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Estrogen & Progesterone Interpretation

Advancing Your Knowledge Using the DUTCH Dozen

Jaclyn Smeaton, ND

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Dr. Jaclyn Smeaton, ND, is the Chief Medical Officer (CMO) at Precision Analytical and a naturopathic physician focused on infertility, reproductive, and genitourinary health. Alongside her work at Hello Fertility, she is a prolific teacher in the field of reproductive endocrinology and hormones and has trained thousands of clinicians on her treatment methodology. Dr. Smeaton has extensive leadership experience in integrative medicine including as president of the American Association of Naturopathic Physicians, as an ambassador for the Academy of Integrative Health and Medicine, and a board member of the Integrative Health Policy Consortium.

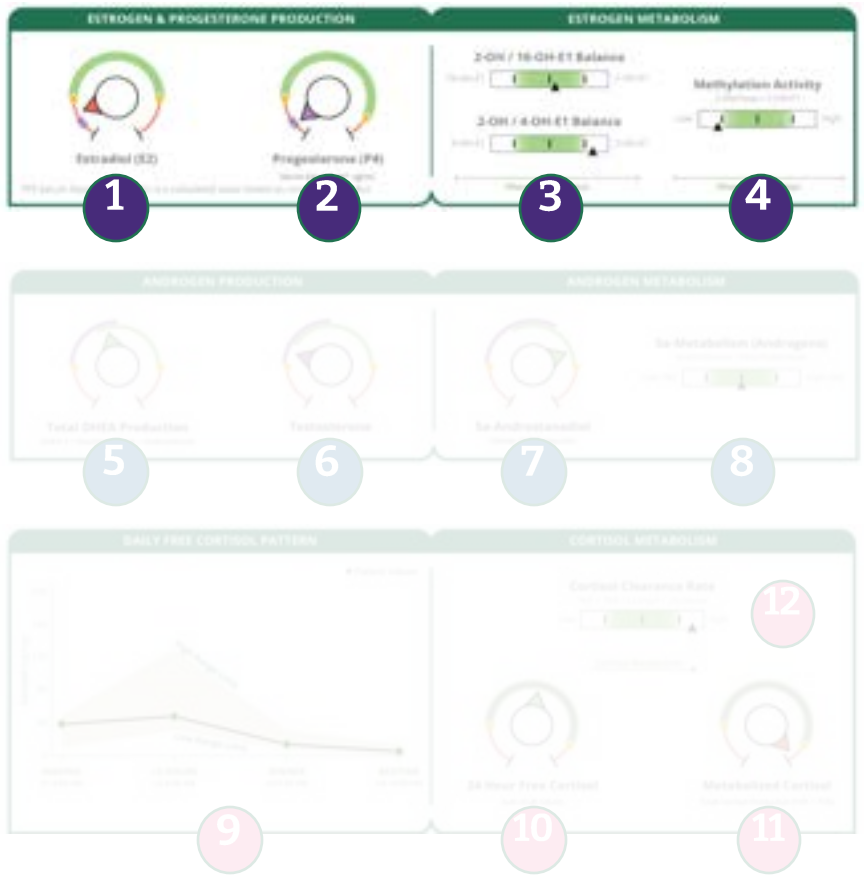
Learning Objectives

1. Understand the purpose and clinical application of the first four DUTCH Dozen assessments relating to **estrogen and progesterone** on the DUTCH Test.

2. Evaluate **estrogen and progesterone production** relative to reproductive status, including the ability to confirm ovulation.

3. Analyze the preference for the **protective 2-OH pathway in phase 1** estrogen metabolism and evaluate **methylation activity in phase 2**.

The DUTCH Dozen



Estrogen Progesterone

1. Assess estrogen levels given the patient's reproductive status
2. Assess progesterone levels given the patient's reproductive status
3. Assess 2-OH preference in phase 1 estrogen metabolism
4. Assess methylation of 2-OH estrogens

Androgens

5. Assess adrenal androgen levels (Total DHEA)
6. Assess testosterone levels
7. Assess cellular production of 5a-DHT via 5a-androstanediol
8. Assess if there is a preference for the more potent alpha metabolism of the androgens

Cortisol

9. Assess the daily free cortisol pattern
10. Assess the daily total of free cortisol in circulation (24hr Free Cortisol)
11. Assess the total cortisol produced by the adrenal glands (Metabolized Cortisol)
12. Assess the rate of cortisol clearance from the body

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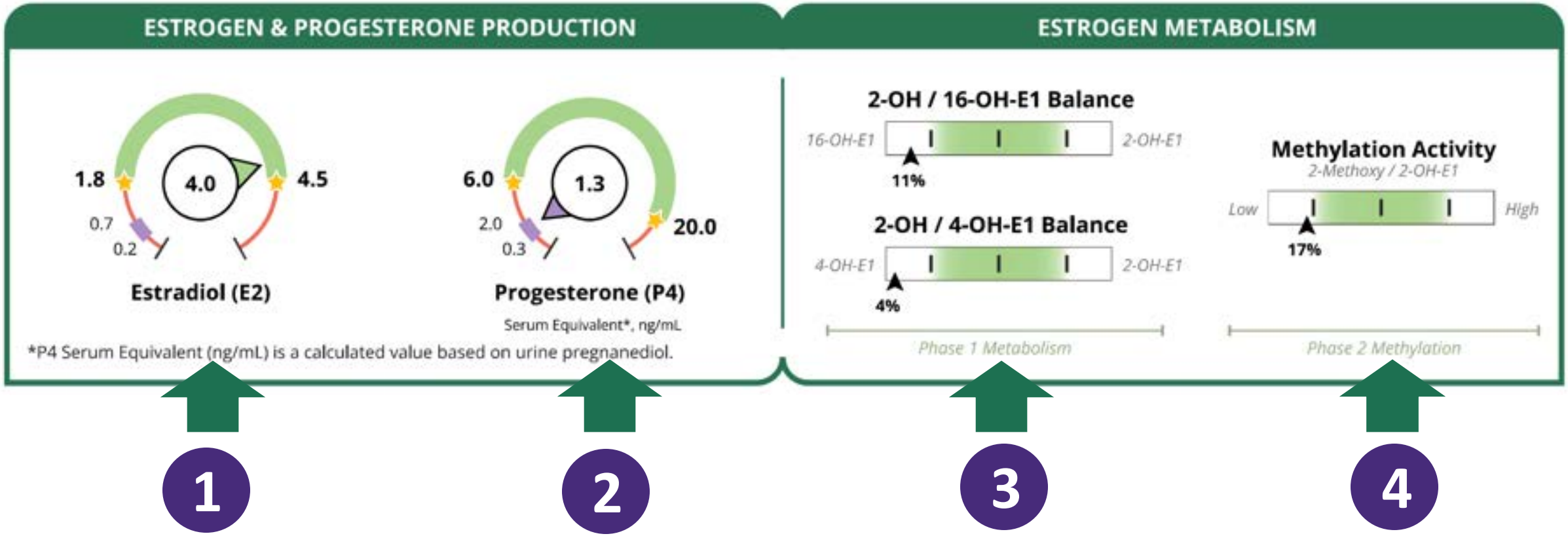
The DUTCH Dozen: Estrogen and Progesterone



