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PCOS and the DUTCH Test

Connecting PCOS and the Development of Autoimmunity

Mark Newman, President/Founder of Precision Analytical
Dr. Kelly Ruef, DUTCH Clinical Educator

Endocr Res. 2015;40(4):204-10. doi: 10.3109/07435800.2015.1015730. Epub 2015 Mar 30.

High prevalence of Hashimoto's thyroiditis in patients with polycystic ovary syndrome: does the imbalance between estradiol and progesterone play a role?

Ayse Arduc [1], Bercem Aycicek Dogan [2], Sevgi Bilmez [3], Narin Imga Nasiroglu [2],

Abstract

Objective: Some similar factors, such as genetic susceptibility and subinflammation/autoimmunity, contribute to development of both polycystic ovary syndrome (PCOS) and Hashimoto's thyroiditis (HT), suggesting a potential pathogenic link between the two common disorders. In this study, we investigated the relationship between PCOS and HT, considering the possible effect of PCOS-related hormonal and metabolic factors on thyroid autoimmunity.

Methods: Eighty-six reproductive-age women diagnosed with PCOS according to Rotterdam criteria and 60 age-BMI matched control women were included in the study. All subjects had thyroid function tests, thyroid peroxidase anti-body (anti-TPO), thyroglobulin anti-body (anti-Tg), LH, FSH, estradiol, progesterone, androgens, fasting glucose, insulin, lipid, homeostasis model assessment insulin resistance (HOMA-IR) levels, thyroid and pelvic ultrasounds.

Results: TSH, anti-TPO ($p = 0.017$), anti-Tg ($p = 0.014$), LH, DHEAS, testosterone, and HOMA-IR levels were significantly higher and progesterone were lower in PCOS women than in controls. Free T4, free T3, FSH, estradiol levels and thyroid volume were similar between the two groups. A higher percentage of PCOS patients had elevated TSH (26.7 and 5%; $p = 0.001$), anti-TPO (26.7 and 6.6%; $p = 0.002$), and anti-Tg (16.2 and 5%; $p = 0.039$). HT was more common in PCOS patients compared to controls (22.1 and 5%; $p = 0.004$). Estradiol ($p = 0.003$) were higher in anti-TPO positive PCOS women than anti-TPO negative ones. Anti-TPO was correlated positively with estradiol, estradiol/progesterone ratio, and TSH.

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Table 1. Characteristics of PCOS patients and controls.

Variables	PCOS ($n = 86$)	Control ($n = 60$)	p Value
Age, year	24.6 ± 5.7	26.17 ± 5.0	0.621
BMI, kg/m^2	24.9 ± 3.6	23.4 ± 2.9	0.173
Fasting blood glucose, mg/dl	83.6 ± 11.5	87.4 ± 6.7	0.055
Fasting insulin, µIU/ml	11.6 (2.0–60.5)	7.3 (2.03–11.7)	**<0.0001**
HOMA-IR	2.5 (0.3–17.6)	1.5 (0.4–2.6)	**<0.0001**
Total cholesterol, mg/dl	182.8 ± 32.4	162.9 ± 26.7	**0.007**
LDL-C, mg/dl	107.2 ± 29.1	85.0 ± 25.3	**0.001**
HDL-C, mg/dl	48.2 ± 13.9	60. 9 ± 13.7	**<0.0001**
Triglyceride, mg/dl	108.0 (28.0–468.0)	58.0 (33.0–175.0)	**<0.0001**
FSH, mIU/ml	5.3 ± 2.3	4.6 ± 3.9	0.2
LH, mIU/ml	10.1 (0.5–51.9)	6.5 (1.3–17.4)	**0.002**
LH/FSH ratio	2.1 ± 1.3	1.8 ± 1.0	0.221
Total testosterone, ng/ml	0.5 (0.1–1.6)	0.2 (0.1–0.4)	**<0.0001**
Free testosterone, pg/ml	2.3 ± 0.9	1.5 ± 0.3	**<0.0001**
Androstenedione, ng/ml	3.5 ± 2.2	2.1 ± 0.4	0.418
DHEAS, µg/dl	275.3 ± 114.5	194.7 ± 67.6	**<0.0001**
Prolactin, ng/ml	13.8 ± 5.0	15.1 ± 3.8	0.134
Estradiol, pg/ml	68.0 (23.40–479.0)	88.5 (11.15–166)	0.584
Progesterone, ng/ml	0.9 (0.17–25)	15 (10.9–23.1)	**<0.0001**

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PCOS and the DUTCH Test

Typical Expected Patterns – The Basics

PCOS Sub-Type	Ovulatory Dysfunction	High Androgens	Polycystic Ovaries
Classic PCOS with All Three Features	✅	✅	✅
PCOS with High Androgens and Irregular Cycles	✅	✅	❌ Normal ovaries
Ovulatory PCOS with High Androgens	❌ Normal cycles	✅	✅
Non-Hyperandrogenic (Lean) PCOS	✅	❌ Normal androgens	✅

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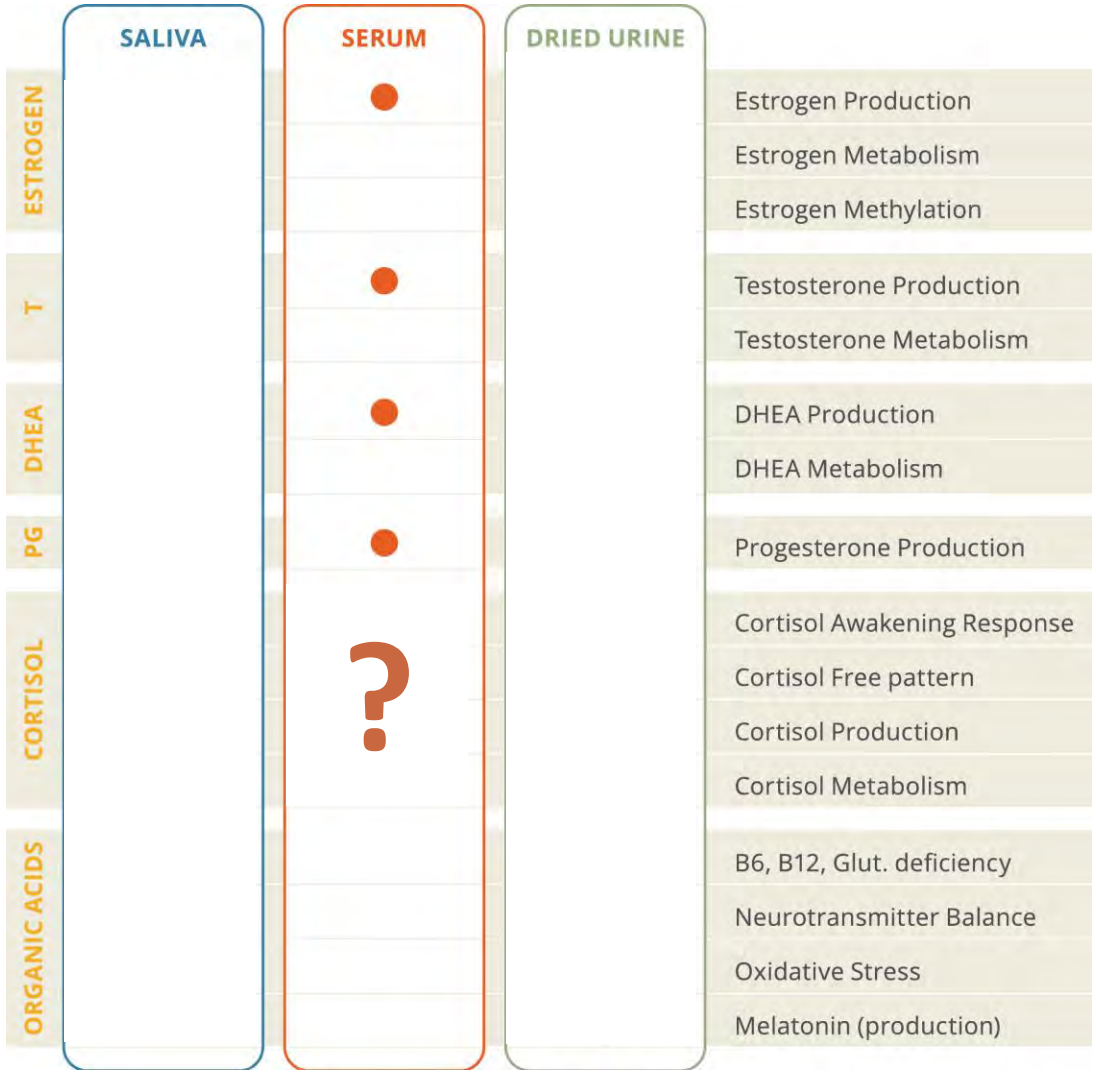
Testing Options



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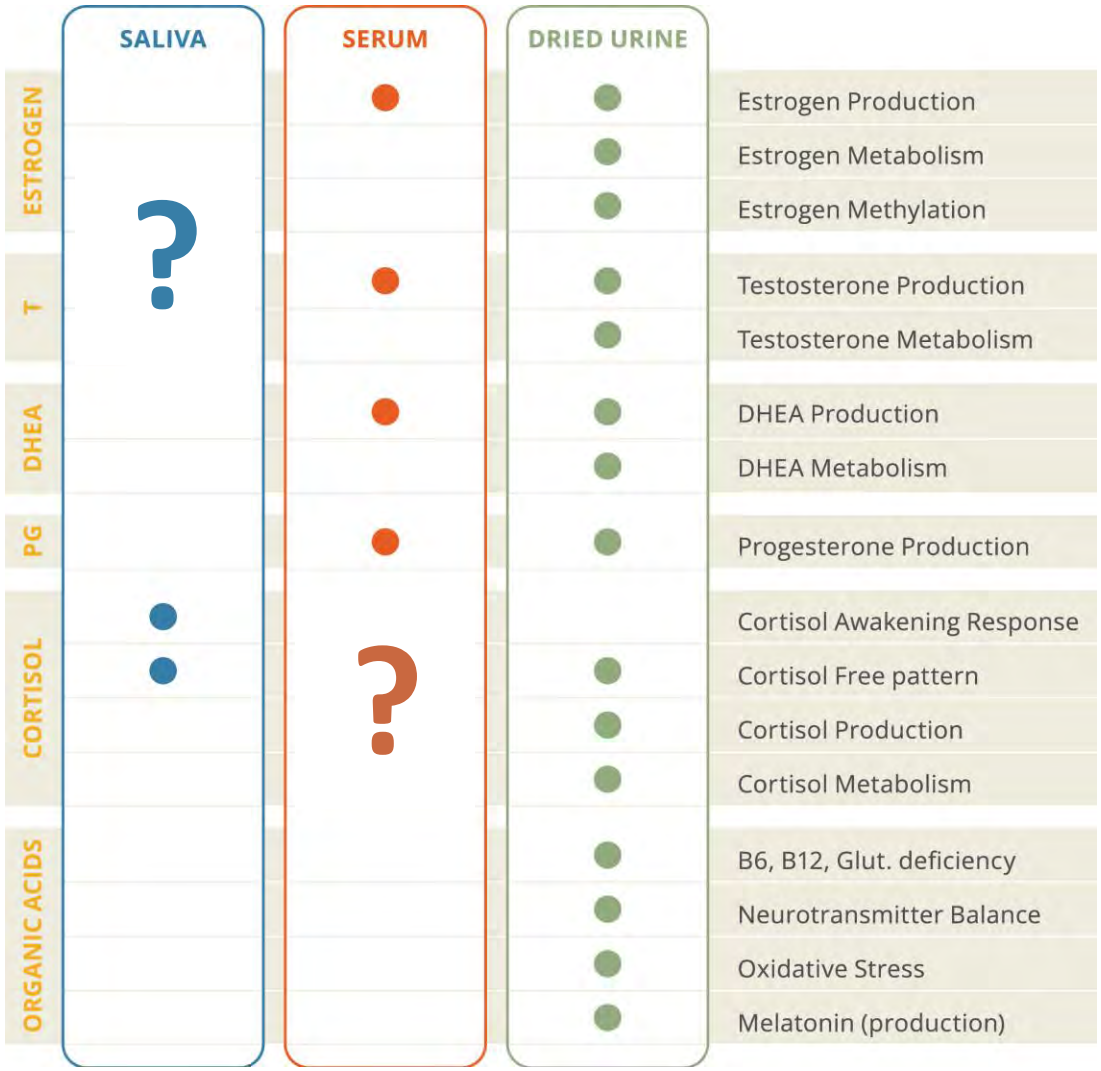
Testing Options



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Basic Facts About PCOS & HT in women

- PCOS is the most common endocrine disorder
- HT is the most common AI disease (~10x more in women)
-Hypothyroidism may lower SHBG, worsening PCOS
-HT is more common (~4x) in women with PCOS

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dutchtest COMPLETE

Accession # 00953359

Female Sample Report
123 A Street
Sometown, CA 90266

DOB: 1982-01-29
Age: 42
Sex: Female
Last Menstrual Period:

Collection Times:

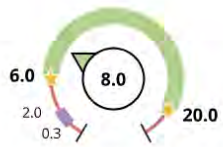
2024-09-06 06:00AM (U)
2024-09-06 08:00AM (U)
2024-09-05 05:00PM (U)
2024-09-05 10:00PM (U)

Ordering Provider:
Internal Research

Hormone Testing Summary

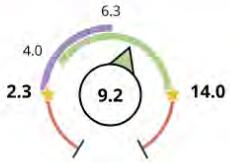
ESTROGEN & PROGESTERONE

Estradiol (E2)



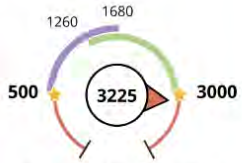
Progesterone
Serum Equivalent*, ng/mL

ANDROGENS



Testosterone

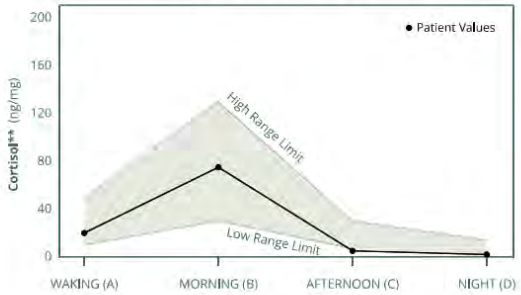
5a-Androstanediol



Total DHEA Production
DHEA-S + Etiocholanolone + Androsterone

CORTISOL

Daily Free Cortisol Pattern



Cortisol Clearance Rate

THF + THE / Cortisol + Cortisone

24hr Free Cortisol
A + B + C + D

Cortisol Metabolism

Metabolized Cortisol
Total Cortisol Production (THF + THE)

Optimal Luteal Range Postmenopausal Range Out of Range Edge of Range

*Progesterone Serum Equivalent is a calculated value based on urine pregnanediol.
**Free cortisol best reflects tissue levels. Metabolized cortisol best reflects total cortisol production.

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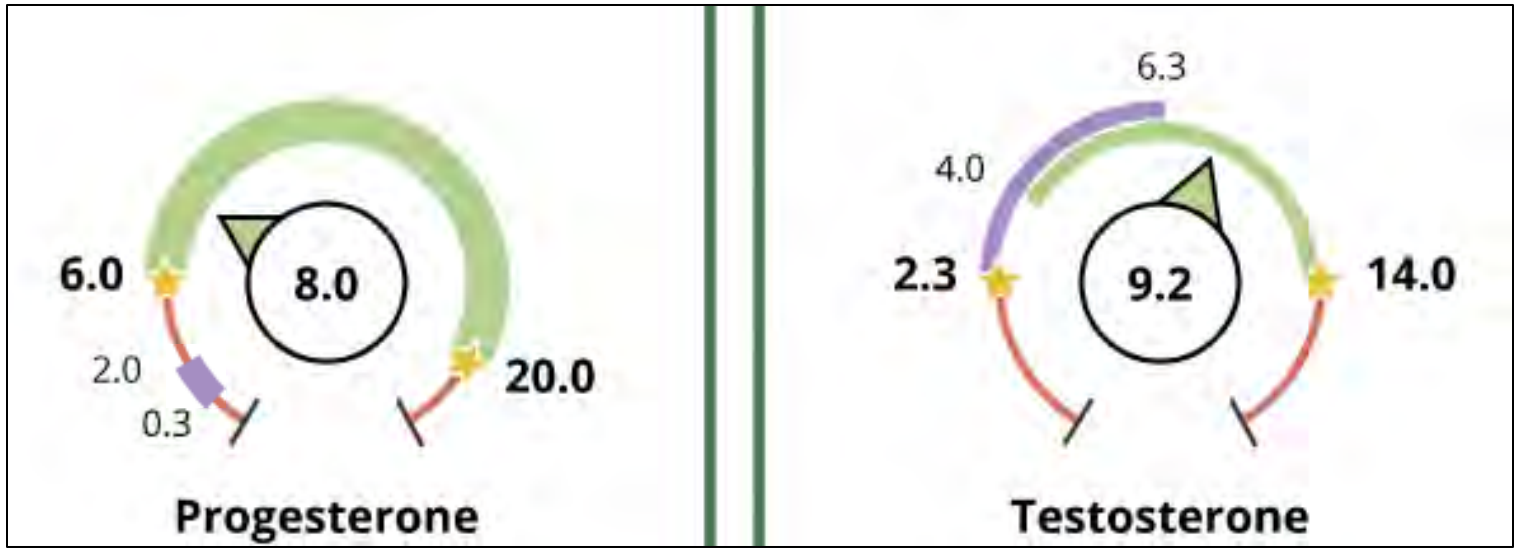
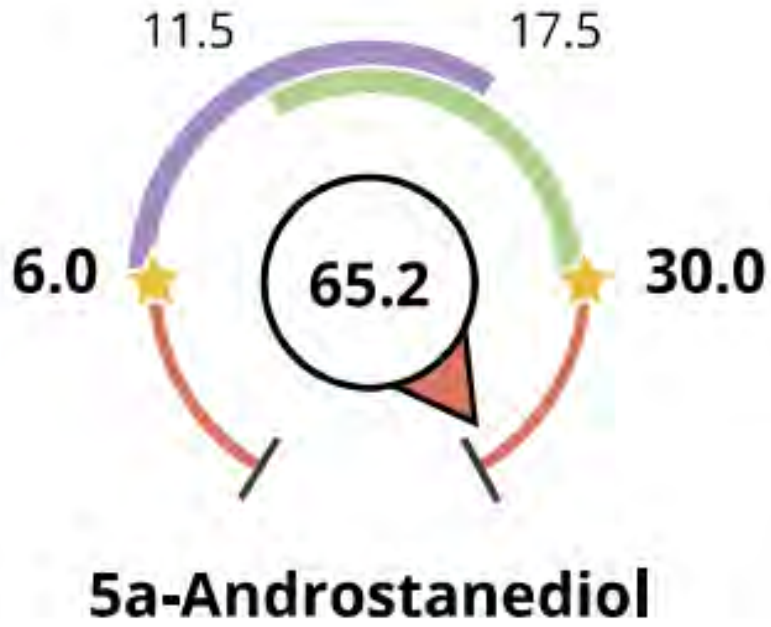
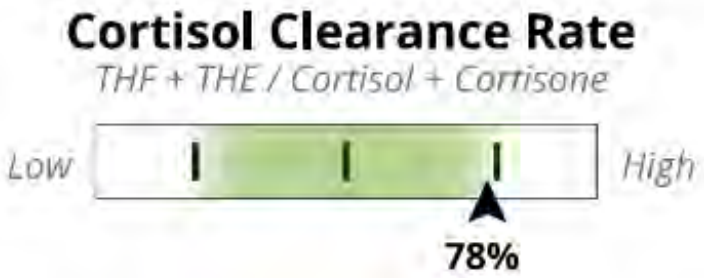
New Report Features

