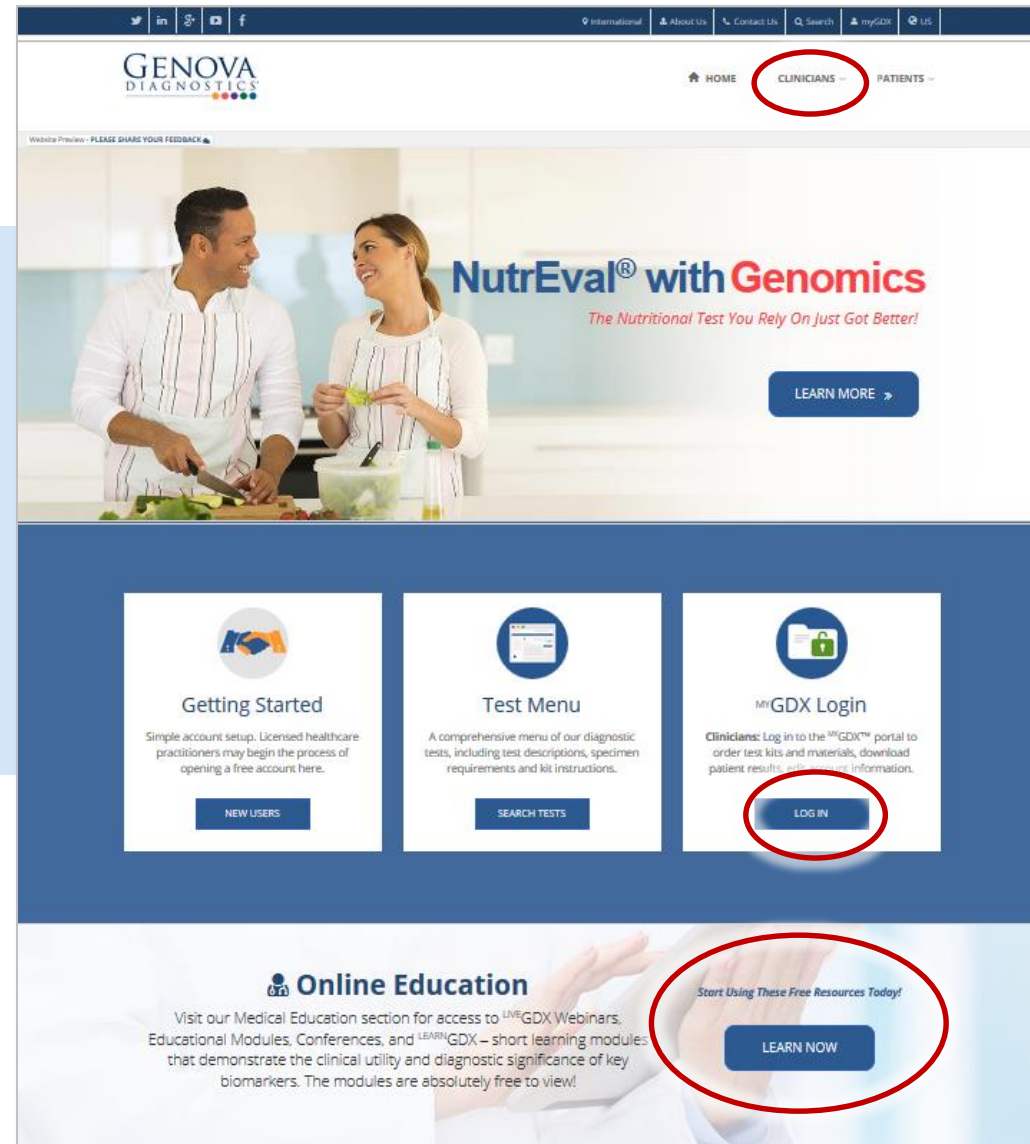
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