The DUTCH Dozen
Estrogen

1

The DUTCH Dozen: 1 Estrogen

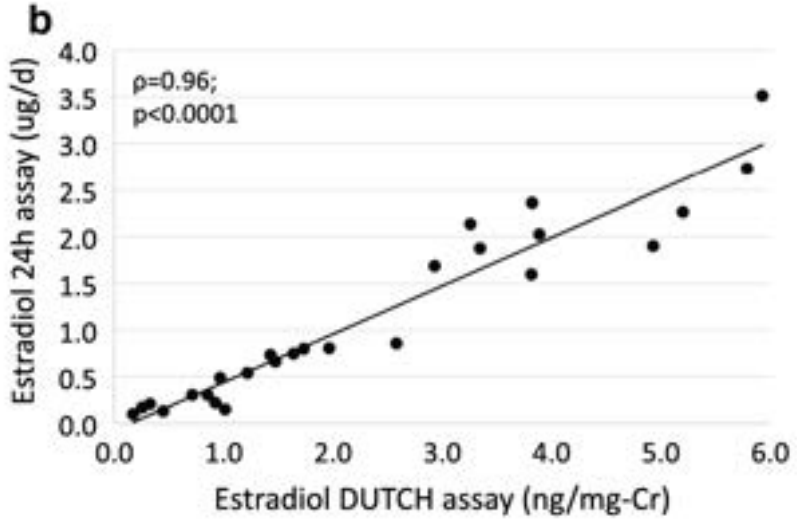
Estrogen

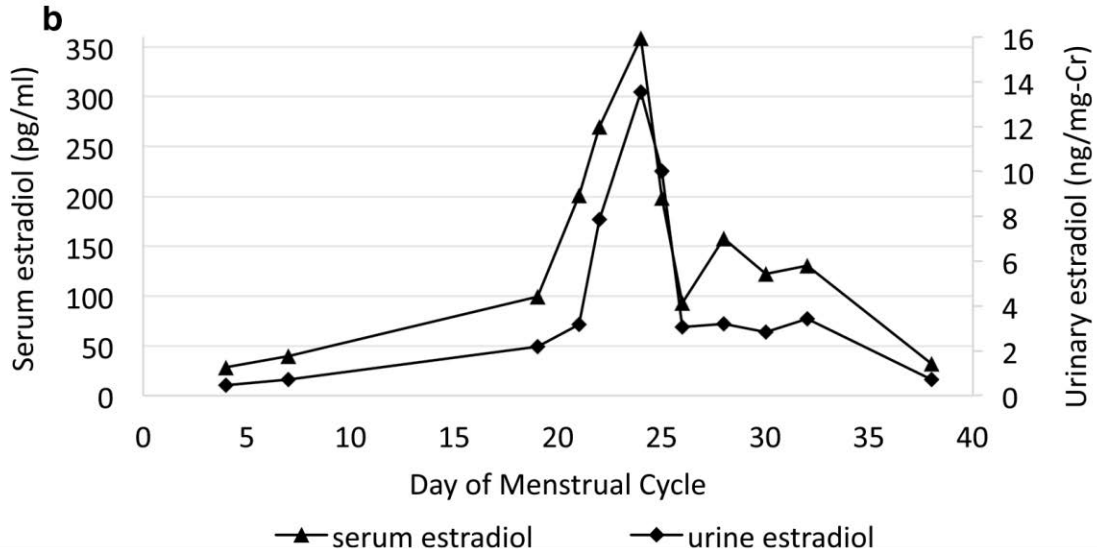
1. Assess estrogen levels given the patient's reproductive status

- The **first assessment** evaluates **estrogen levels** based on the patient's reproductive status.

The DUTCH Dozen: 1 Estrogen

- The DUTCH Test measures estradiol metabolites, **estradiol-glucuronide** (majority) and **estradiol-sulfate**.
- DUTCH dried urine estradiol correlates with both 24-hour liquid urine and serum estradiol.