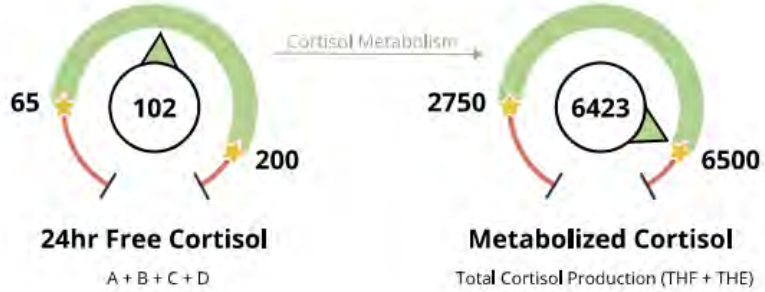




Postmenopausal Range

Optimal Luteal Range





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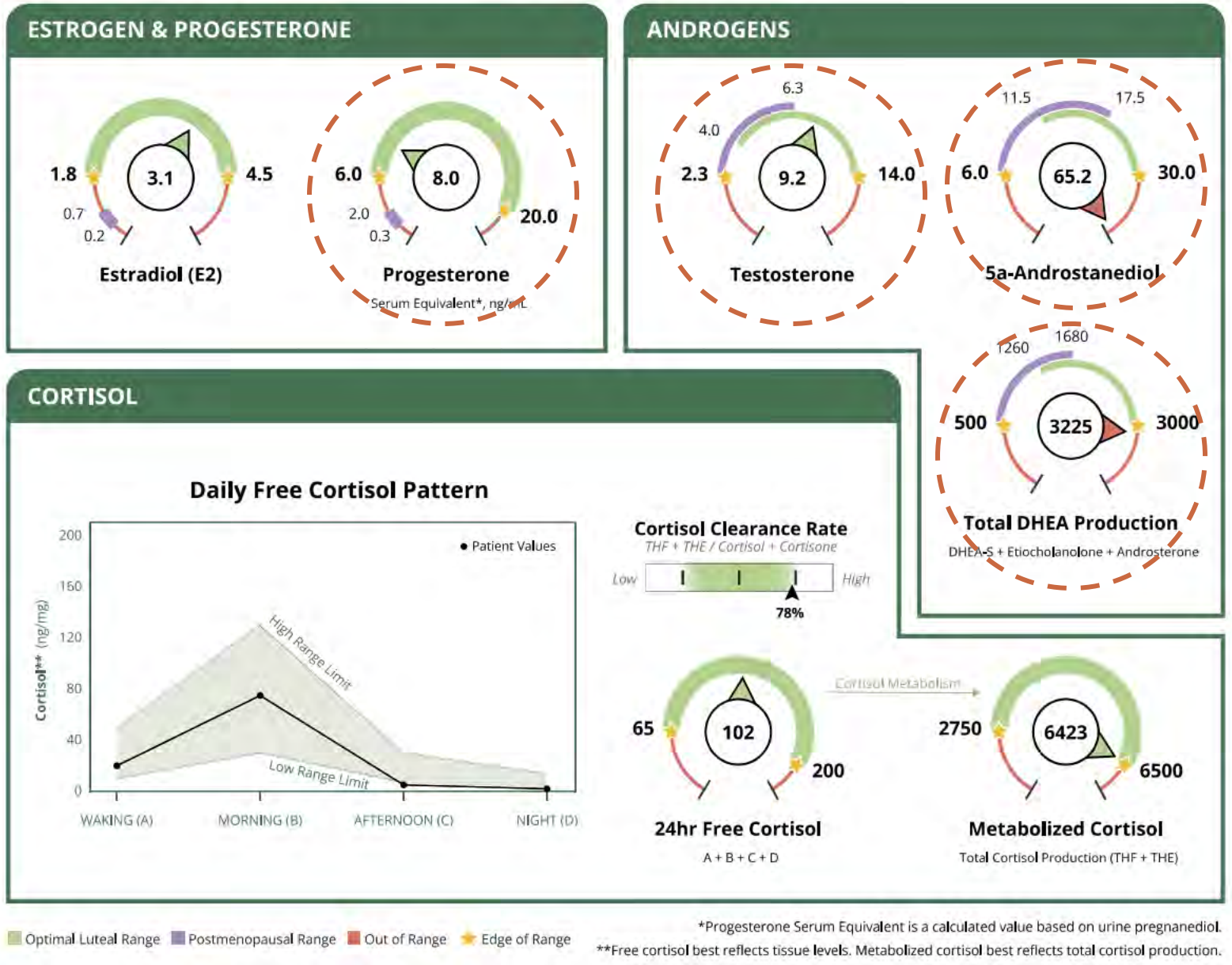
Hormone Testing Summary



PCOS?

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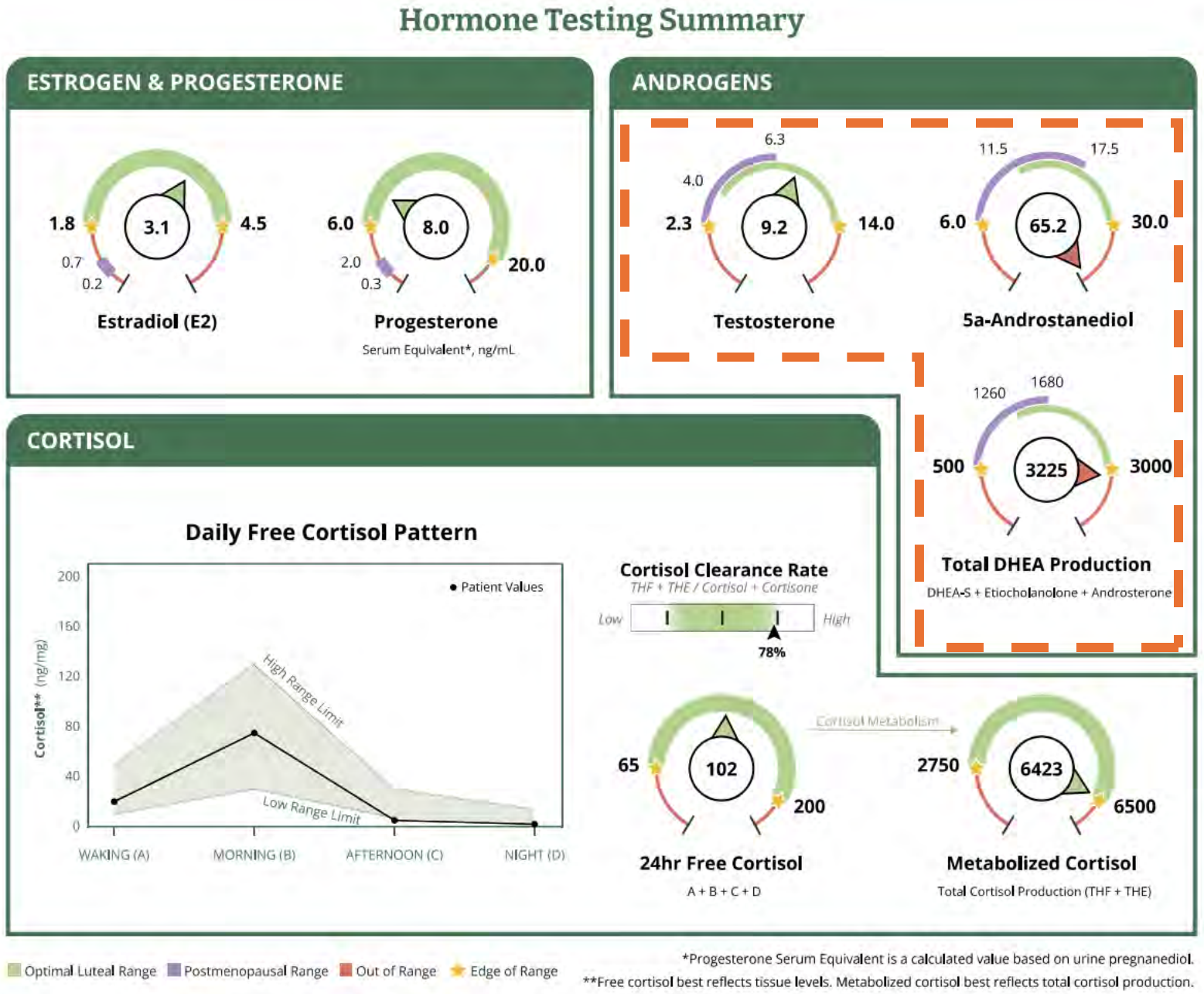
Androgens



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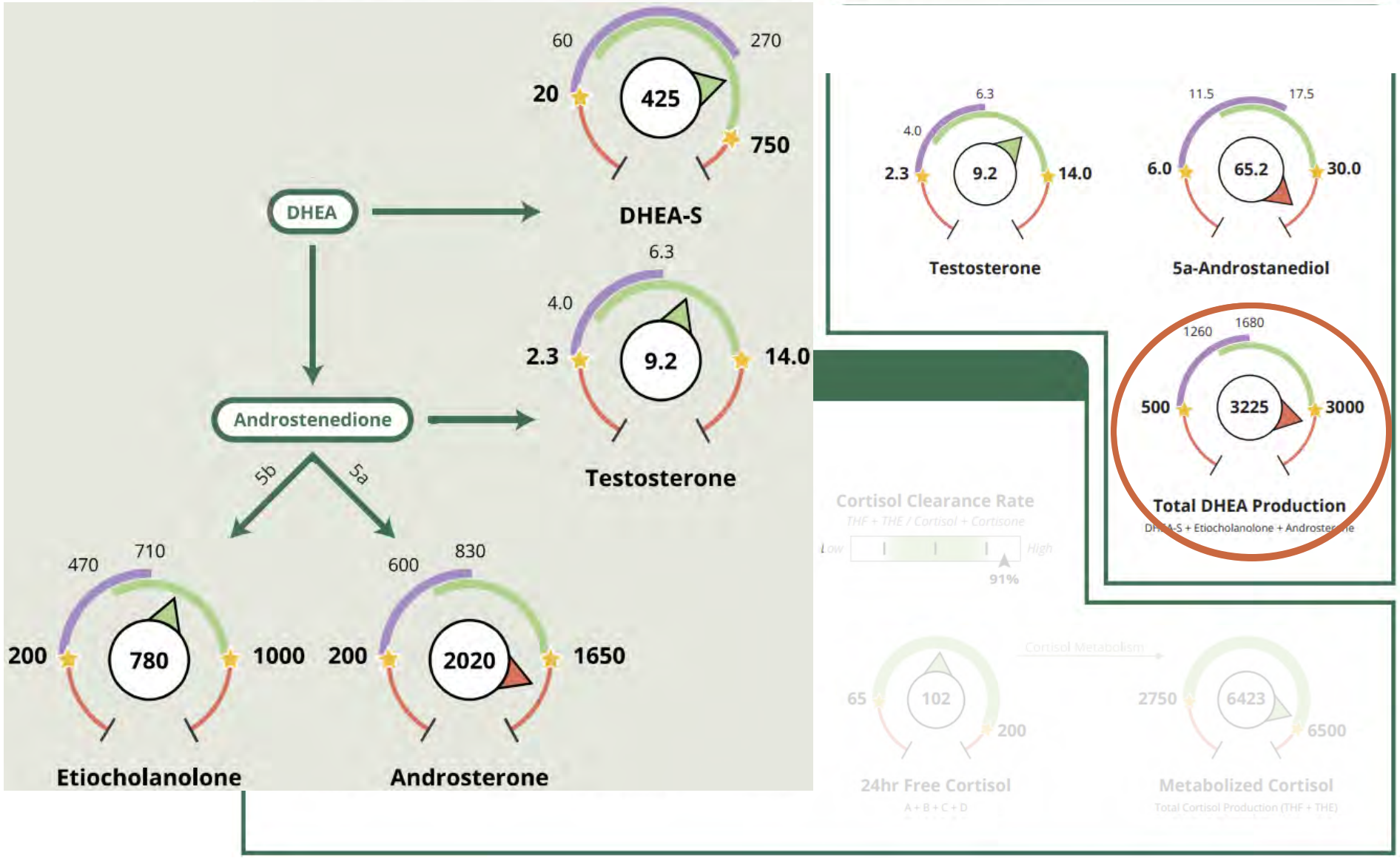

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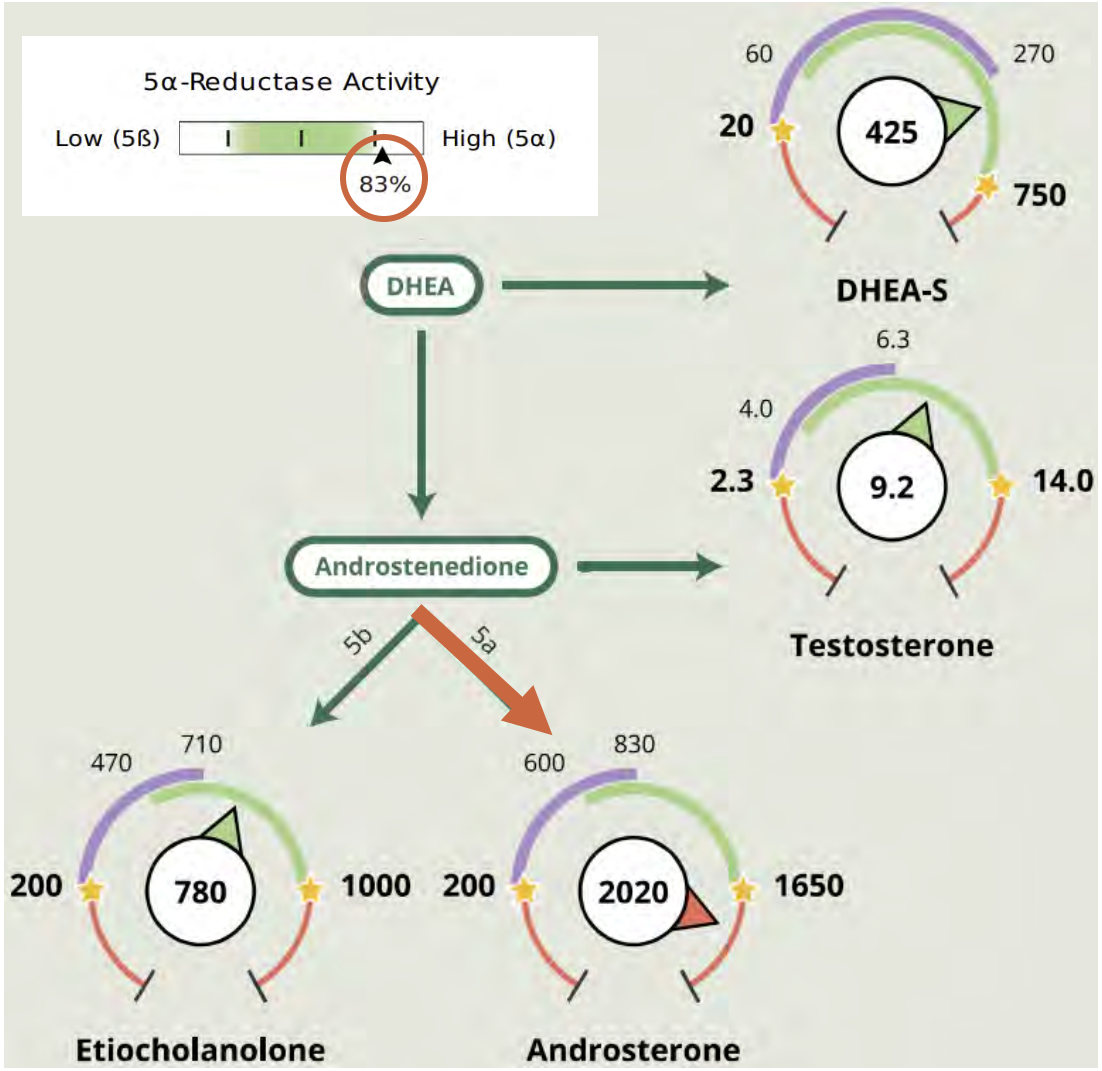

Patient Results

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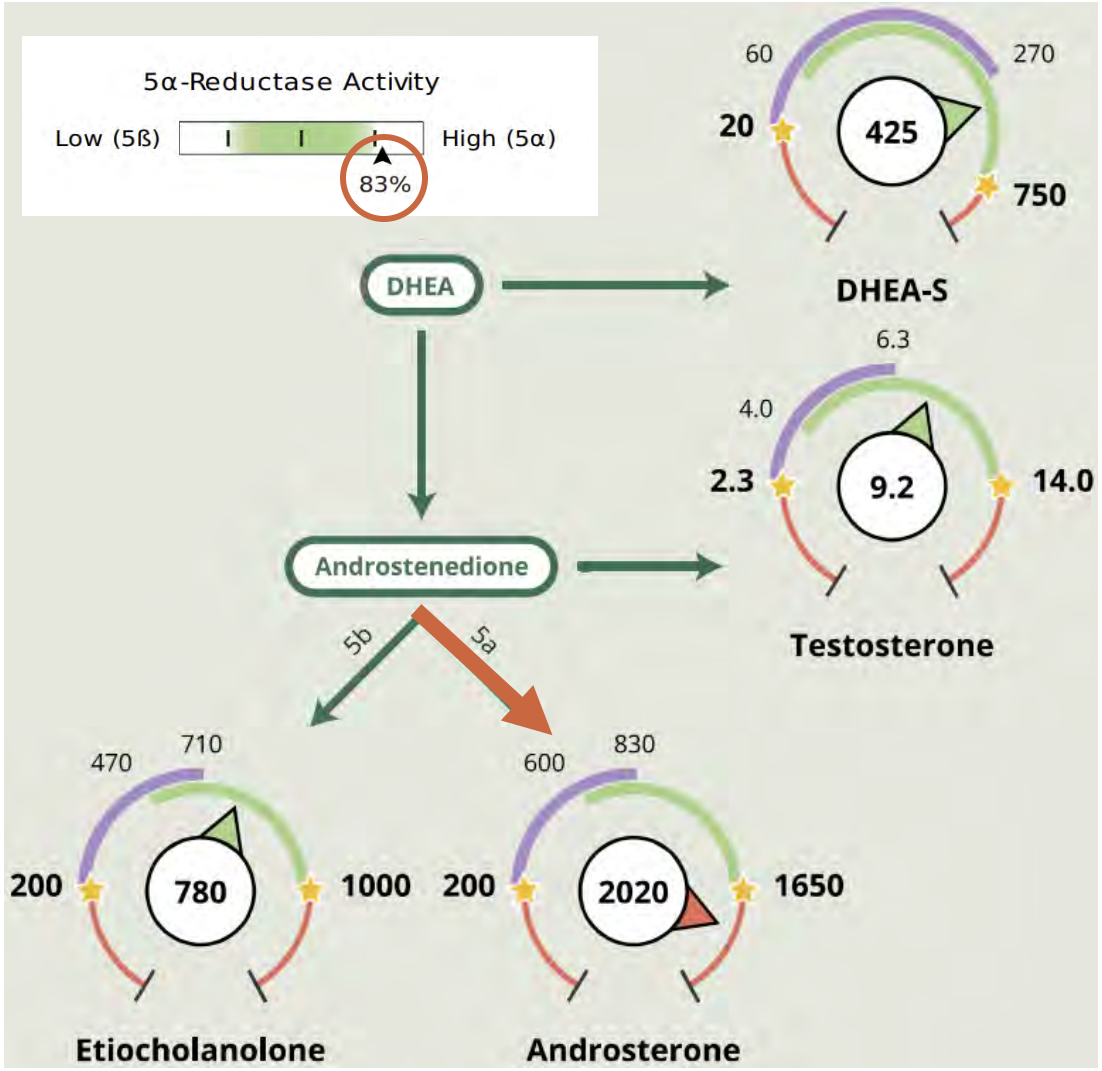