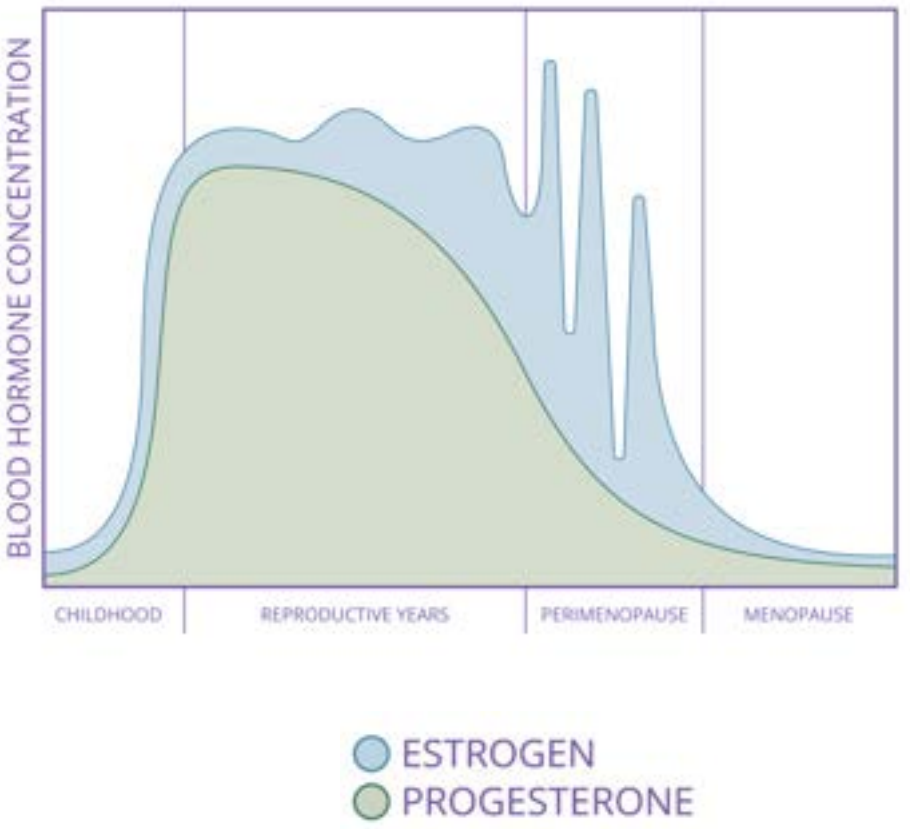


Newman M, et al. BMC Chem. 2019;13(1):20.

The DUTCH Dozen: 1 Estrogen

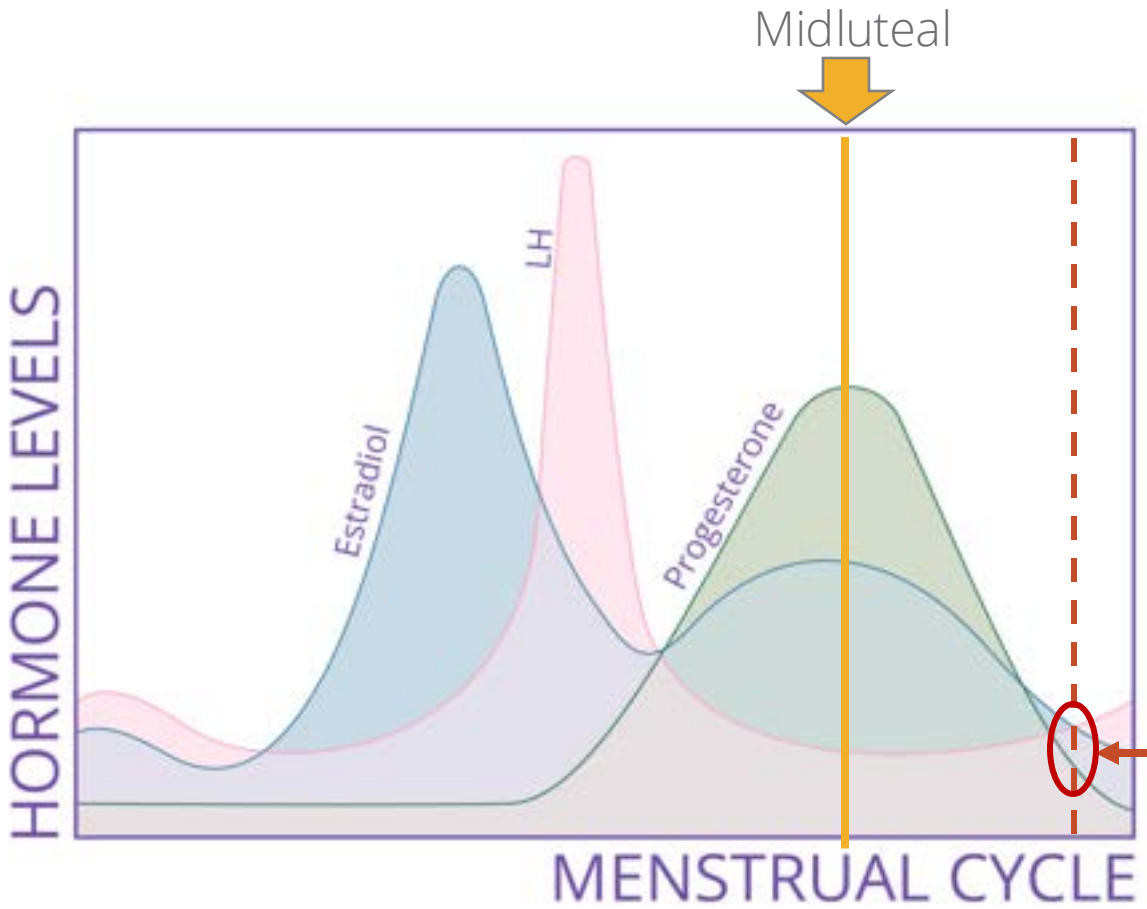
Estrogen and progesterone fluctuate throughout a woman's lifetime

- **Pre-menopause** starts with menarche and ends at the onset of the menopausal transition. Cycles are typically regular.
- **The menopausal transition**, also known as **peri-menopause**, is the stage in between pre-menopause and pos menopause. Cycles can be irregular.
- **Menopause** is the cessation of the monthly hormone cycle ar fertility in women. Average age is 51 (range 40-58).
- **In menopause the ovaries stop making estrogen and progesterone.**



The DUTCH Dozen: 1 Estrogen

Estrogen & progesterone also fluctuate throughout the ***month***



Timing collection to the mid-luteal phase is important!

Collect 5-7 days after ovulation. Next period should come 4-10 days after collection.

Correctly timing to the mid-luteal phase can help evaluate:

- If ovulation occurred
- If progesterone is adequate
- The P/E ratio
- Estrogen levels (Low? Normal? High?)