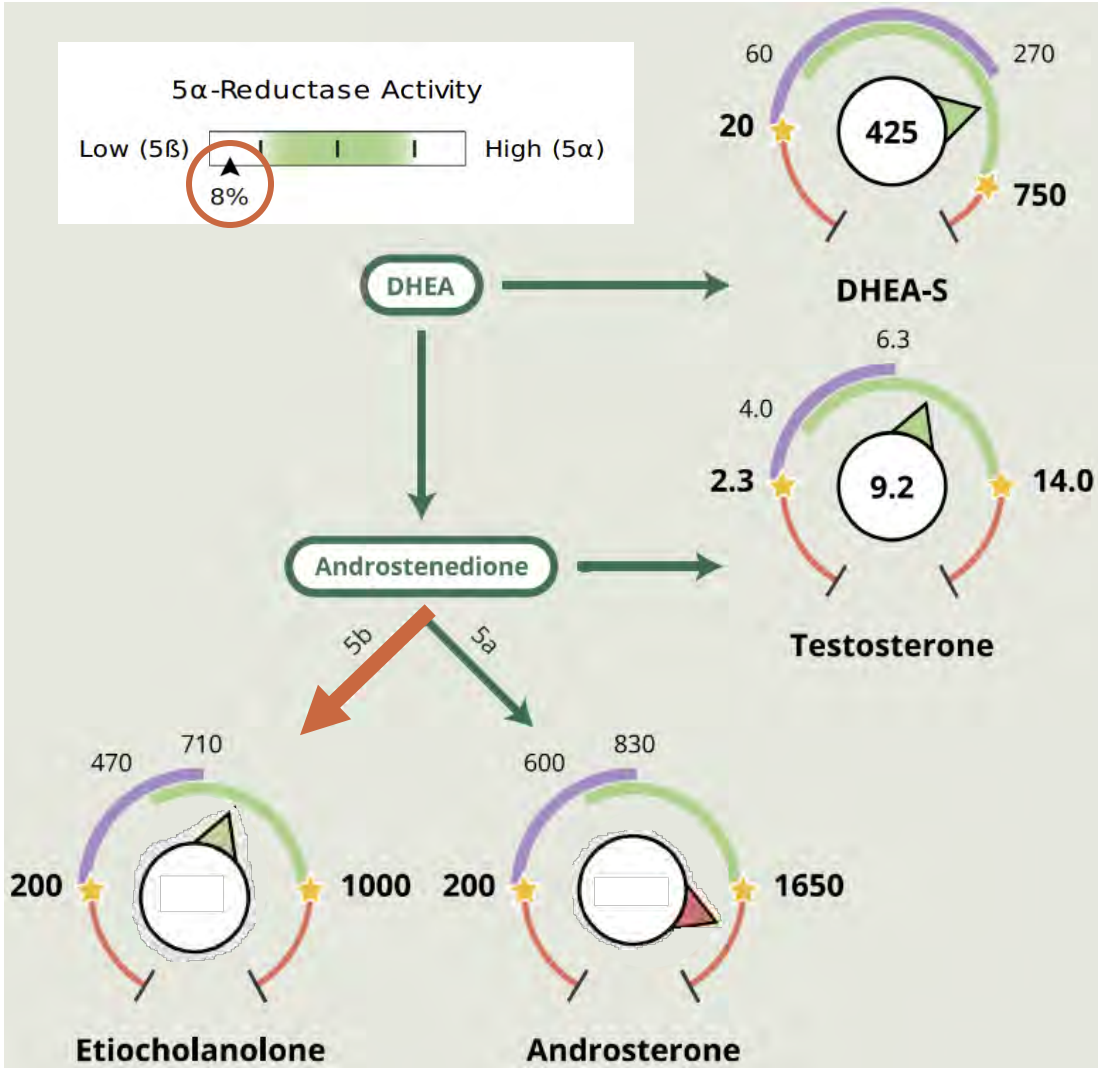

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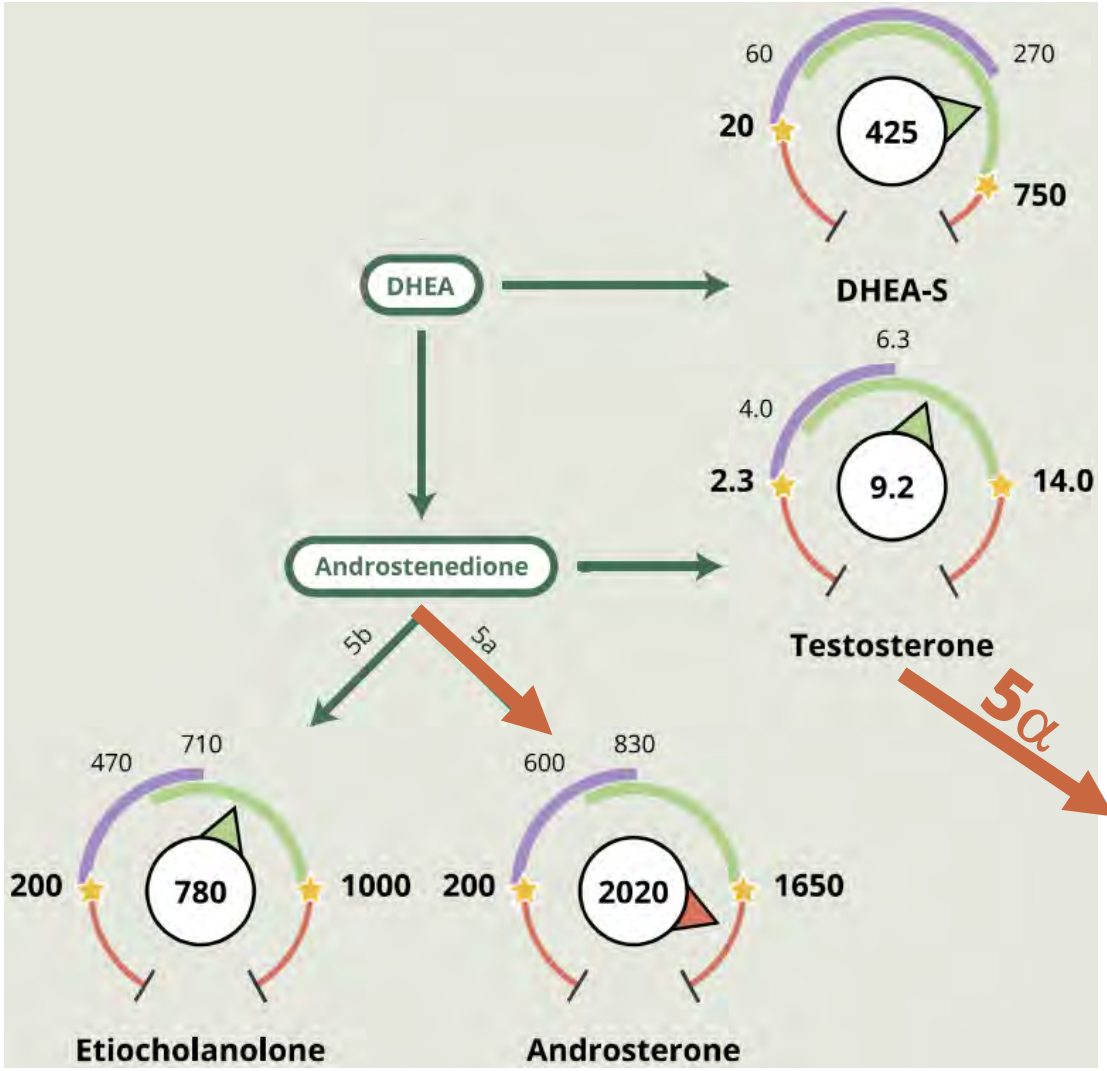

5a-DHT

5a-DHT is 3X as potent as T

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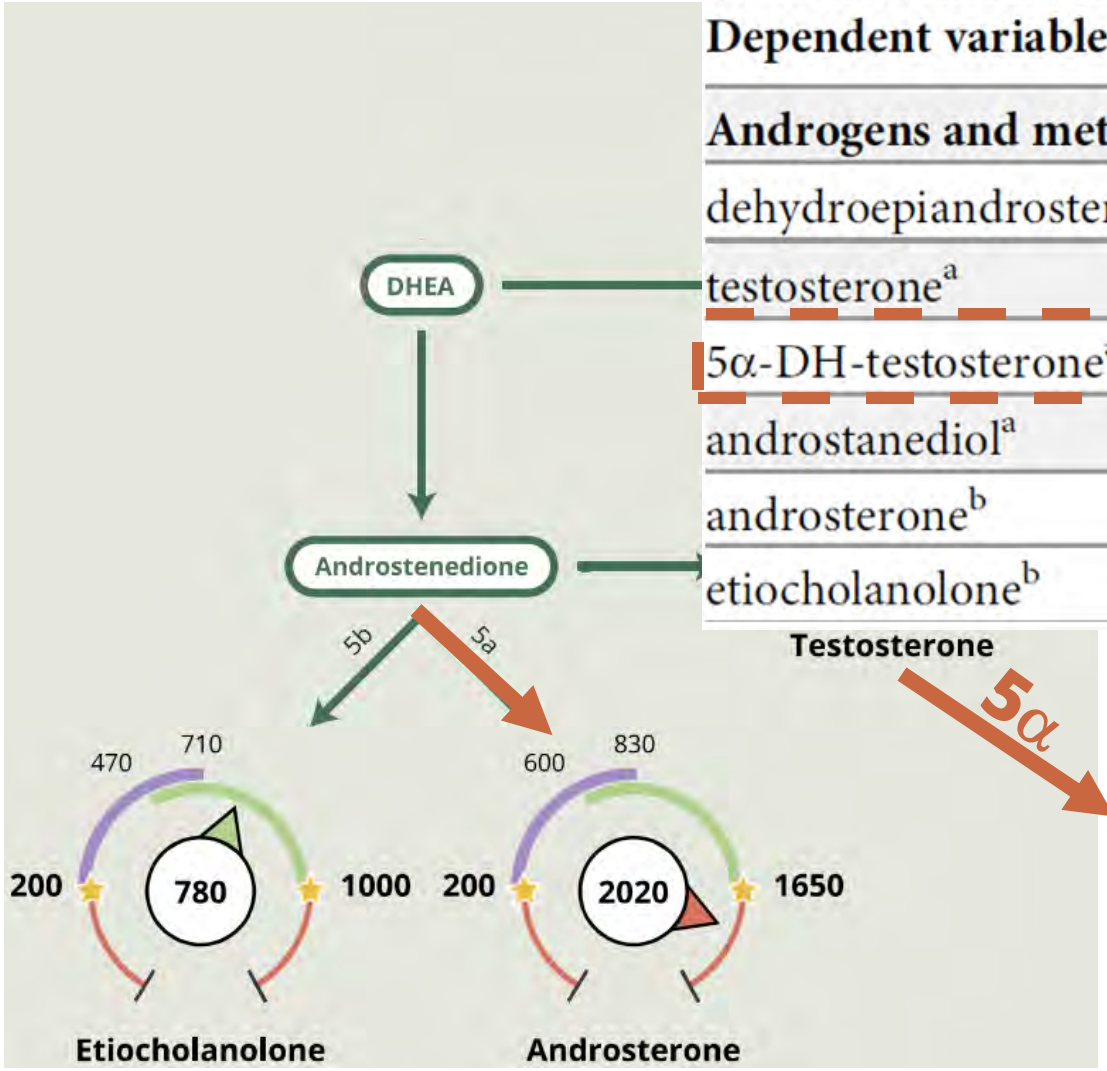

Steroid hormone, nmol/24h Dependent variable in Models	Controls		PCOS	
	Median	25th-75th	Median	25th-75th
Androgens and metabolites				
dehydroepiandrosterone[a]	293	136–853	1435	390–3895
testosterone[a]	34	21–58	52	34–84
5α-DH-testosterone[a]	36	23–55	56	44–88
androstanediol[a]	108	65–142	250	185–350
androsterone[b]	3983	2651–5433	8354	4909–11808
etiocholanolone[b]	4075	2823–5709	5893	4558–8210

PLOS ONE https://doi.org/10.1371/journal.pone.0203903 October 11, 2018

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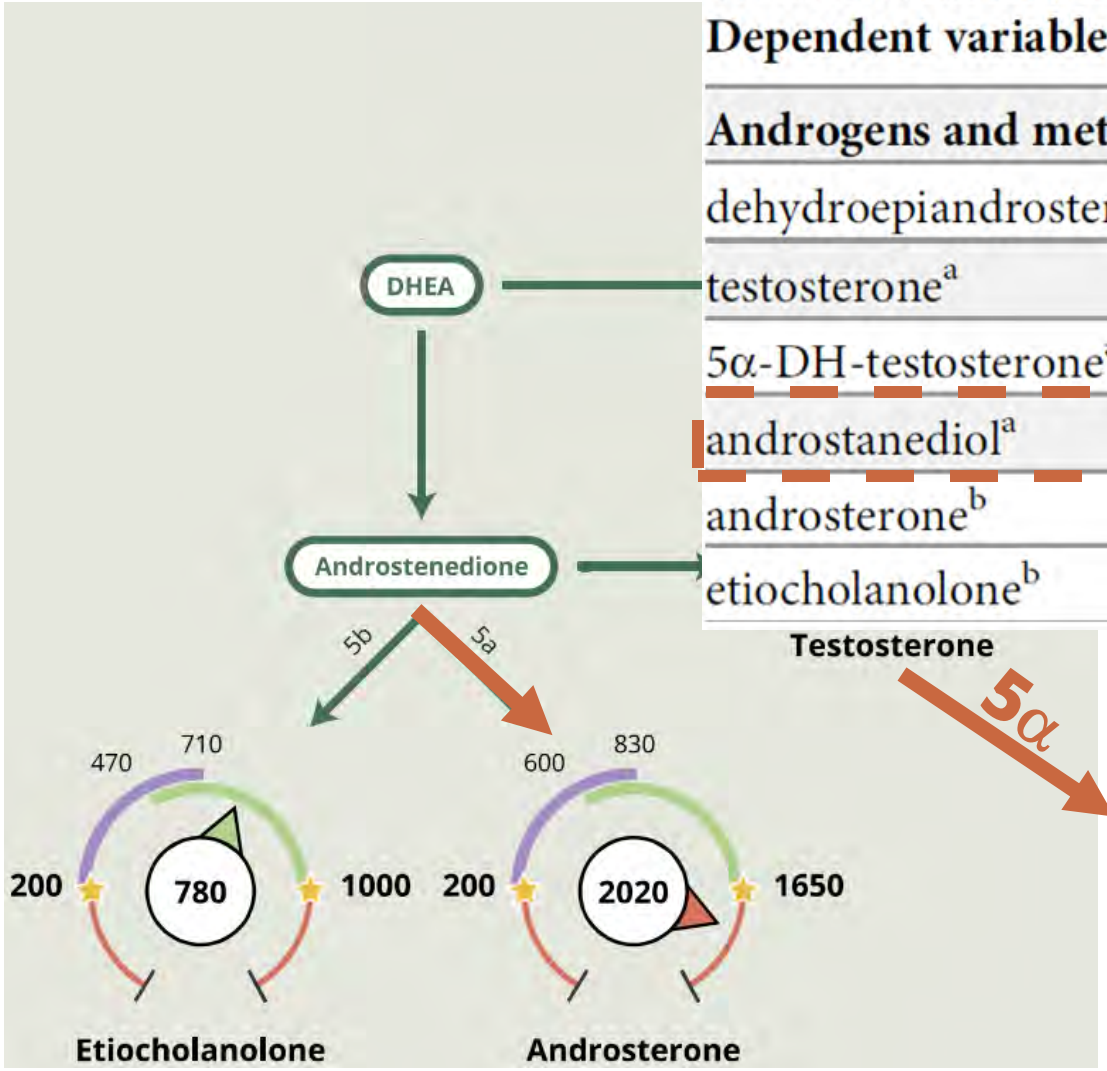

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5a-DHT

5a-Androstanediol

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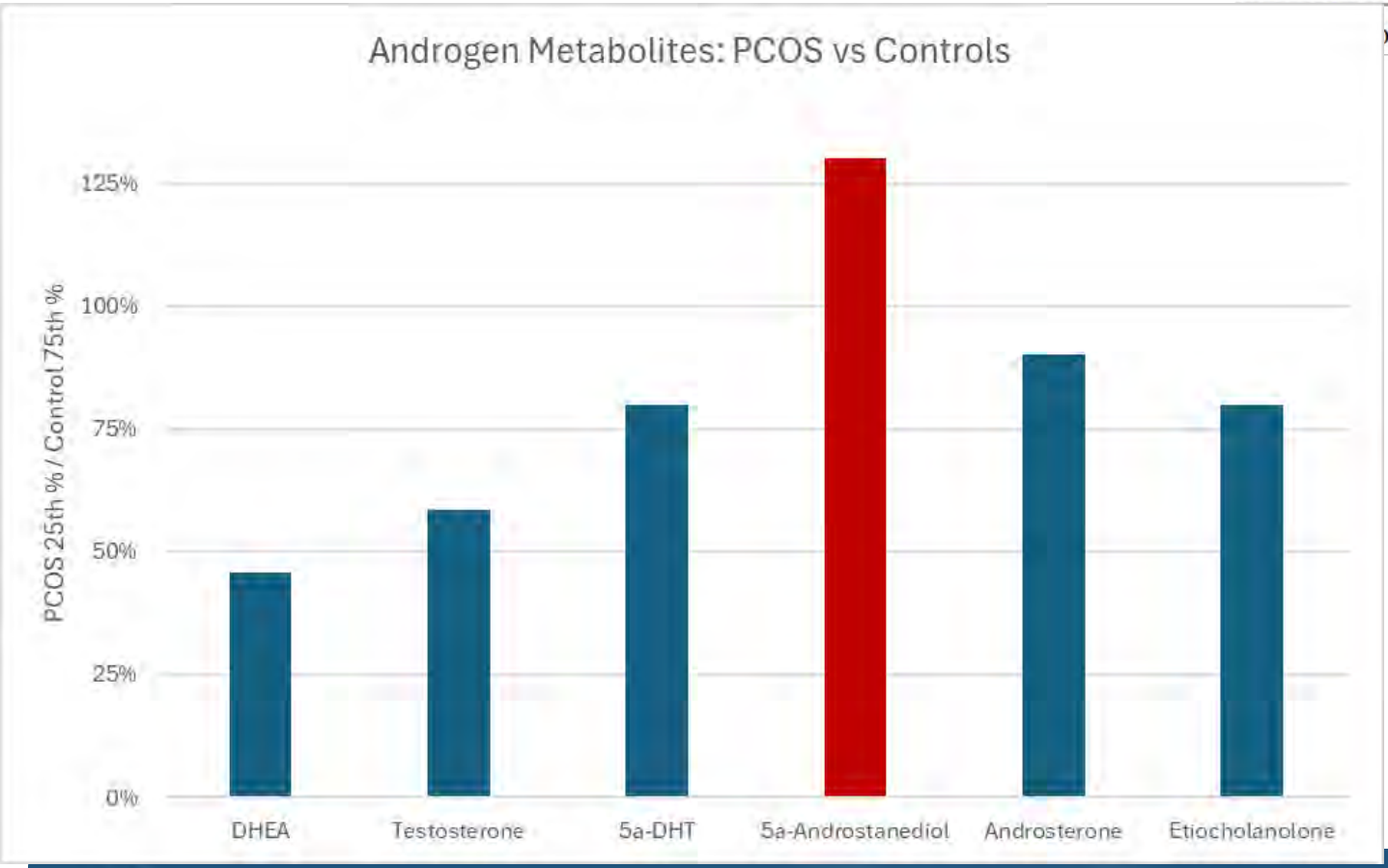

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Why not focus on 5a-DHT?

The unique value of 5a-Androstanediol

Evolving our understanding of the most meaningful measurements

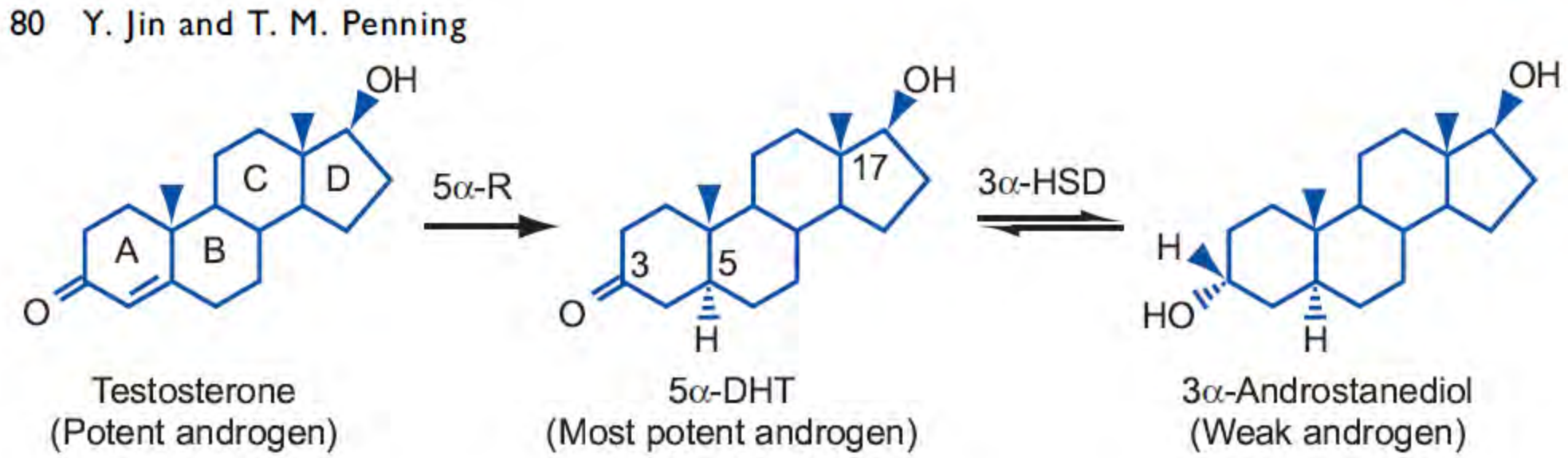

Figure 1. Conversion of androgens of different potencies mediated by 5α-R and 3α-HSD.