If the patient collects too late:

- E & P may look low
- It may be difficult to know if they ovulated
- The P/E ratio may not be as clinically useful

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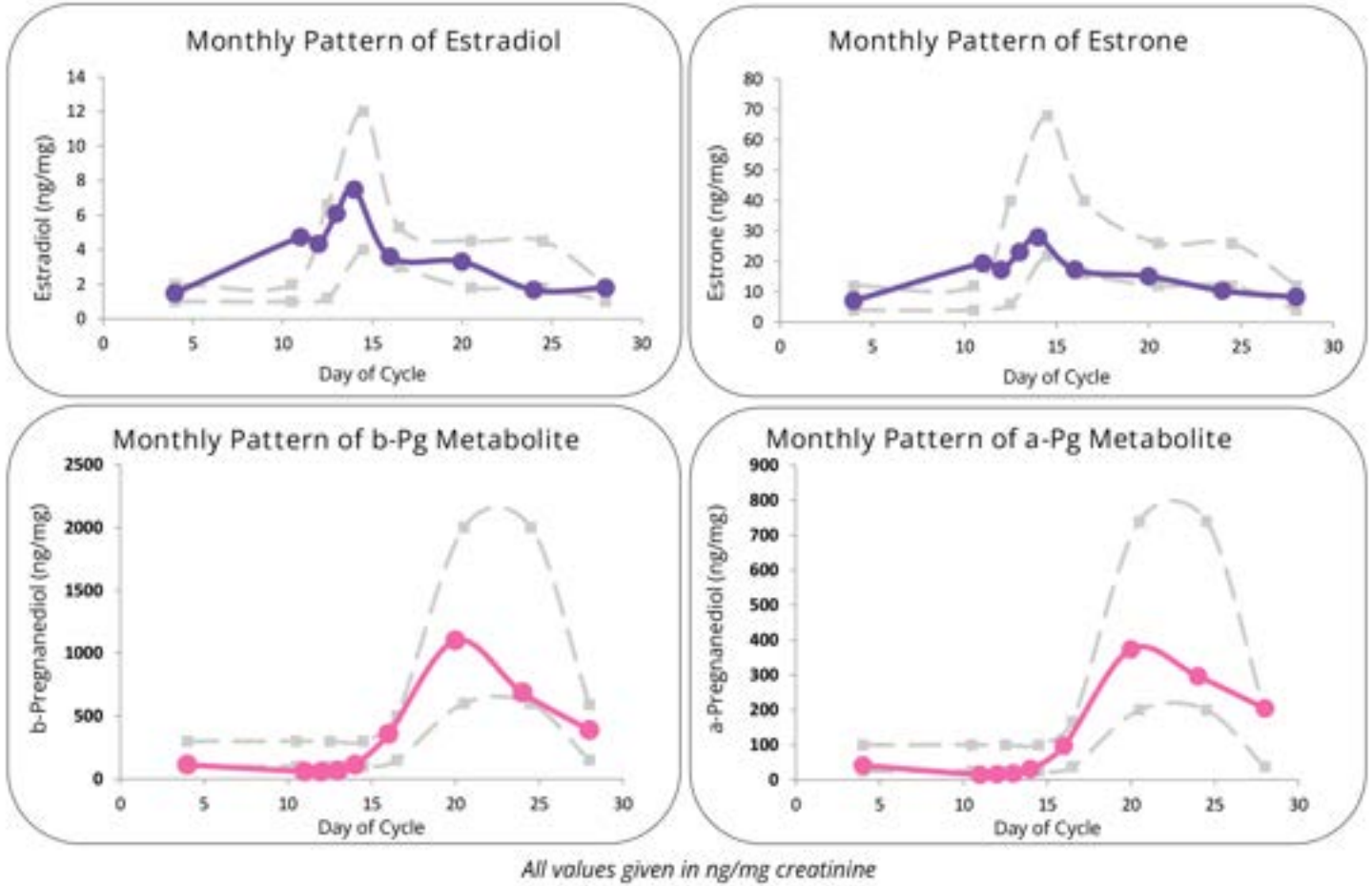
The DUTCH Dozen: 1 Estrogen

Patients do not need to time their cycle with the DUTCH Cycle Mapping!

At **9 points** throughout the cycle, it graphs out:

- **Estradiol (E2)**
- **Estrone (E1)**
- **a-pregnanediol**
- **b-pregnanediol**



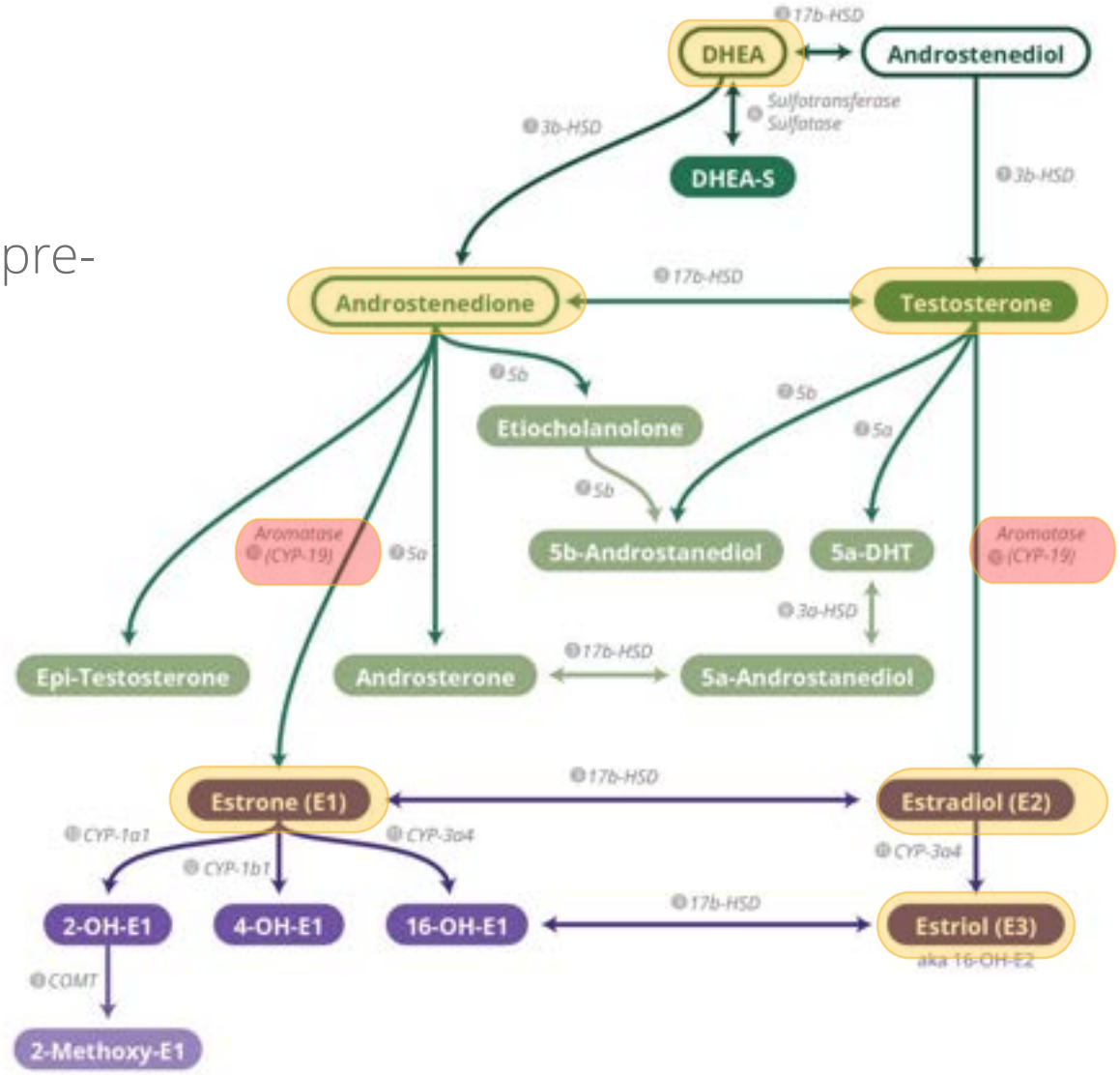
All values given in ng/mg creatinine

The DUTCH Dozen: 1 Estrogen

Estrogen is primarily made in the ovaries (pre-menopause), but can also be made from androgens via aromatization.

In order of strongest to weakest receptor binding affinity:

- **Estradiol (strongest)**
- **Estrone**
- **Estriol**



The DUTCH Dozen: 1 Estrogen

Where **E2** is Made in **Pre-menopausal** Women

Periphery (including fat tissue)

ADRENALS

DHEA-S (100%)

DHEA (80%)

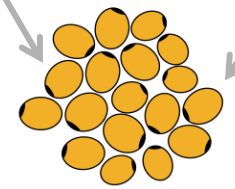
Androstenedione (50%)

Testosterone (25%)

Estradiol (via DHEA)

Progesterone (minimal)

Periphery (including fat tissue)



OVARIES

Estradiol (majority)

Progesterone (majority)

Androstenedione (50%)

Testosterone (25%)

DHEA (20%)

DHEA-S (0%)

Testosterone (50%)

Yesiladali M, et al. Diagnostics (Basel). 2022;12(9).

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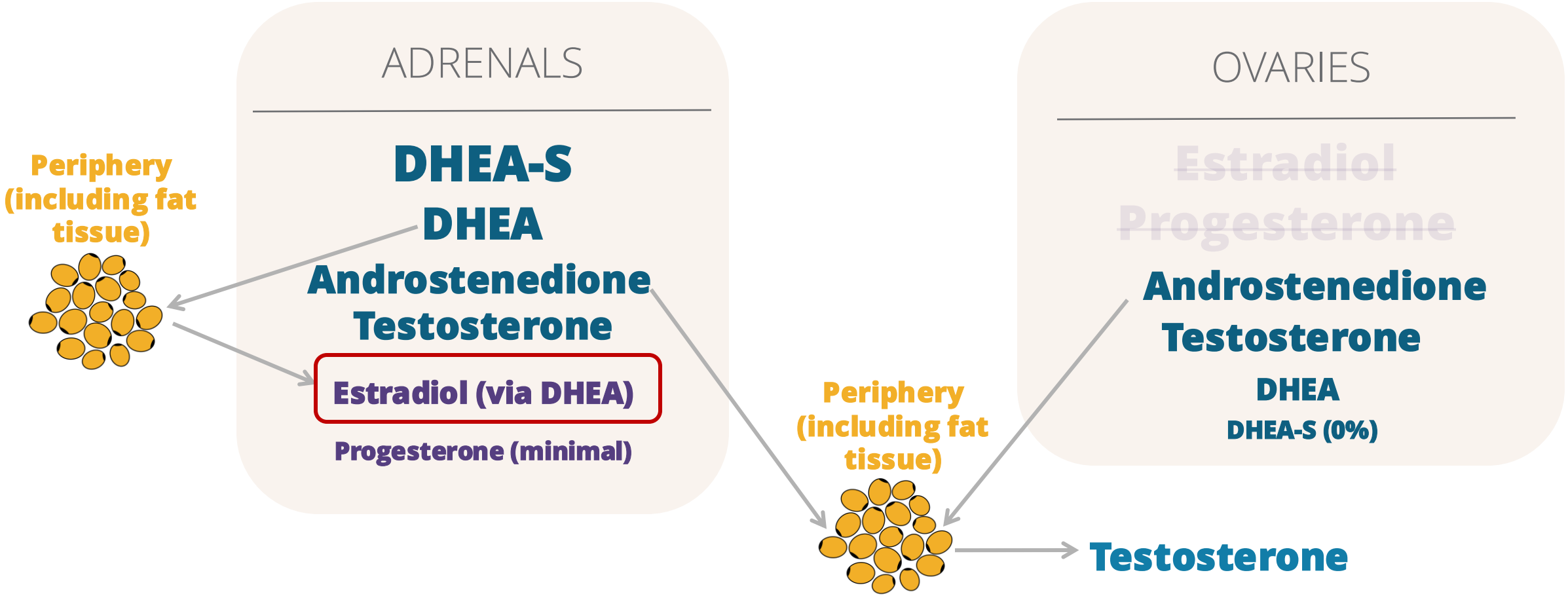
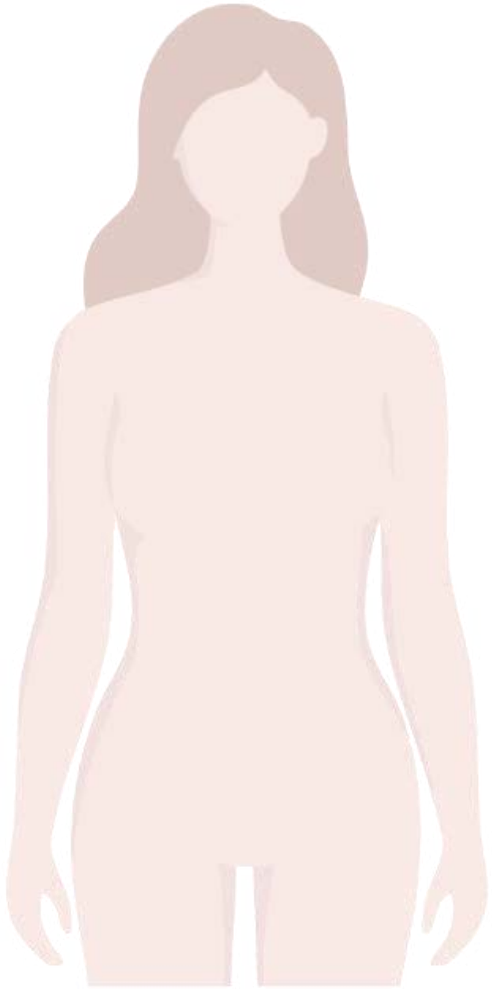
The DUTCH Dozen: 1 Estrogen