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Evolving our understanding of the most meaningful measurements

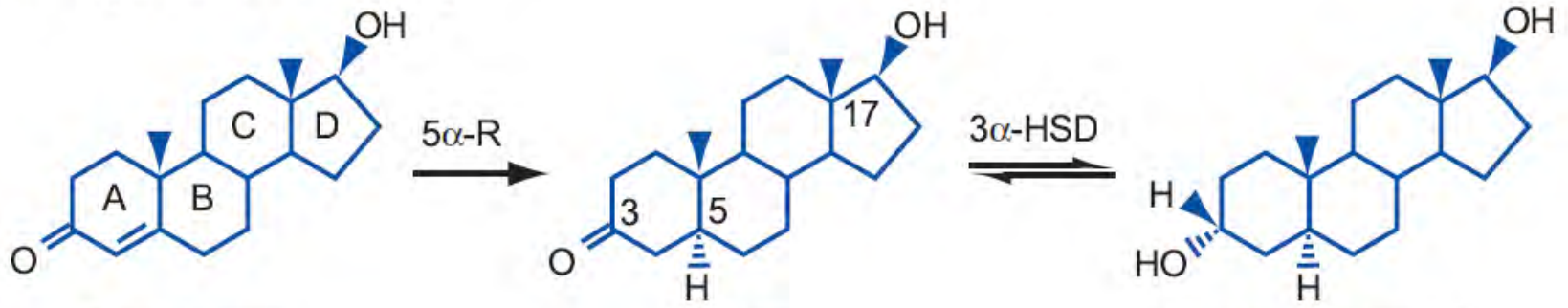

Figure 1. Conversion of androgens of different potencies mediated by 5α-R and 3α-HSD.

Secreted primarily by the testis in men, testosterone is the principal circulating androgen with a high affinity of 10^{-10} M for AR. In androgen target cells, testosterone is converted to 5α-dihydrotestosterone (5α-DHT), which is the most potent natural androgen known, with an affinity of 10^{-11} M for AR.[4,5]

5α-DHT is subsequently inactivated to the weak androgen 3α-androstanediol (K_d of 10^{-6} M for AR) by the action of 3α-hydroxysteroid dehydrogenase.

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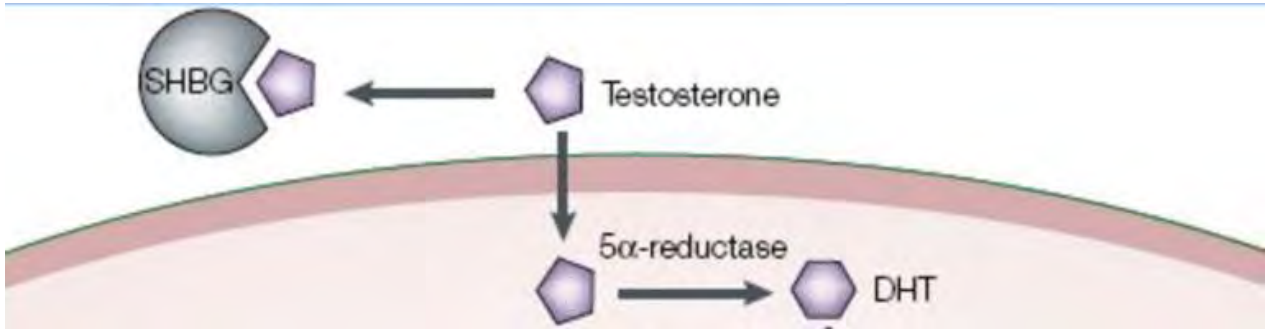

The most meaningful Testosterone is free

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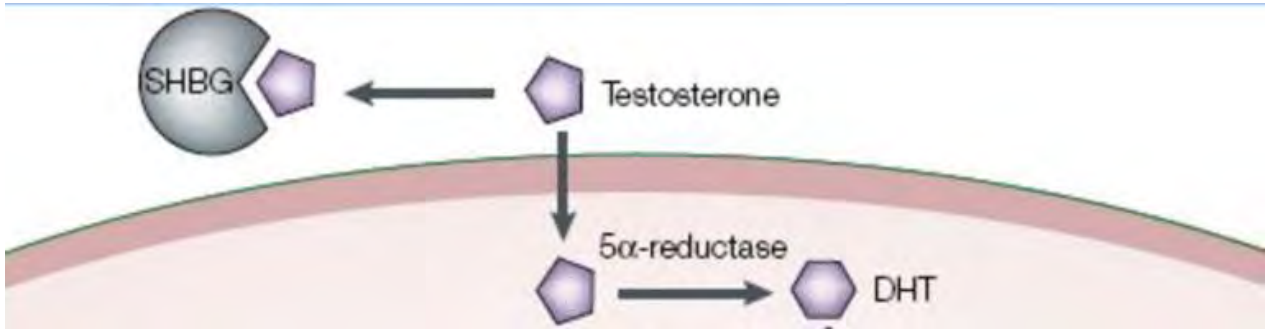

The most meaningful Testosterone is free

The most meaningful DHT is intracellular

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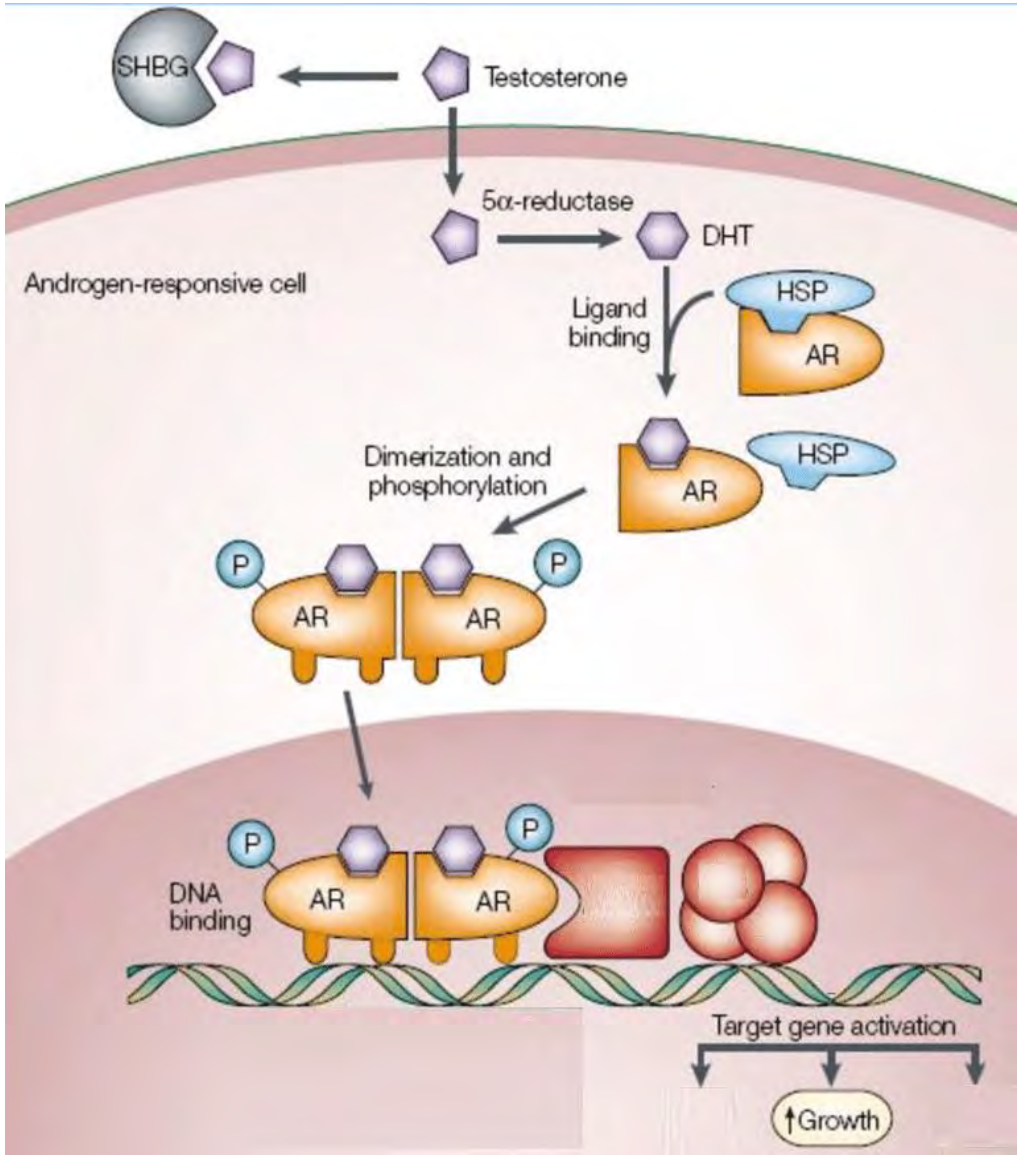

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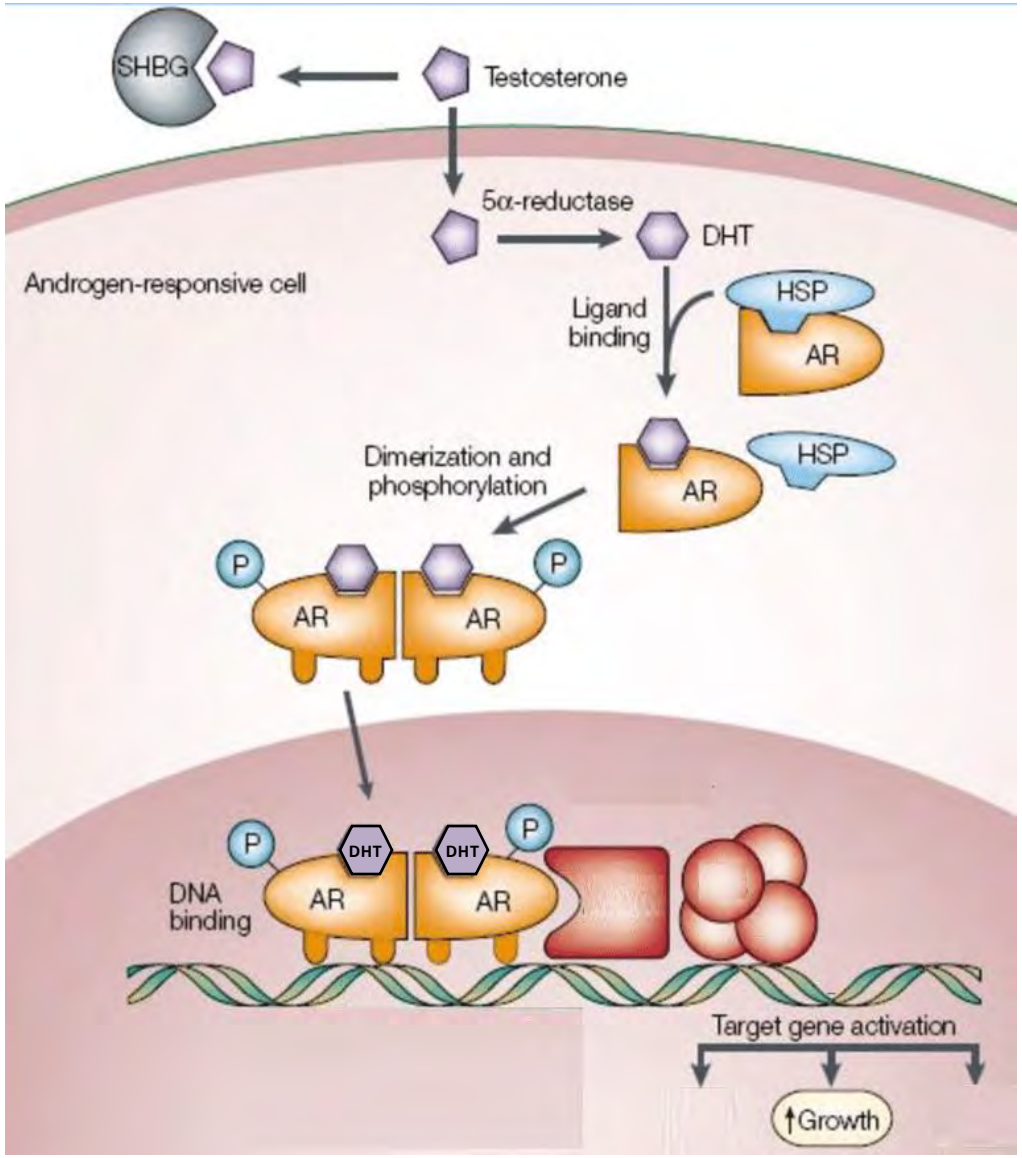

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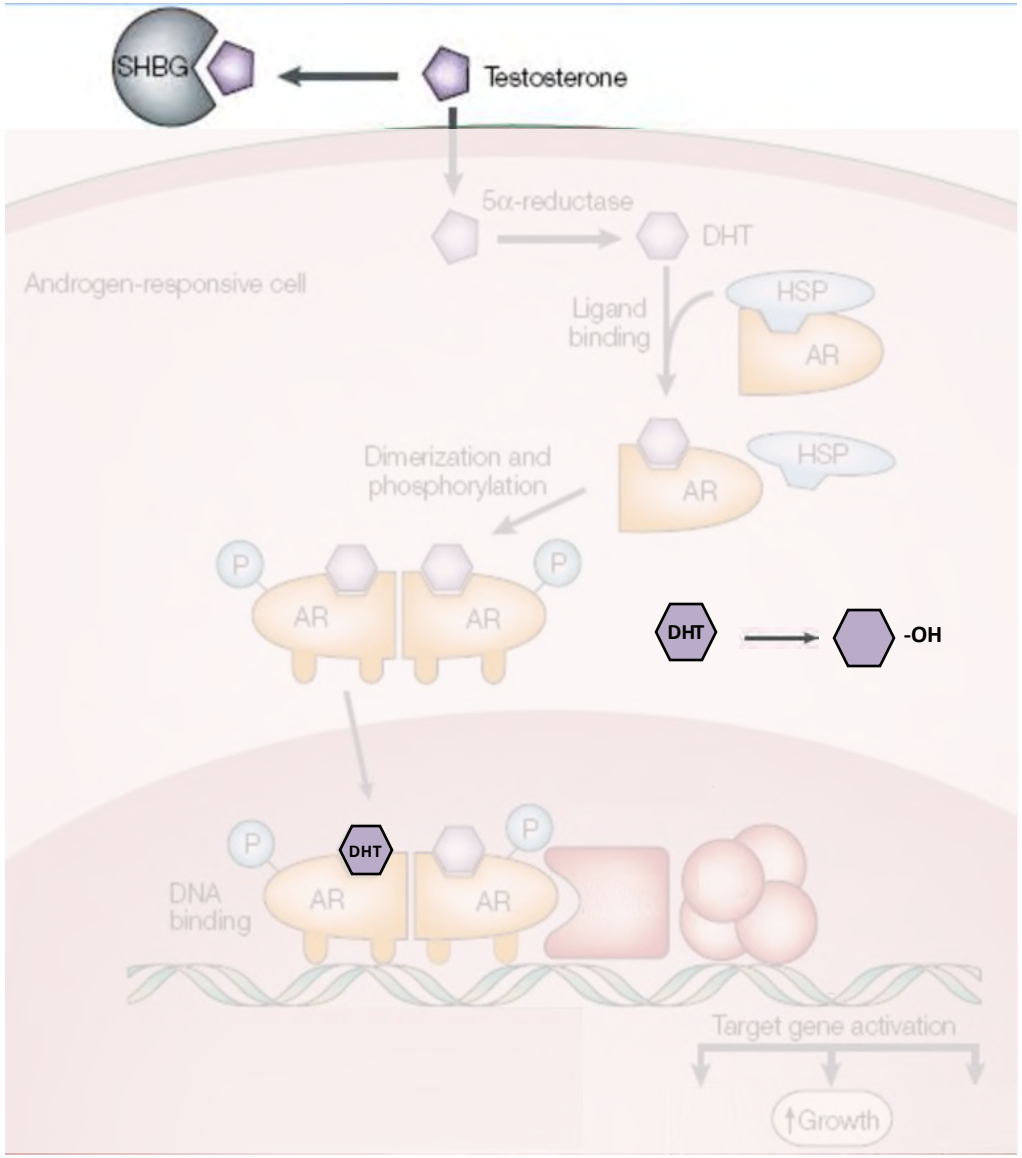

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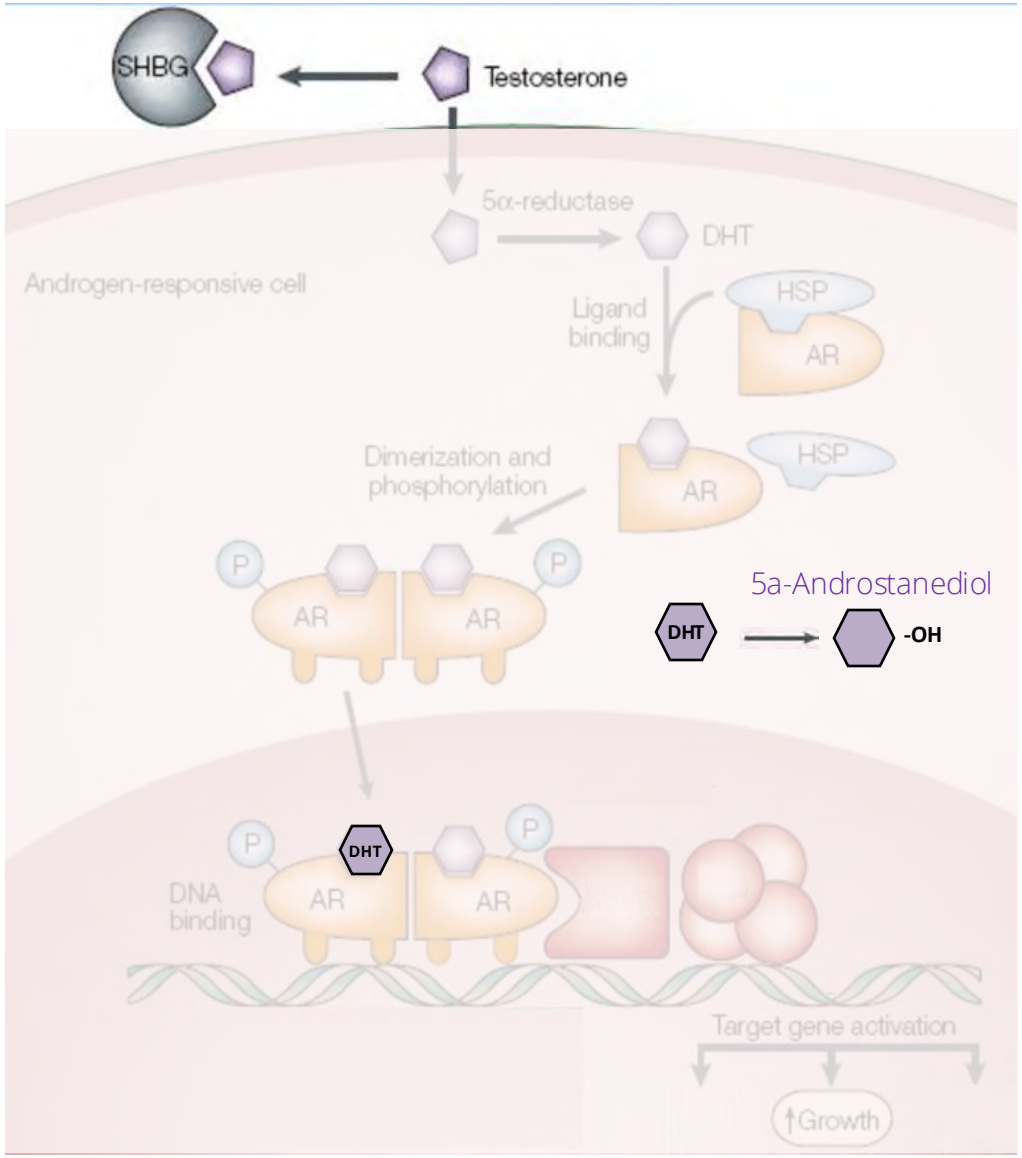

Testosterone

5a-DHT

5a-Androstanediol

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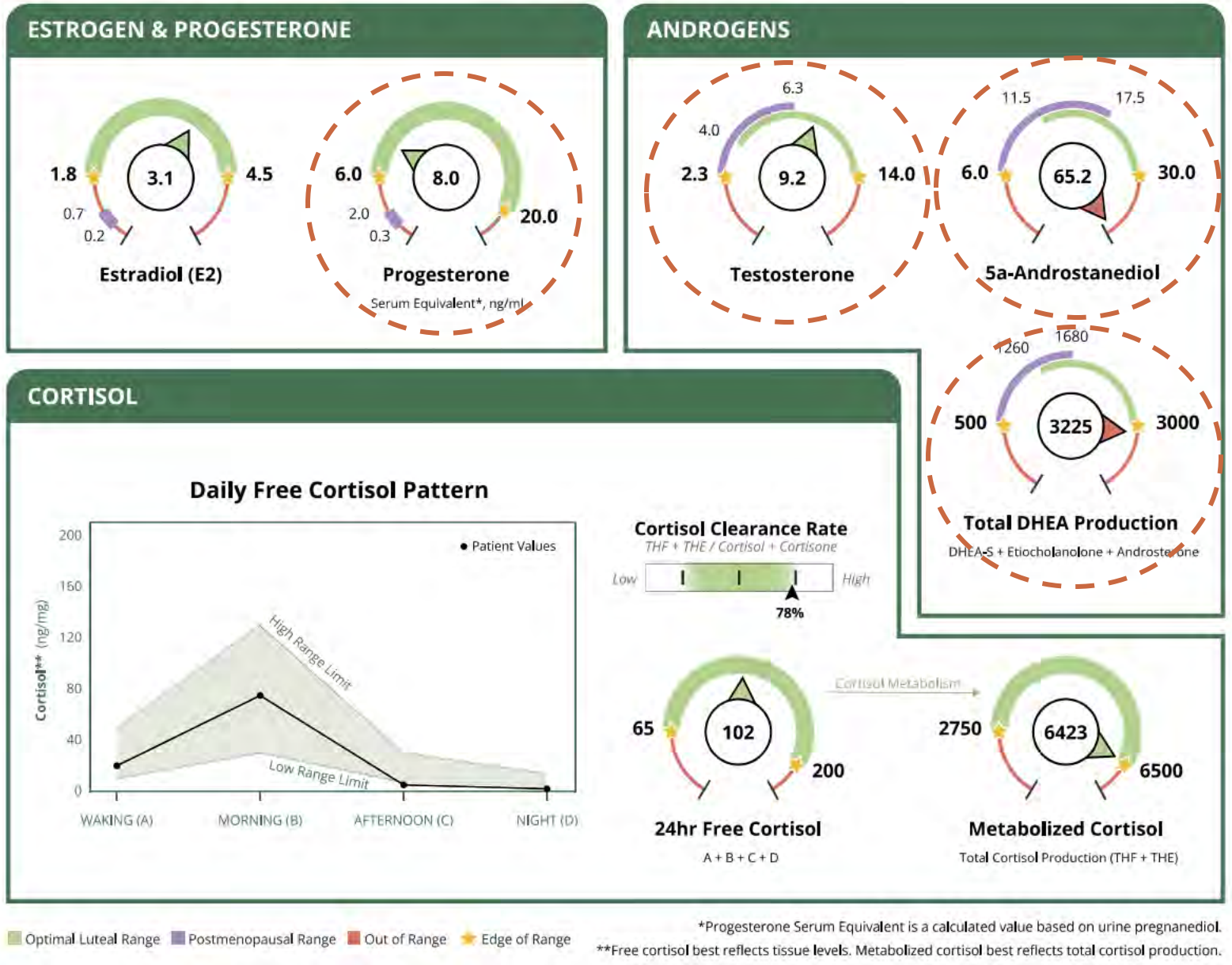
Hormone Testing Summary



PCOS?