Where **E2** is Made in **Post-menopausal (PMP)** Women



The DUTCH Dozen: 1 Estrogen



Estrogen's Actions

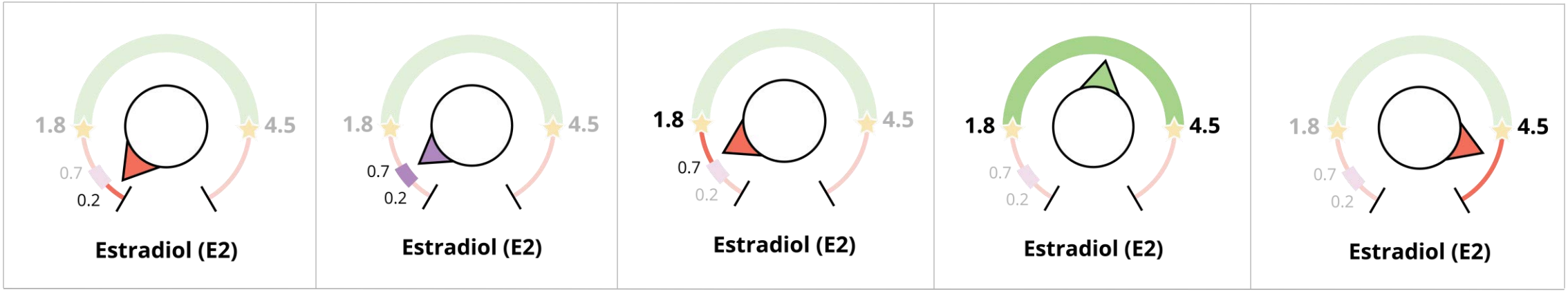
- **Brain:** Mood, cognition, memory, and focus, thermoregulation, sleep, energy
- **Hair (scalp) growth**
- **Skin:** Elasticity, collagen, repair, moisture
- **Muscle mass**
- **Nervous system:** Parasympathetic balance
- **Joint health**
- **Bone density:** Inhibits bone resorption, increases vitamin D
- **Breast health:** Stimulates breast cell growth
- **Liver function:** Maintains healthy cholesterol, triglycerides
- **Weight management:** Increases metabolic rate, **Insulin sensitivity**
- **Uterine health**
- **Genitourinary system:** Elasticity, acidity, microflora, moisture, lubrication
- **Fertility:** Builds the endometrium
- **Cardiovascular:** Clotting homeostasis, vasodilation, lowers blood pressure, endothelial function, lowers LDL and increases HDL, lowers homocysteine

The DUTCH Dozen: 1 Estrogen

On the DUTCH Test, the patient's E2 result will be within one of these 5 areas on the DUTCH dial:

Key to Reading the Dial

- Optimal Luteal Range
- Postmenopausal Range



- Below the post-menopausal range
- Within the post-menopausal range
- Above the post-menopausal range but below the luteal range
- Within the luteal range
- Above the luteal range

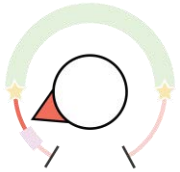
Pre-Menopausal E2: Causes

Postmenopausal (PMP)
0.2-0.7 ng/mg

Ovaries NOT Cycling Due To:
- Conditions & medications that **suppress** the HPO axis, including combo OCPs (1)
- Diminished ovarian reserve, POI, perimenopause
- Low androgens affecting follicle development
- Medically induced, such as in oophorectomy (3)
- Hypogonadism, Hypopituitarism

Very Low Below PMP
0.0-0.2 ng/mg

Ovaries NOT Cycling and Subphysiologic E2 Levels Due To:
- Low aromatase activity, such as with low body fat percentage (4)
- Very low DHEA (5)
- HPA axis suppressive medications, including glucocorticoids (9)
- Adrenal insufficiency, including Addison's Disease



Low
0.7-1.8 ng/mg

Ovaries Cycling but E2 is Low Due To:
- Incorrect timing of sample collection in the follicular phase (E2 reference range 1-2 ng/mg) (6)
- Conditions that impair (but do not fully suppress) the HPO axis (2)
- Low androgens affecting follicle development

Ovaries NOT Cycling but E2 Levels are Above the PMP Range Due To:
- High aromatase activity, typically obesity-related (12)

Normal
1.8-4.5 ng/mg

Ovaries Cycling and Producing Normal Luteal E2

Ovaries NOT cycling but E2 levels are in the luteal range due to:
- Profound aromatase activity, typically obesity-related (12)
- Hormone therapy (14)

High
>4.5 ng/mg

Ovaries Cycling but E2 is High Due To:
- Incorrect timing of sample collection in the ovulatory phase (E2 reference range 4-12 ng/mg) (16)
- Perimenopause
- Metabolic issues, including obesity (13)
- High aromatase activity, typically obesity-related (12)
- Suboptimal estrogen detoxification
- Hormone therapy (14)