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What about Estrogen?

DUTCH is a Comprehensive Look at Estrogen

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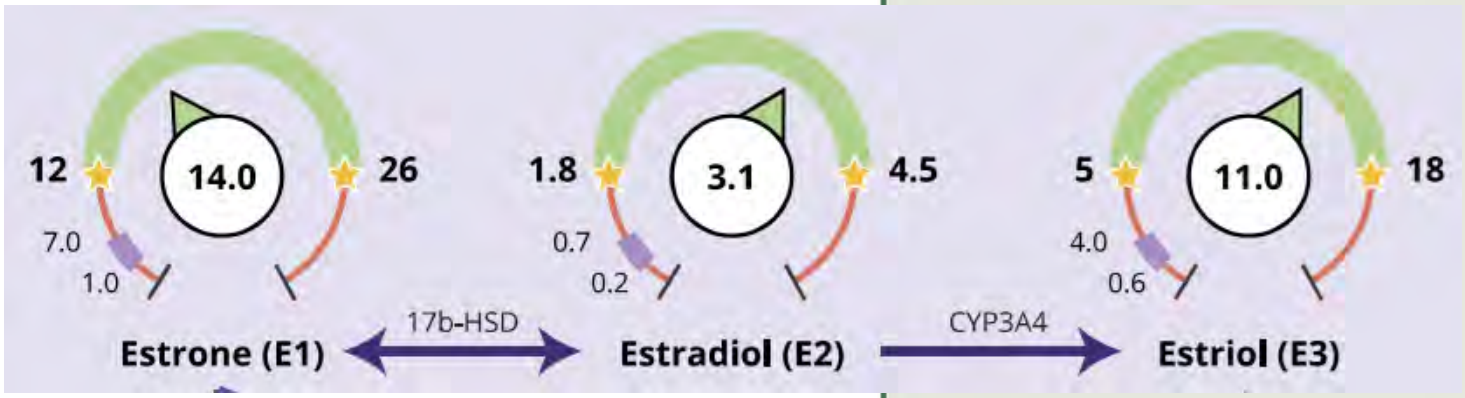
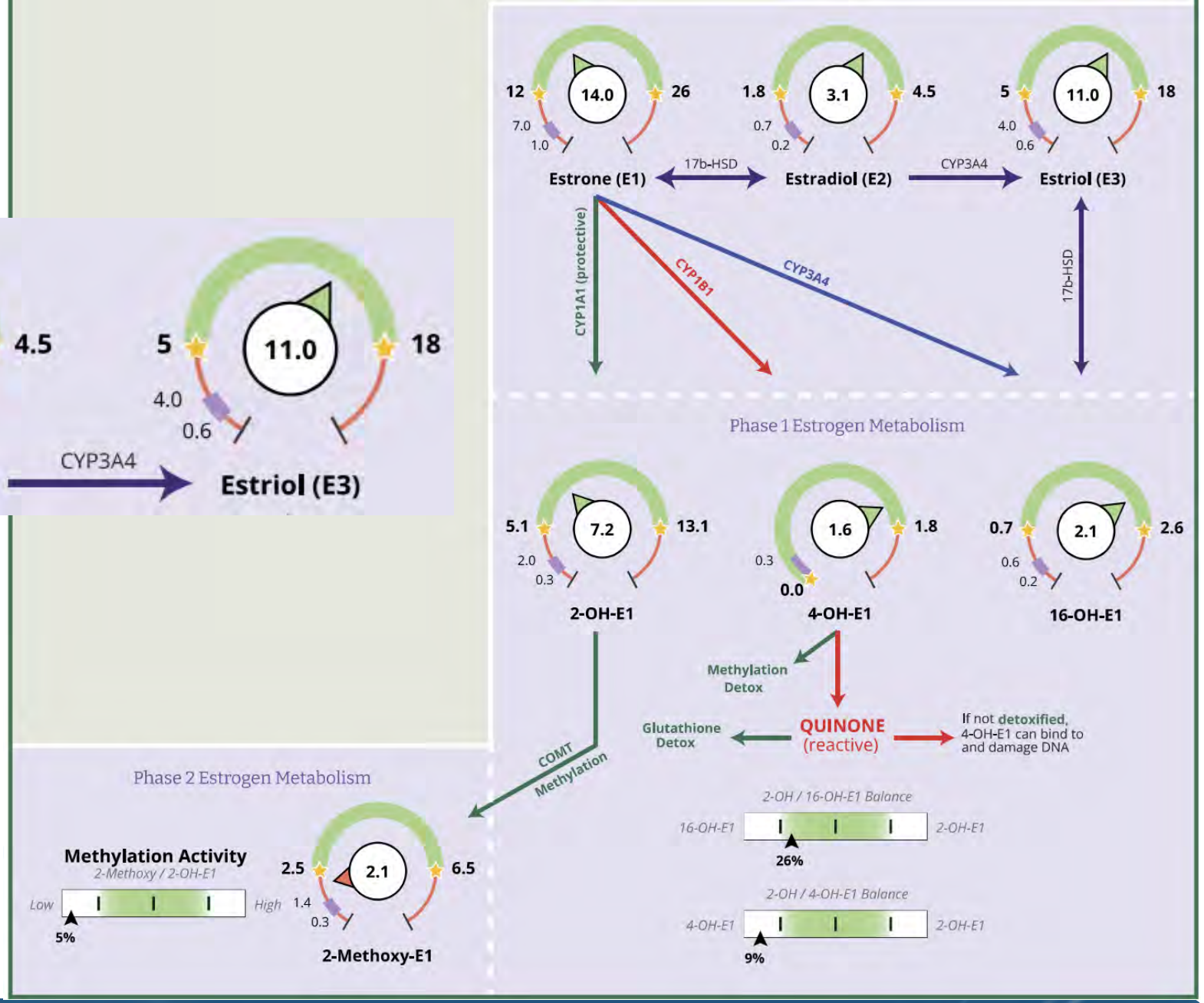
1. Estrogen Status





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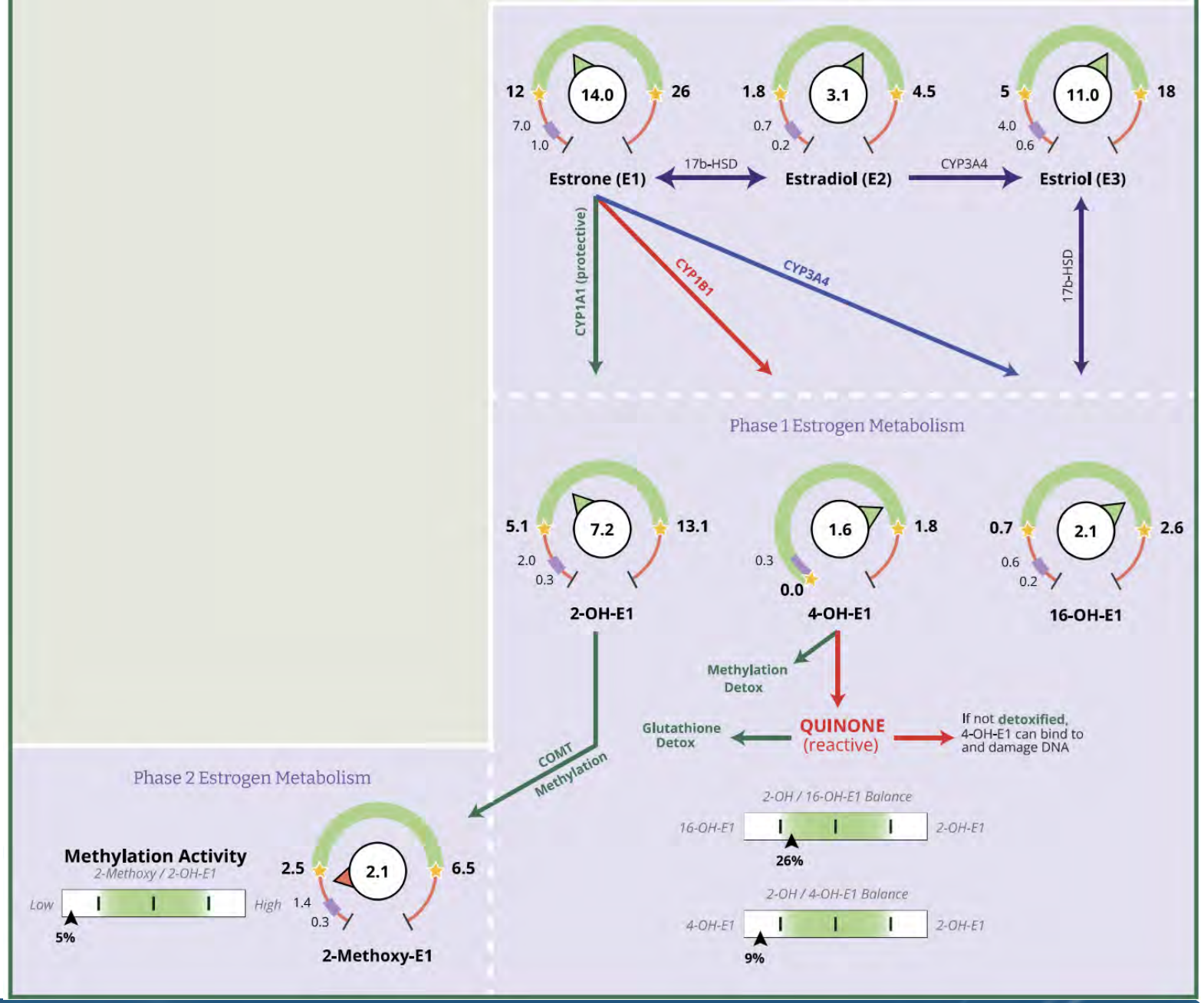
1. Estrogen Status
2. Phase 1 Metabolism
3. Methylation (Phase 2)



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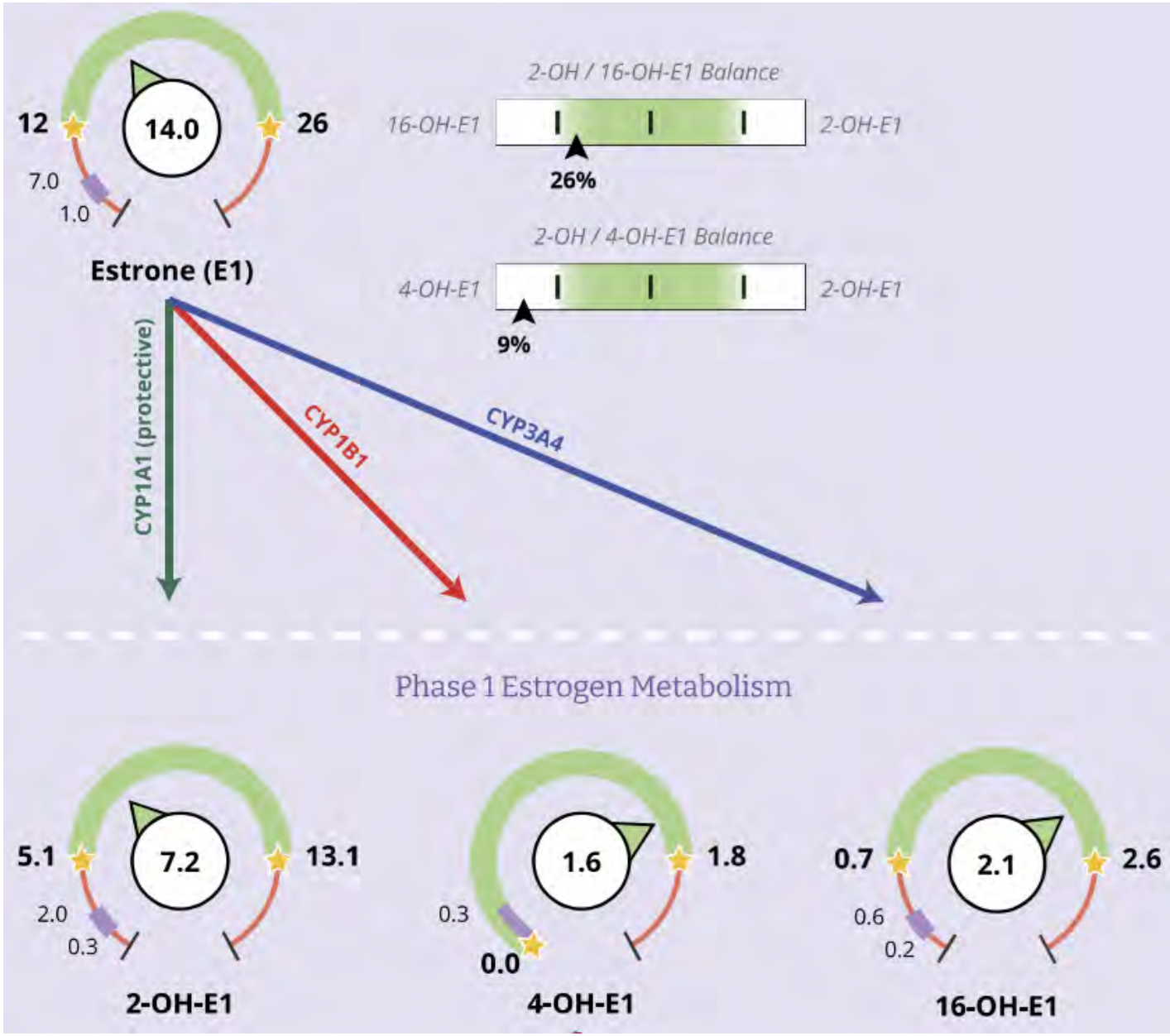
2. Phase 1 Metabolism



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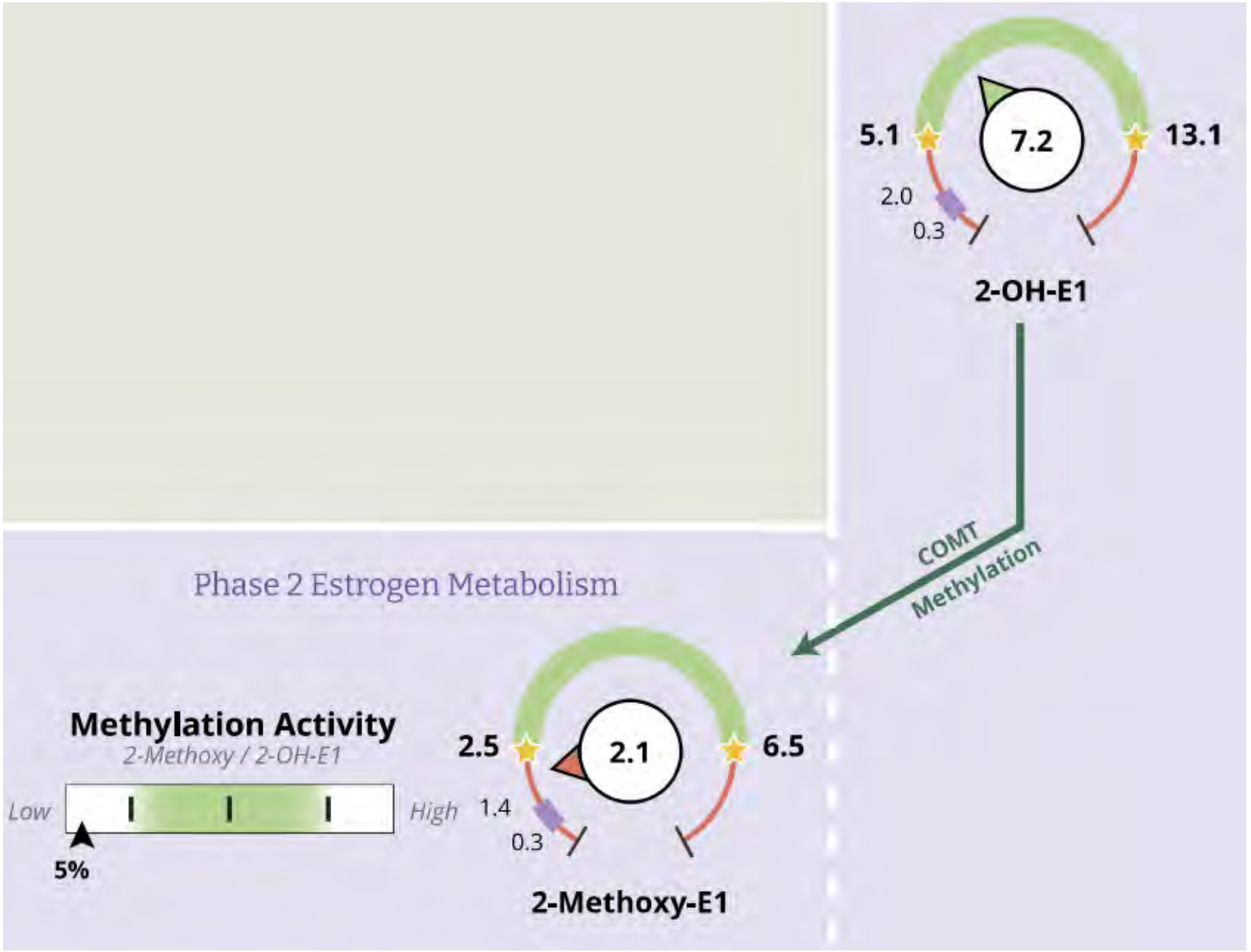
3. Methylation

Poor methylation may be due to genetic or nutritional influences



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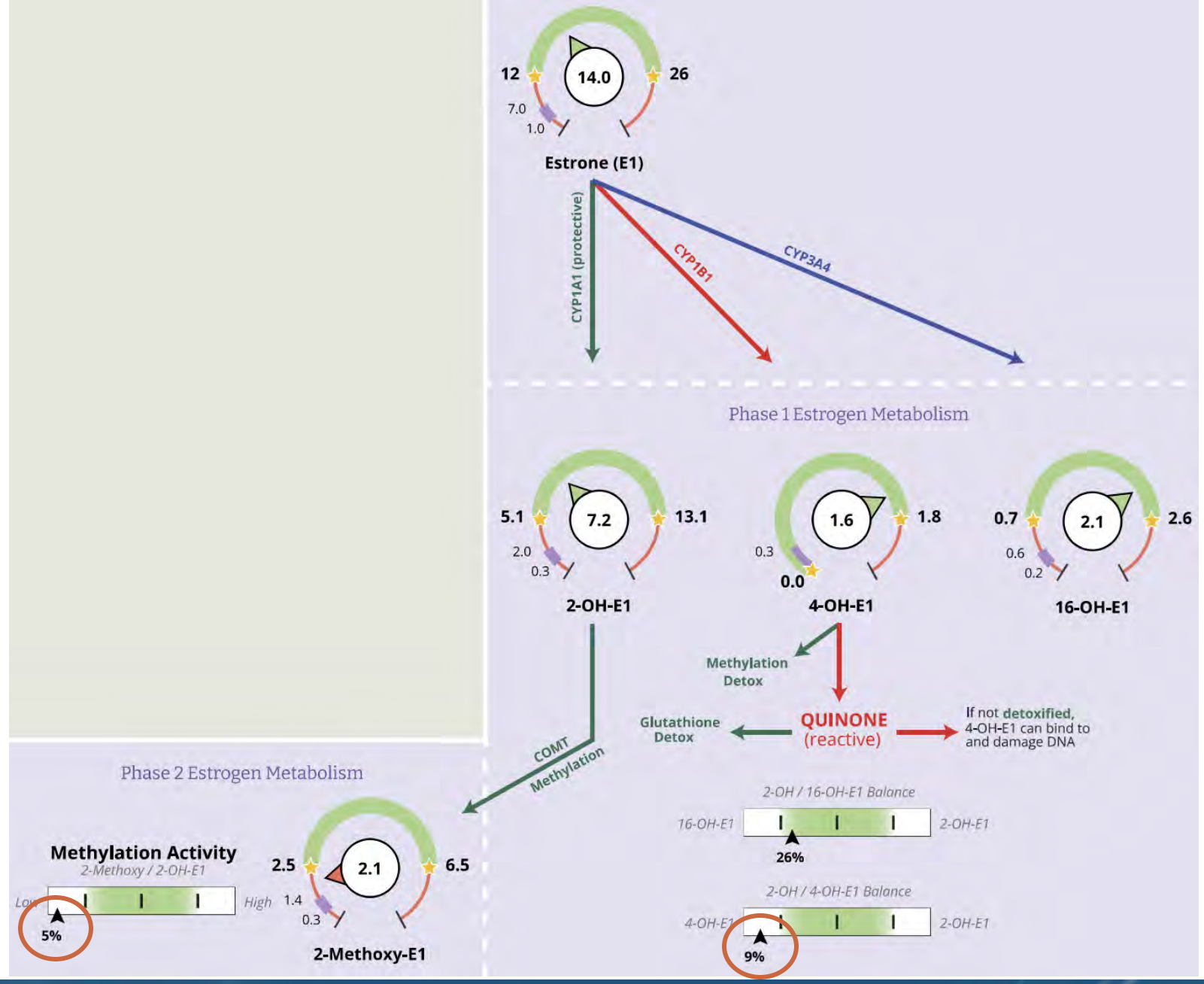

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What about Estrogen?