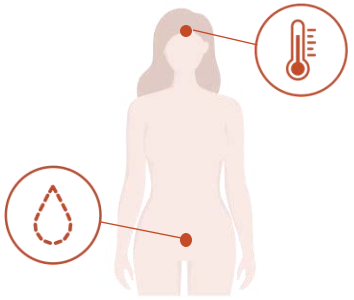
Ovaries NOT cycling but E2 levels are above the luteal range due to:
- Hormone therapy (14)

Very High

Supraphysiologic E2 Levels Due To:
- Oral or sublingual estrogen therapy (1st pass affects urine metabolites only, not serum) (15)
- Pregnancy
- Hormone-producing neoplasms (rare)

Pre-Menopausal E2: Effects

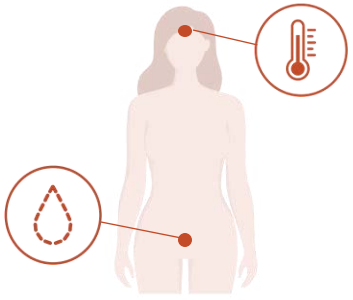
PMP
0.2-0.7 ng/mg



Low Estrogen Signs & Symptoms:

- Hot flashes and night sweats
- Vaginal dryness
- Mood disturbances (e.g., low mood or depression)
- Brain fog
- Low libido
- Insomnia
- Weight gain
- Joint pain
- Skin changes
- Decreased bone mineral density
- Increased cardiovascular risk

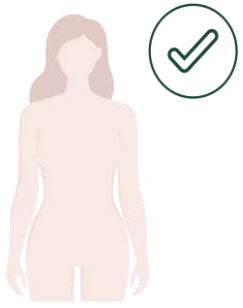
Low
0.7-1.8 ng/mg



Mildly Low Estrogen Signs & Symptoms:

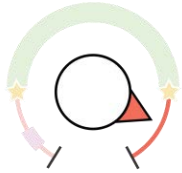
- May or may not experience symptoms of low estrogen. Symptoms may be subtle or absent.
- Vaginal dryness
- Mood changes, including low mood
- Reduced libido

Normal
1.8-4.5 ng/mg

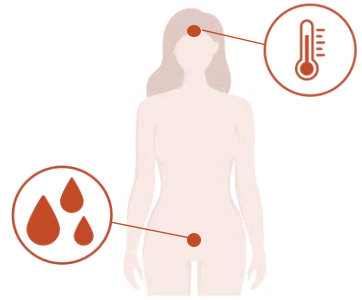


Normal Estrogen Levels are Associated With:

- Stable, positive mood
- Healthy energy levels
- Restorative sleep
- Normal sexual drive and function
- Weight management with a healthy lifestyle
- Healthy reproductive function
- Healthy cognition and memory
- Maintenance of bone mineral density, joint health, hair growth, skin elasticity, and more!



High
>4.5 ng/mg



High Estrogen Signs & Symptoms*:

- Heavy bleeding or prolonged menstrual bleeding
- Breast tenderness or fibrocystic changes
- Uterine fibroid growth
- Gallstones
- Increased risk of endometrial hyperplasia or cancer, and breast tumors or cancer

*An appropriate dose of oral or sublingual estradiol taken near the time of testing may increase urinary estrogen metabolites due to first-pass metabolism, without reflecting serum estradiol levels or causing symptoms of estrogen excess.

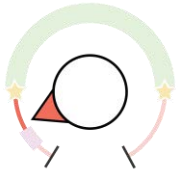
Post-Menopausal (PMP) E2: Causes

PMP
0.2-0.7 ng/mg

Normal PMP E2 Levels:
- Most PMP E2 originates from adrenal DHEA
- Patient may be on low-dose (localized) vaginal E2 therapy that does not increase systemic E2 levels

Very Low Below PMP
0.0-0.2 ng/mg

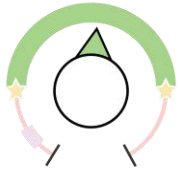
Subphysiologic E2 Levels Due To:
- Low aromatase activity, such as with aromatase inhibiting pharmaceuticals (4)
- Very low adrenal DHEA (5)
- HPA axis suppressive medications, including glucocorticoids (9)
- Adrenal insufficiency, including Addison's Disease



Mildly Above PMP
0.7-1.8 ng/mg

E2 Levels that are just above the PMP Range May be Normal for Some PMP Women (17)

E2 levels are mildly above the PMP range due to:
- High aromatase activity, typically obesity-related (12)
- Low-moderate dose E2 therapy (14)



Above PMP
1.8-4.5 ng/mg

E2 Levels are Significantly Above the PMP Range Due To:
- Moderate-high dose E2 therapy (14)
- Profound aromatase activity, typically obesity-related (12)
- Perimenopause: If <1.5 years from final menstrual period (FMP), consider endogenous production

High
>4.5 ng/mg

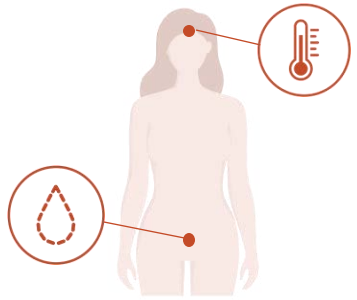
E2 Levels are Above the Luteal Range (very high for PMP) Due To:
- High dose E2 therapy (14)
- Perimenopause: If <1.5 years from FMP, consider endogenous production

Very High

Supraphysiologic E2 Levels Due To:
- Oral or sublingual estrogen therapy (1st pass affects urine metabolites only, not serum) (15)
- Hormone-producing neoplasms (rare)