Are E2 levels different in PCOS?

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Table 1. Characteristics of PCOS patients and controls.

Variables	PCOS ($n = 86$)	Control ($n = 60$)	p Value
Age, year	24.6 ± 5.7	26.17 ± 5.0	0.621
BMI, kg/m^2	24.9 ± 3.6	23.4 ± 2.9	0.173
Fasting blood glucose, mg/dl	83.6 ± 11.5	87.4 ± 6.7	0.055
Fasting insulin, µIU/ml	11.6 (2.0–60.5)	7.3 (2.03–11.7)	**<0.0001**
HOMA-IR	2.5 (0.3–17.6)	1.5 (0.4–2.6)	**<0.0001**
Total cholesterol, mg/dl	182.8 ± 32.4	162.9 ± 26.7	**0.007**
LDL-C, mg/dl	107.2 ± 29.1	85.0 ± 25.3	**0.001**
HDL-C, mg/dl	48.2 ± 13.9	60. 9 ± 13.7	**<0.0001**
Triglyceride, mg/dl	108.0 (28.0–468.0)	58.0 (33.0–175.0)	**<0.0001**
FSH, mIU/ml	5.3 ± 2.3	4.6 ± 3.9	0.2
LH, mIU/ml	10.1 (0.5–51.9)	6.5 (1.3–17.4)	**0.002**
LH/FSH ratio	2.1 ± 1.3	1.8 ± 1.0	0.221
Total testosterone, ng/ml	0.5 (0.1–1.6)	0.2 (0.1–0.4)	**<0.0001**
Free testosterone, pg/ml	2.3 ± 0.9	1.5 ± 0.3	**<0.0001**
Androstenedione, ng/ml	3.5 ± 2.2	2.1 ± 0.4	0.418
DHEAS, µg/dl	275.3 ± 114.5	194.7 ± 67.6	**<0.0001**
Prolactin, ng/ml	13.8 ± 5.0	15.1 ± 3.8	0.134
Estradiol, pg/ml	68.0 (23.40–479.0)	88.5 (11.15–166)	0.584
Progesterone, ng/ml	0.9 (0.17–25)	15 (10.9–23.1)	**<0.0001**

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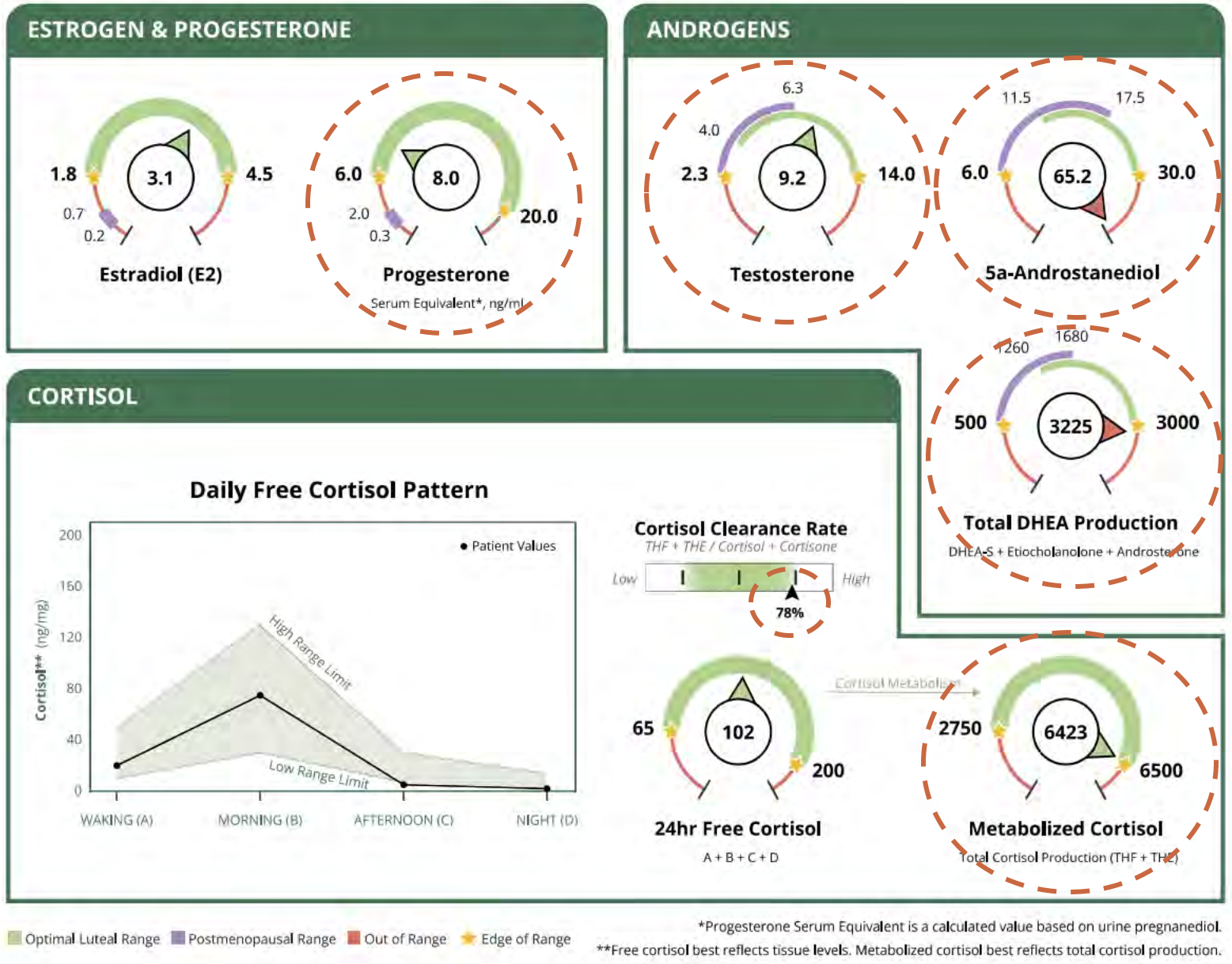
Hormone Testing Summary



PCOS?

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What makes a woman with PCOS at risk of developing Autoimmunity?

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Stress and autoimmunity

Ljudmila Stojanovich [1]

Affiliations + expand

PMID: 19931651 DOI: 10.1016/j.autrev.2009.11.014

Abstract

The etiology of autoimmune disease is multifactorial, including genetic, environmental, hormonal, and immunological factors. Nevertheless, the onset of autoimmune disorders remains enigmatic. Physical and psychological stresses have been suggested in the development of autoimmune disease, since numerous animal and human studies demonstrated the effect of stressors on immune function. Moreover, many retrospective studies had found that a high proportion (up to 80%) of patients reported uncommon emotional stress before disease onset. This, however, is not surprising as the disease itself causes significant stress in the patient. Recent reviews discuss the possible role of psychological stress, and of the major stress-related hormones, in the pathogenesis of autoimmune disease and presume that the stress-triggered neuroendocrine hormones lead to immune dysregulation, which ultimately results in autoimmune disease by altering or amplifying cytokine production. However, there is no evidence based research to support this concept. Nonetheless, stress reactions should be discussed with autoimmune patients. Applied implications are discussed, concentrating on the need for multidisciplinary care interventions that target patients' disease symptoms and help them cope with their illness.

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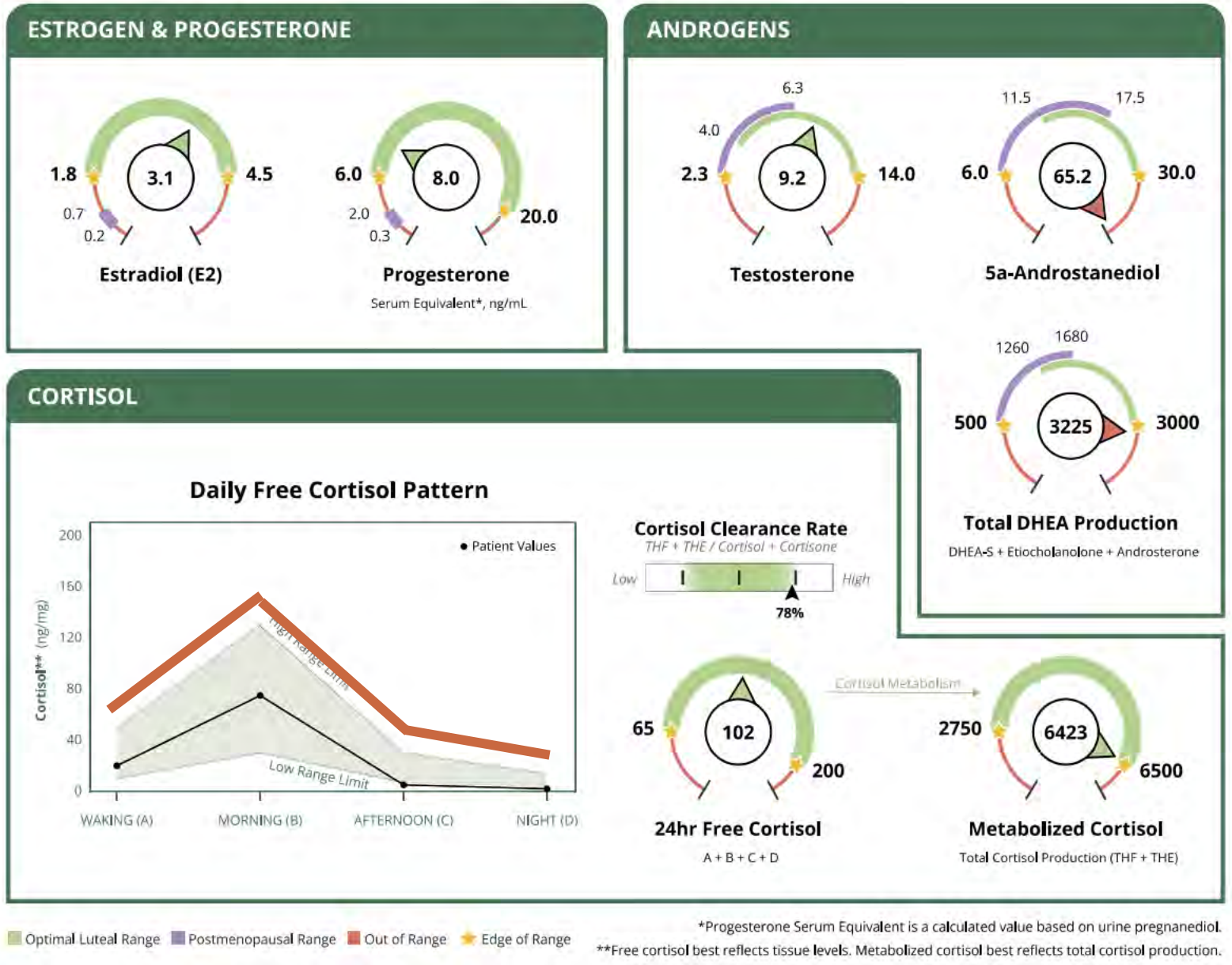
Hormone Testing Summary



PCOS & AI Link?

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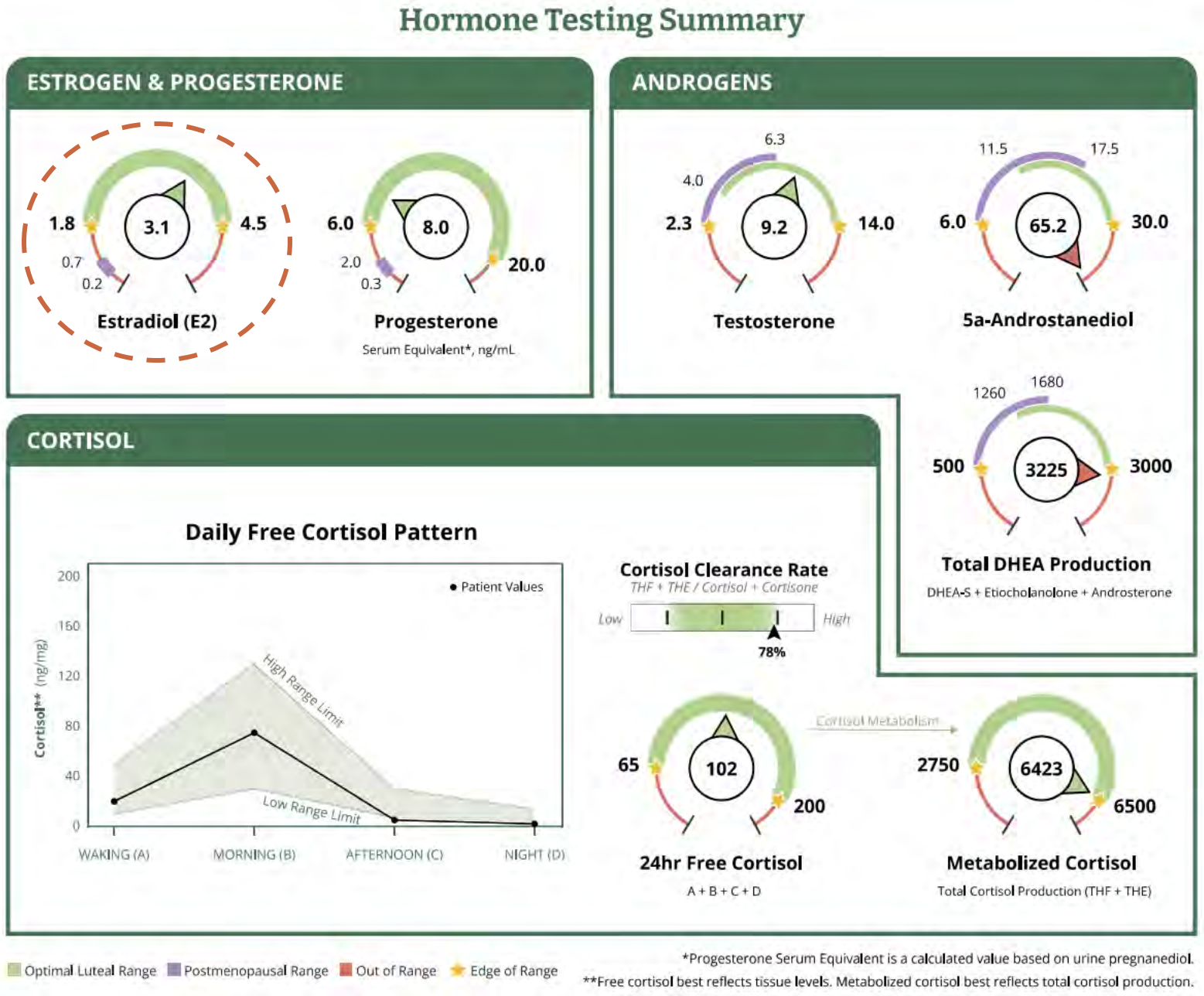

PCOS & AI Link?

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Endocr Res. 2015;40(4):204-10. doi: 10.3109/07435800.2015.1015730. Epub 2015 Mar 30.

High prevalence of Hashimoto's thyroiditis in patients with polycystic ovary syndrome: does the imbalance between estradiol and progesterone play a role?

Ayse Arduc [1], Bercem Aycicek Dogan [2], Sevgi Bilmez [3], Narin Imga Nasiroglu [2],

Abstract

Objective: Some similar factors, such as genetic susceptibility and subinflammation/autoimmunity, contribute to development of both polycystic ovary syndrome (PCOS) and Hashimoto's thyroiditis (HT), suggesting a potential pathogenic link between the two common disorders. In this study, we investigated the relationship between PCOS and HT, considering the possible effect of PCOS-related hormonal and metabolic factors on thyroid autoimmunity.

Methods: Eighty-six reproductive-age women diagnosed with PCOS according to Rotterdam criteria and 60 age-BMI matched control women were included in the study. All subjects had thyroid function tests, thyroid peroxidase anti-body (anti-TPO), thyroglobulin anti-body (anti-Tg), LH, FSH, estradiol, progesterone, androgens, fasting glucose, insulin, lipid, homeostasis model assessment insulin resistance (HOMA-IR) levels, thyroid and pelvic ultrasounds.

Results: TSH, anti-TPO ($p = 0.017$), anti-Tg ($p = 0.014$), LH, DHEAS, testosterone, and HOMA-IR levels were significantly higher and progesterone were lower in PCOS women than in controls. Free T4, free T3, FSH, estradiol levels and thyroid volume were similar between the two groups. A higher percentage of PCOS patients had elevated TSH (26.7 and 5%; $p = 0.001$), anti-TPO (26.7 and 6.6%; $p = 0.002$), and anti-Tg (16.2 and 5%; $p = 0.039$). HT was more common in PCOS patients compared to controls (22.1 and 5%; $p = 0.004$). Estradiol ($p = 0.003$) were higher in anti-TPO positive PCOS women than anti-TPO negative ones. Anti-TPO was correlated positively with estradiol, estradiol/progesterone ratio, and TSH.

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Table 3. Comparison of clinical, biochemical, and hormonal parameters of PCOS patients based on anti-TPO status.

Variables	Anti-TPO positive ($n = 23$)	Anti-TPO negative ($n = 63$)	p Value
Age, year	24.6 ± 6.3	24.0 ± 5.5	0.68
BMI, kg/m^2	25.7 ± 2.0	25.1 ± 4.0	0.75
Fasting blood glucose, mg/dl	82.0 ± 9.6	85.2 ± 12.4	0.295
Fasting insulin, µIU/ml	11.3 (2.3–54.2)	12.8 (2.0–60.5)	0.417
HOMA-IR	2.2 (0.4–13.1)	2.7 (0.3–17.6)	0.374
Total cholesterol, mg/dl	190.0 ± 29.1	187.4 ± 33.0	0.825
LDL-C, mg/dl	103.6 ± 40.6	112.6 ± 25.6	0.52
HDL-C, mg/dl	49.8 ± 12.9	49.7 ± 14.6	0.996
Triglyceride, mg/dl	98.5 (53.0–468.0)	109.0 (28.0–368.0)	0.976
TSH, µIU/ml	3.1 (0.20–17.9)	2.7 (0.5–11.2)	0.178
Free T4, ng/dl	1.1 ± 0.2	1.2 ± 0.2	0.436
Free T3, pg/ml	3.1 ± 0.5	3.3 ± 0.4	0.383
Anti-Tg, IU/ml	182 (0.9–1098)	12.6 (0.9–431)	**<0.0001**
FSH, mIU/ml	5.6 ± 3.0	5.4 ± 1.9	0.659
LH, mIU/ml	7.6 (0.5–51.9)	7.5 (0.5–51.9)	0.187
LH/FSH ratio	2.3 ± 1.2	2.2 ± 1.5	0.795
Total testosterone, ng/ml	0.5 (0.1–1.0)	0.6 (0.1–1.0)	0.808
Free testosterone, pg/ml	2.3 ± 1.0	2.4 ± 0.8	0.664
Androstenedione, ng/ml	3.9 ± 3.9	3.3 ± 1.5	0.625
DHEAS, µg/dl	298.2 ± 122.2	275.4 ± 108.4	0.468
Prolactin, ng/ml	14.6 ± 4.4	13.3 ± 5.3	0.399
Estradiol, pg/ml	107.0 (23.40–374.00)	57 (28–479.0)	**0.003**
Estradiol/progesterone ratio	105.5 (14.9–474.3)	61.5 (13.9–508.0)	0.281
Progesterone, ng/ml	0.7 (0.3–11.7)	0.9 (0.2–16.5)	0.434
Thyroid volume, ml	11.4 (3.3–25.9.0)	11.1 (5.1–26.1)	0.48

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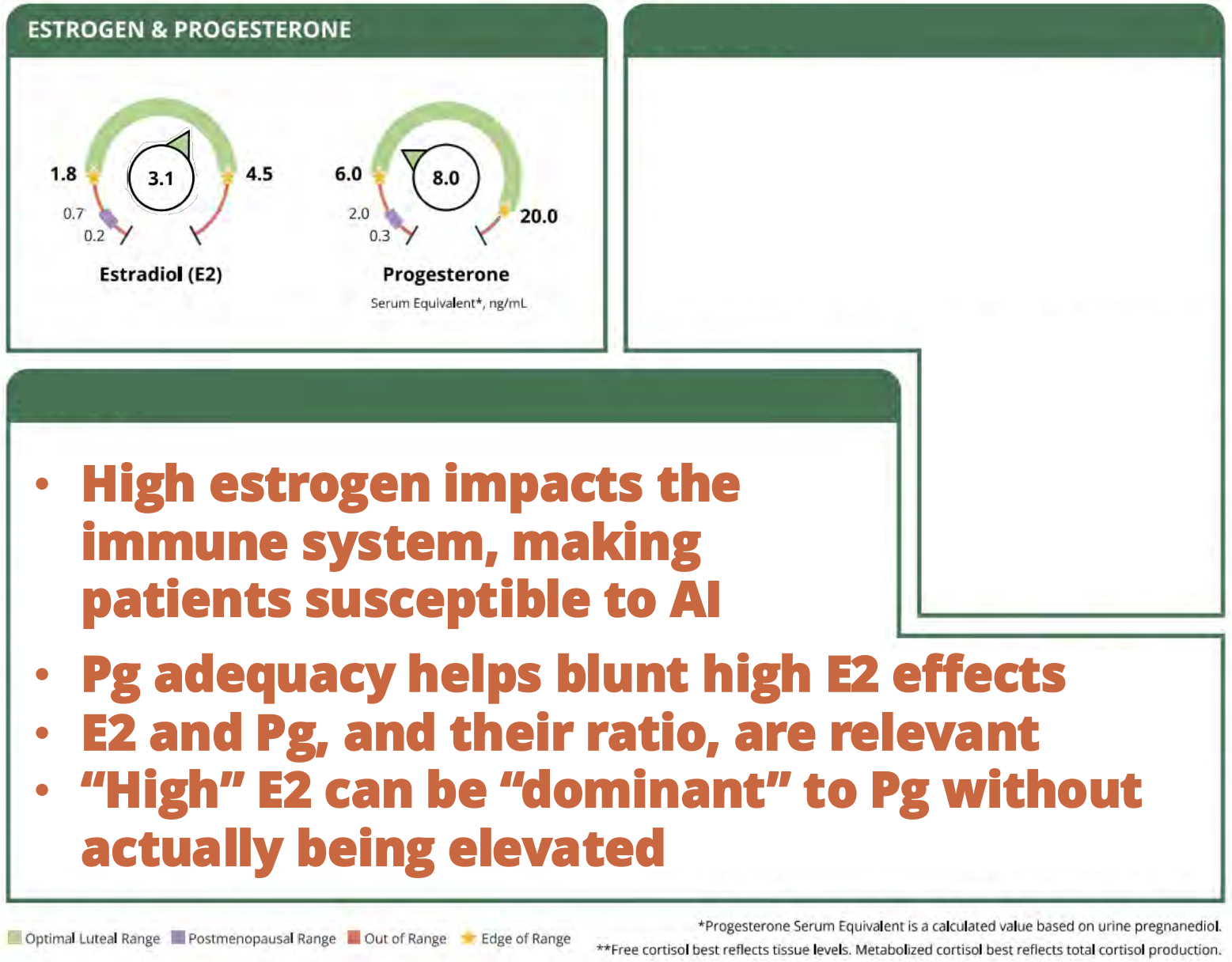
Hormone Testing Summary



PCOS & AI Link?

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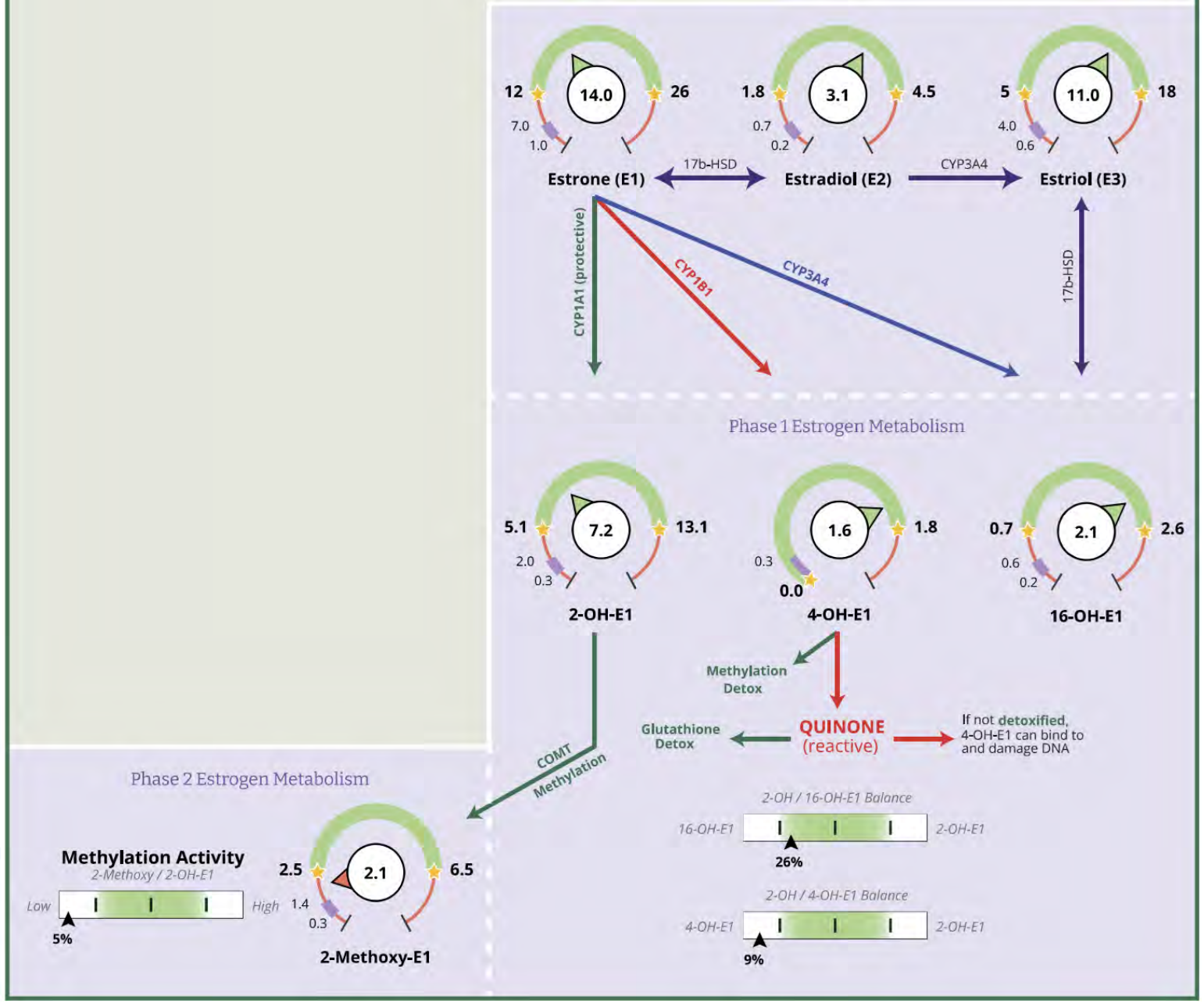
1. Estrogen Status
2. Phase 1 Metabolism
3. Methylation (Phase 2)

Poor phase 1 or methylation can increase E1, E2 and 16OHE1



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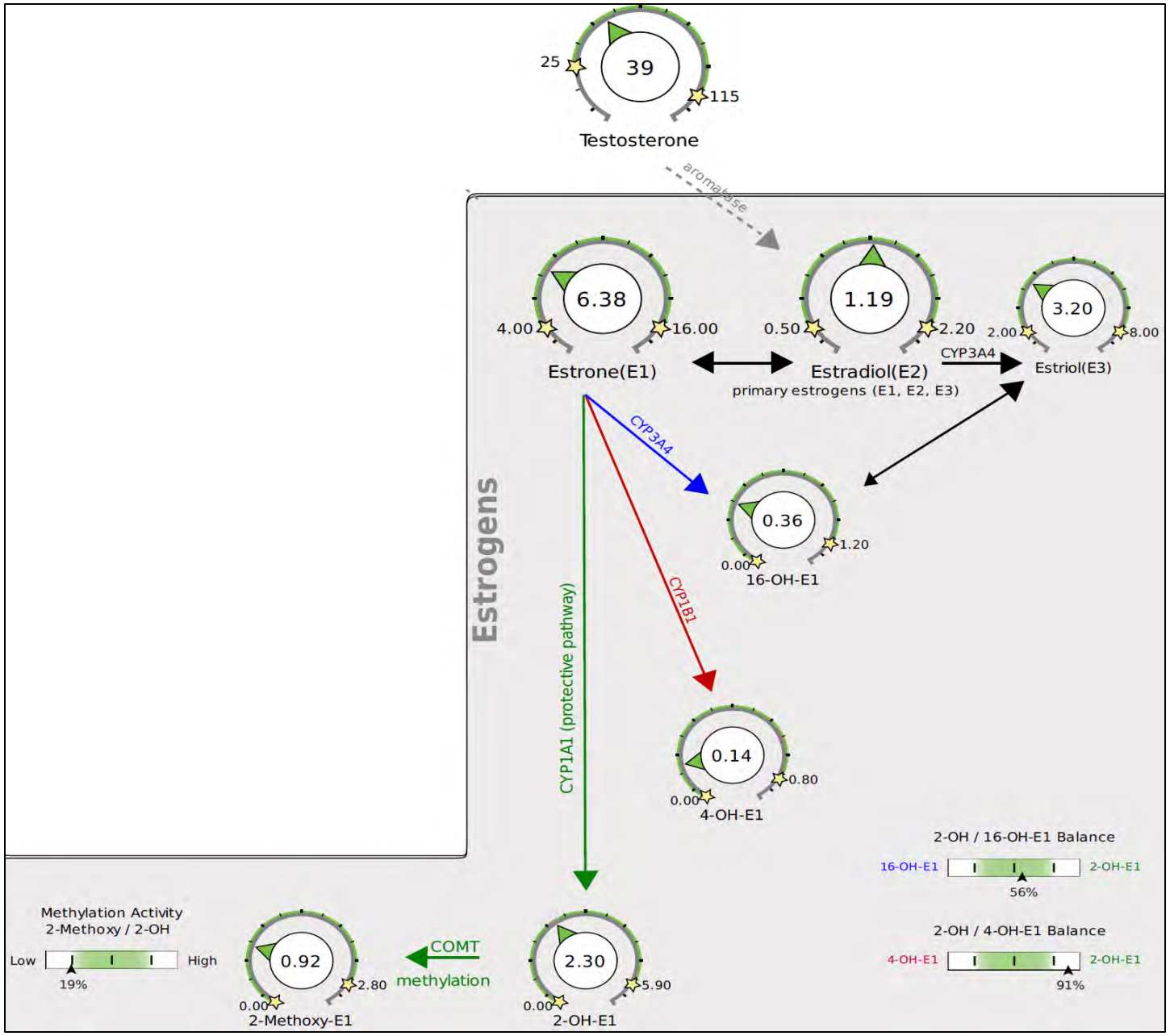

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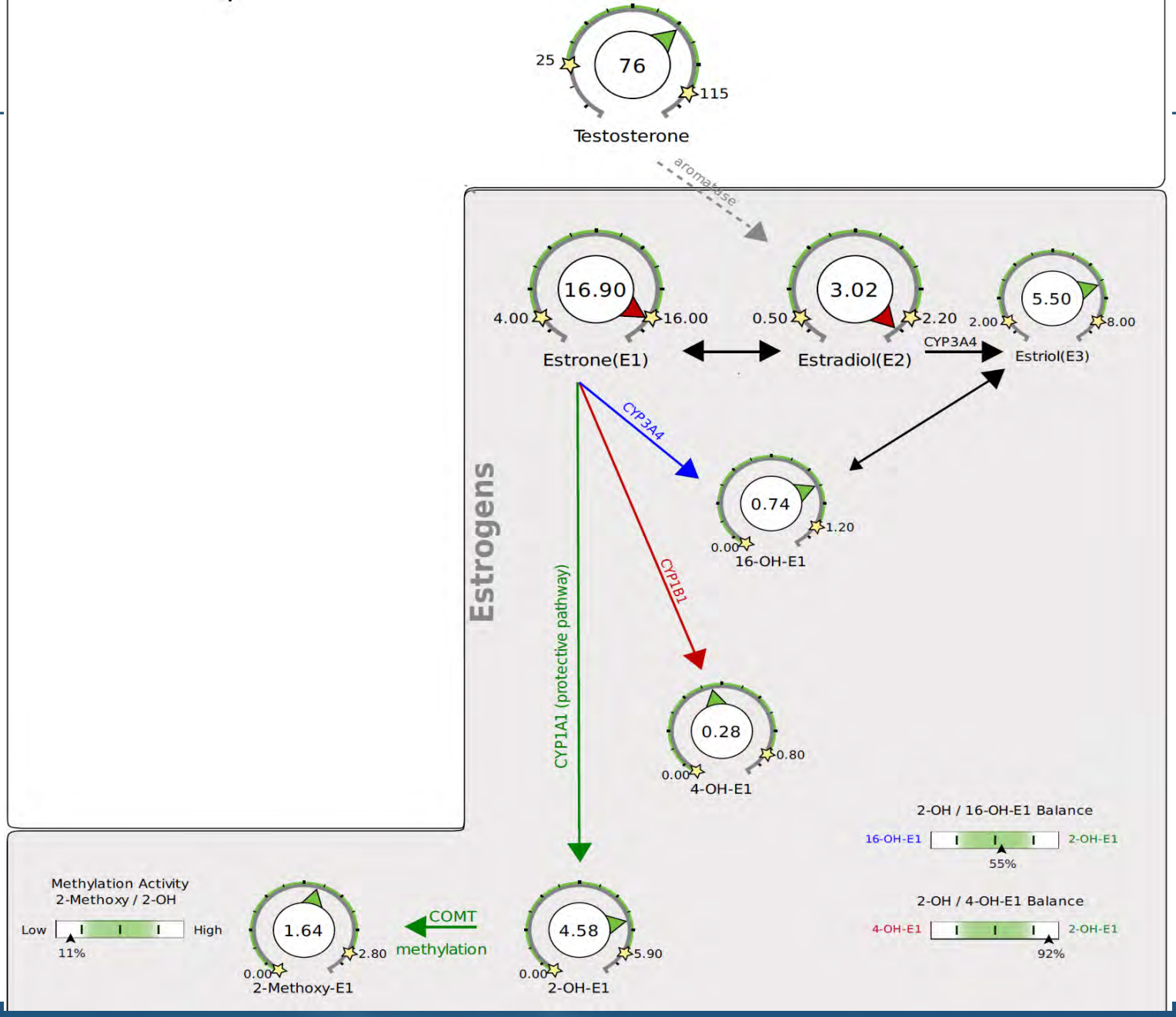

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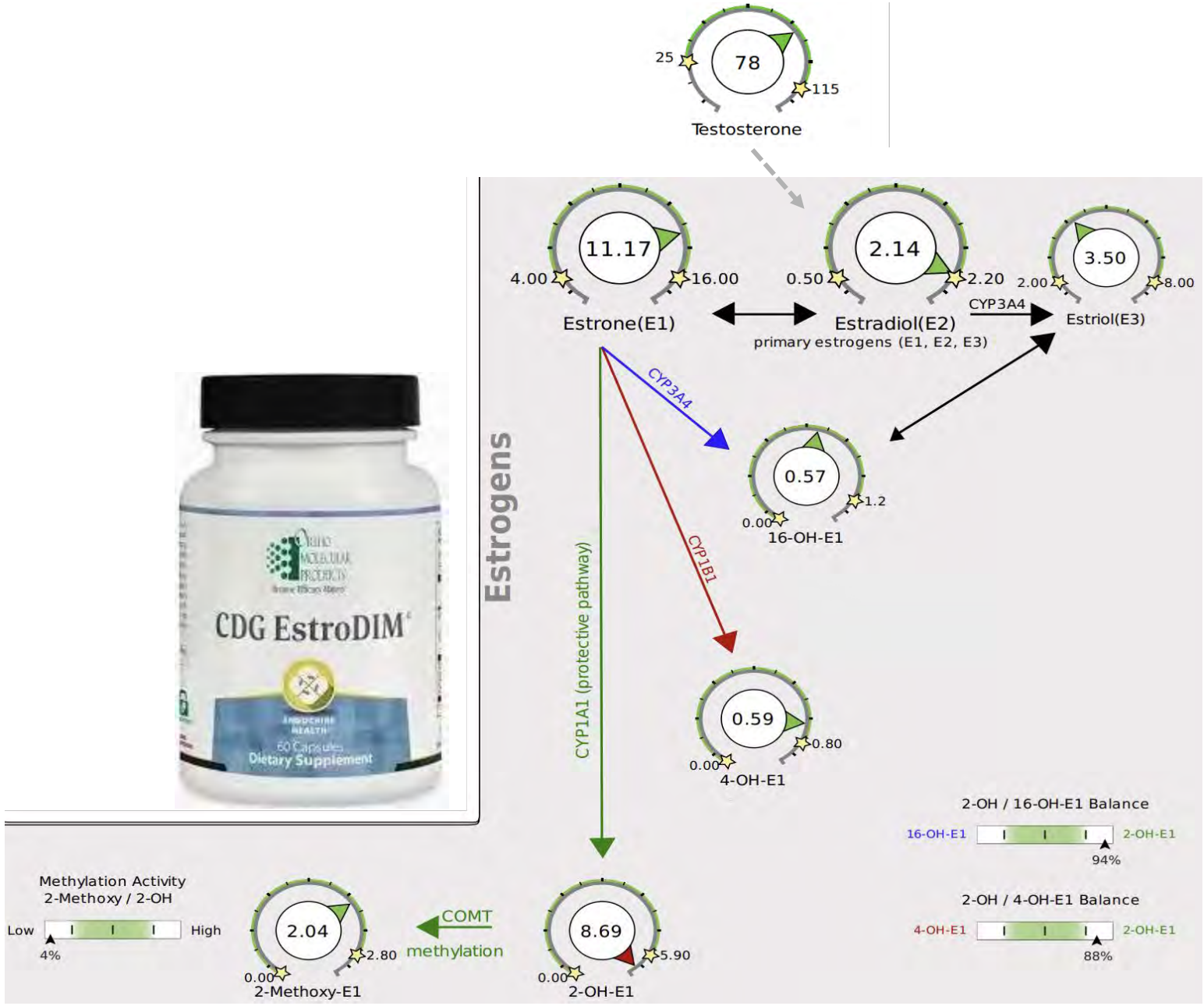

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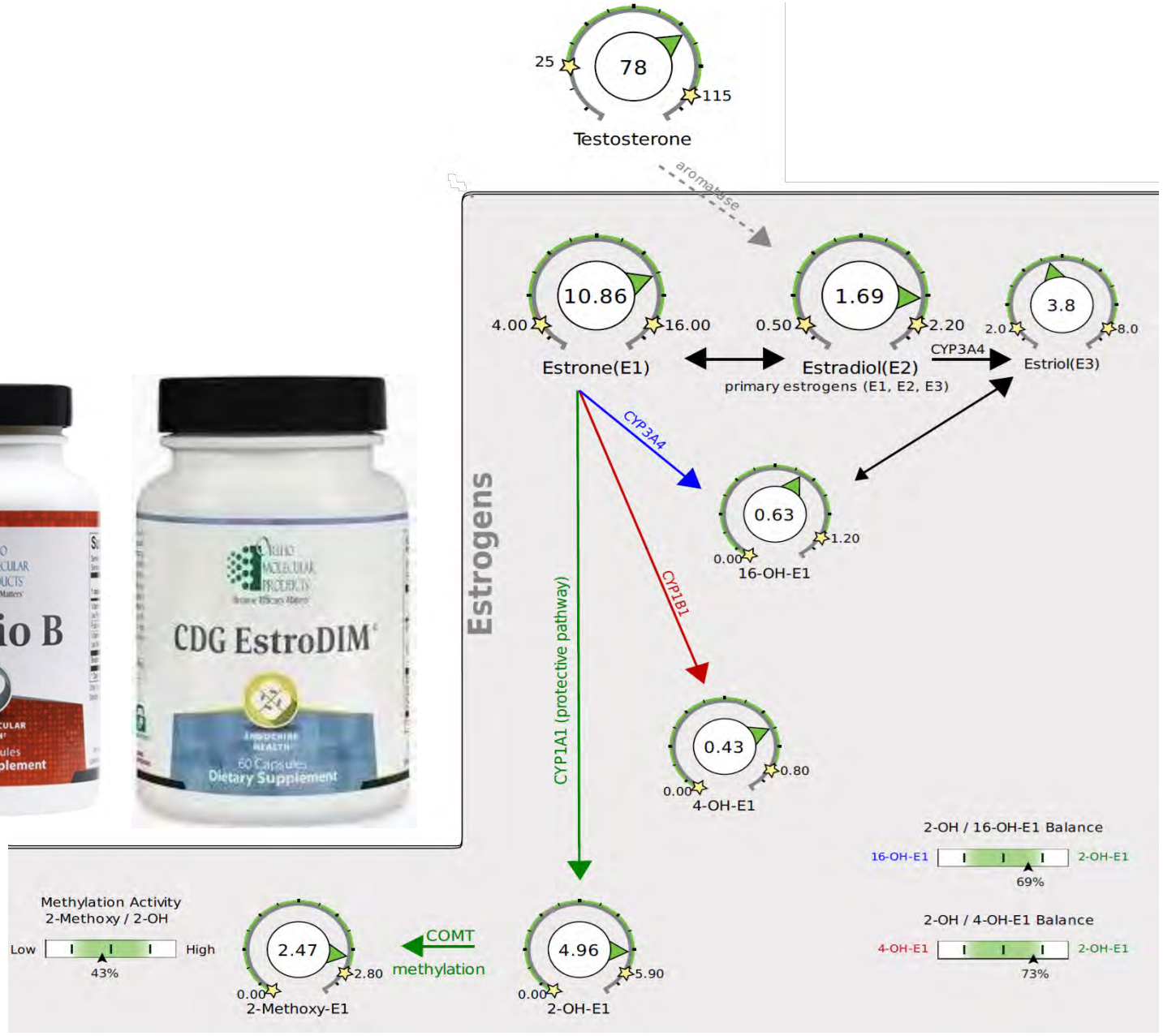

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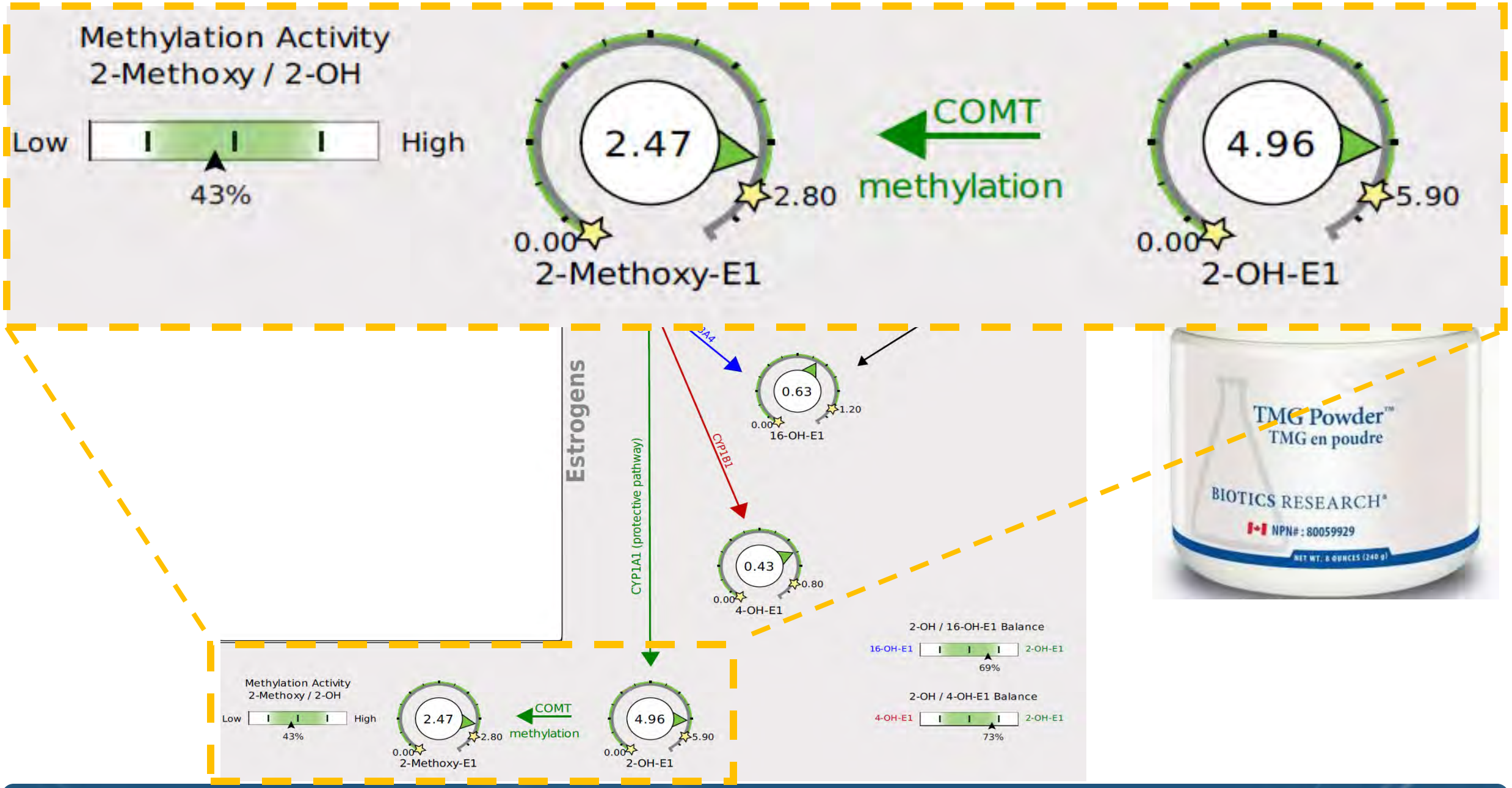

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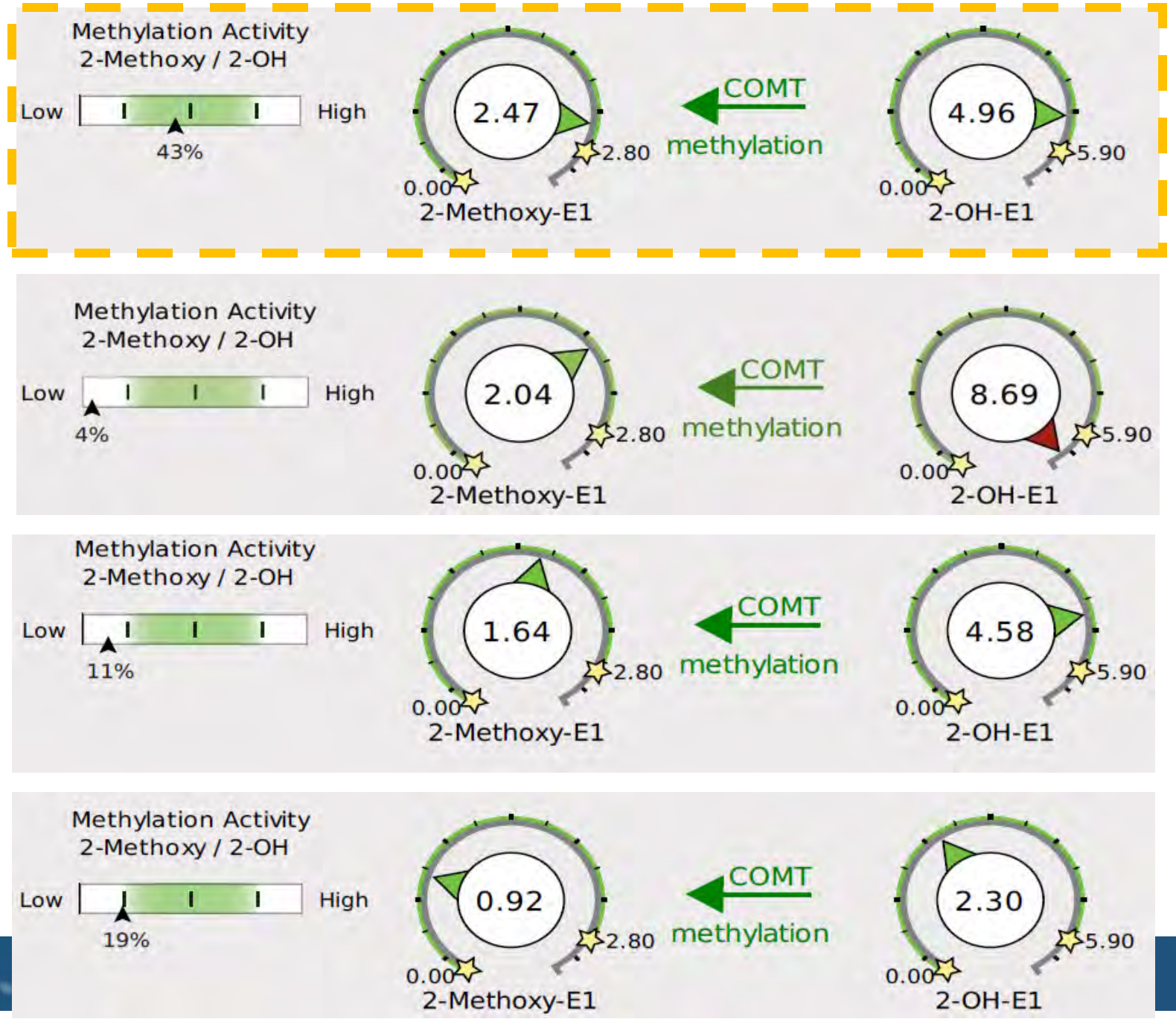

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Why do Estrogen Metabolites Matter?

- “Sluggish” metabolism increases E1/E2
- Higher 16OH-E1 increases estrogenic action

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Why do OATs Matter in PCOS?

- Indirect impact on estrogen and metabolism
- Indirect and direct impact on/from PCOS

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Organic Acid Tests (OATs)

TEST		RESULT	UNITS	NORMAL RANGE
Nutritional Organic Acids (Urine)				
Vitamin B12 Marker - May be deficient if high				
Methylmalonate (MMA)	Above range	4.9	ug/mg	0 - 2.5
Vitamin B6 Markers - May be deficient if high				
Xanthurenate	Above range	1.23	ug/mg	0.12 - 1.2
Kynurenate	Above range	5.3	ug/mg	0.8 - 4.5
Biotin Marker - May be deficient if high				
b-Hydroxyisovalerate	Within range	7.9	ug/mg	0 - 12.5
Glutathione Marker - May be deficient if low or high				
Pyroglutamate	Above range	90.0	ug/mg	28 - 58
Gut Marker - Potential gut putrefaction or dysbiosis if high				
Indican	High end of range	90.4	ug/mg	0 - 100
Neuro-Related Markers (Urine)				
Dopamine Metabolite				
Homovanillate (HVA)	Within range	4.4	ug/mg	3 - 11
Norepinephrine/Epinephrine Metabolite				
Vanilmandelate (VMA)	Above range	7.3	ug/mg	2.2 - 5.5
Neuroinflammation Marker				
Quinolinate	Above range	13.2	ug/mg	0 - 9.6
Additional Markers (Urine)				
Melatonin - Waking				
6-OH-Melatonin-Sulfate	Below range	1.3	ng/mg	10 - 85
Oxidative Stress / DNA Damage - Waking				
8-Hydroxy-2-deoxyguanosine (8-OHdG)	Within range	3.8	ng/mg	0 - 5.2

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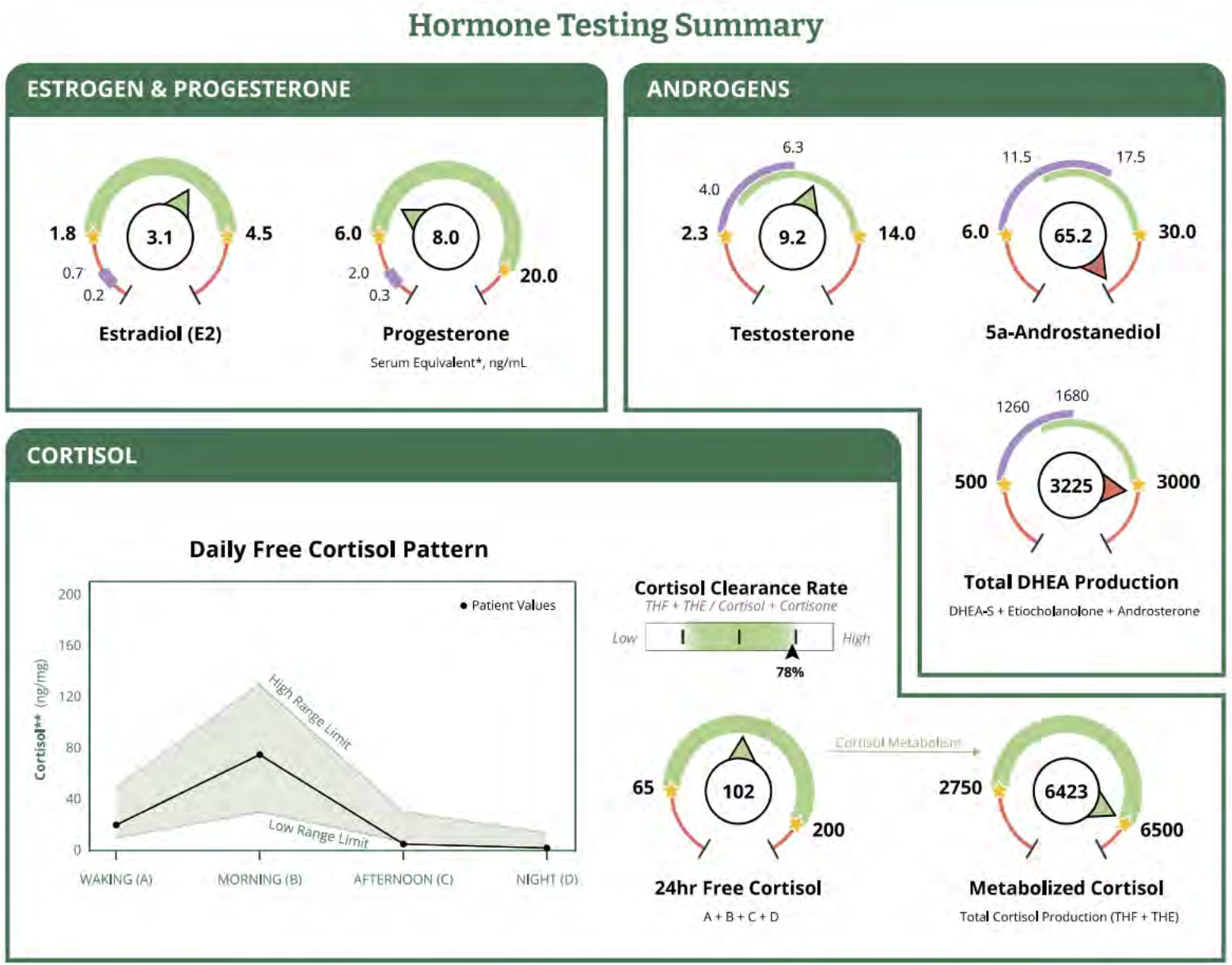

Treatment?

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Treating PCOS Women

Different with low normal Pg vs anovulatory Pg?
High DHEA/T vs High 5a?
How does it change a PCOS case with active AI?
What changes when menopause comes?

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Why Would PCOS Women Get More Sarcopenia?

PUTTING the DOCTOR on the SPOT!!!

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- PCOS women: higher androgens
- PCOS women: more sarcopenia

>50% of PCOS women defined as Sarcopenic Obese!!!

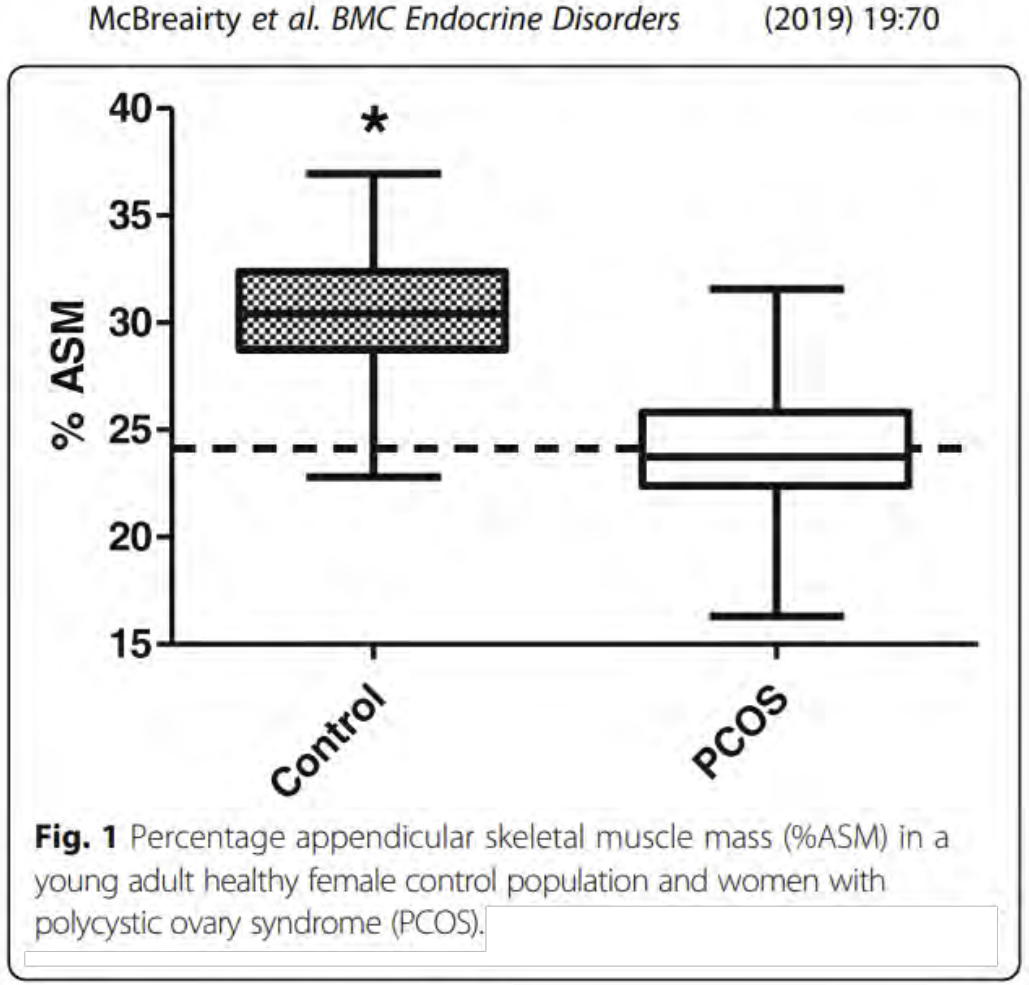

Fig. 1 Percentage appendicular skeletal muscle mass (%ASM) in a young adult healthy female control population and women with polycystic ovary syndrome (PCOS).

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Dr. Kelly's List of Common Treatment Targets

Obesity

Insulin Resistance

Inflammation

Elevated estrogen (or high 16OHE1)

Elevated Androgens (or 5a-metabolism)

Low B12

Low Melatonin

Low Biotin

Gut issues (high indican?)

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Dried Urine Test for Comprehensive Hormones

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Thank You!

Mark Newman, MS

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