Post-Menopausal (PMP) E2: Effects

PMP
0.2-0.7 ng/mg

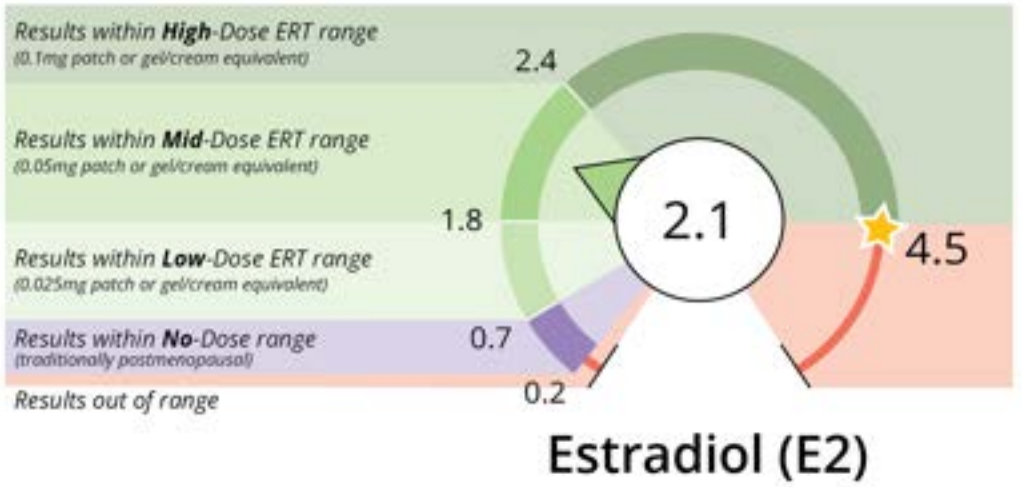


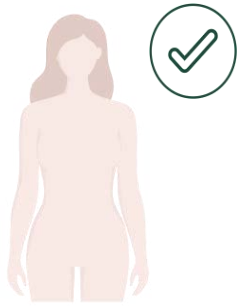
Low Estrogen Symptoms:

- Hot flashes, night sweats
- Vaginal dryness, vaginal atrophy
- Mood disturbances (depression)
- Brain fog
- Low sex drive
- Insomnia
- Weight gain
- Joint pain
- Skin issues
- Decreased bone mineral density
- Increased cardiovascular risk

PMP Levels with Estrogen Replacement Therapy (ERT)

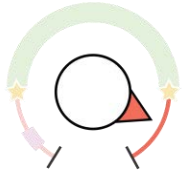
Observed Ranges



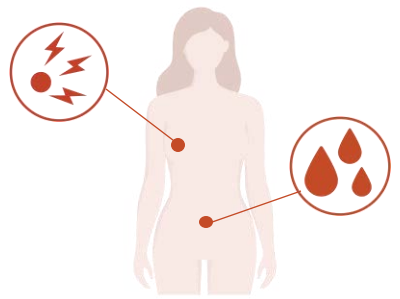


Healthy Estrogen Levels are Associated with:

- Positive mood
- Healthy energy levels
- Good sleep
- Modest sex drive and function
- Weight management with healthy lifestyle
- Good cognition, memory, bone density, joint health, hair growth, skin elasticity, and more!



High
>4.5 ng/mg



High Estrogen Symptoms*:

- Breakthrough bleeding, especially if not adequately opposed with progesterone
- Tender or fibrocystic breasts
- Uterine fibroid growth
- Gallstones
- Increased risk of endometrial hyperplasia or cancer, and breast tumors or cancer

*An appropriate dose of oral or sublingual estradiol taken near the time of testing may increase urinary estrogen metabolites due to first-pass metabolism, without reflecting serum estradiol levels or causing symptoms of estrogen excess.

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Polling Question

Game time!

(Expected, non-actionable results)

Match the description to the dial:

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1

42-year-old female
Breast cancer diagnosis
Lupron and Letrozole

2

25-year-old female
Collected during ovulation
(E2 RR 4-12 ng/mg)

3

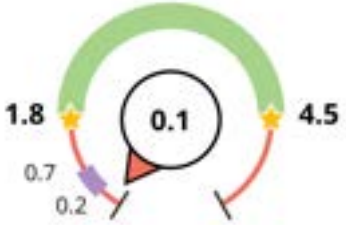
39-year-old female
36 weeks pregnant

Estradiol (E2)

A

Estradiol (E2)

B



Estradiol (E2)

C

Question 1: Match the description to the correct E2 dial

Polling Question

Game time!

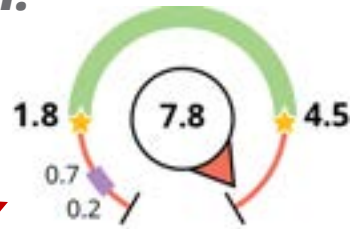
(Expected, non-actionable results)

Match the description to the dial:

1 **42-year-old female**
Breast cancer diagnosis
Lupron and Letrozole

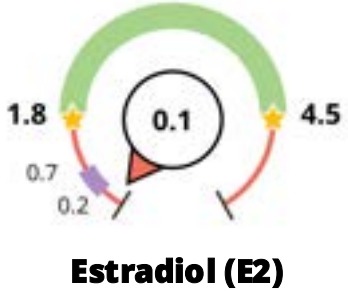
2 **25-year-old female**
Collected during ovulation
(E2 RR 4-12 ng/mg)

3 **39-year-old female**
36 weeks pregnant



A

B



C

Polling Question

Game time!

(Expected, non-actionable results)

Match the description to the dial:

1

17-year-old female
Combo OCP

Estradiol (E2)

A

2

48-year-old female
PMP
Oral estradiol (0.5mg)
on day of test

Estradiol (E2)

B

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Question 2: Match the description to the correct E2 dial

Polling Question

Game time!

(Expected, non-actionable results)

Match the description to the dial:

1

17-year-old female
Combo OCP

Estradiol (E2)

A

2

48-year-old female
PMP
Oral estradiol (0.5mg)
on day of test

Estradiol (E2)

B

Polling Question

Game time!

(Problematic, actionable results)

Match the description to the correct dial:

1

22-year-old female
Amenorrhea
BMI 17.5

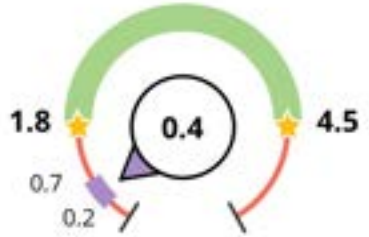
2

41-year-old female
Collected during Ovulation; breast tenderness

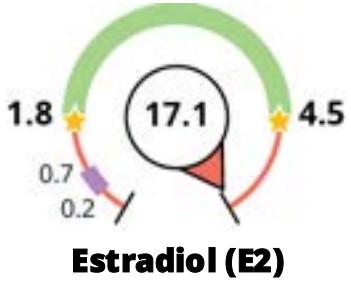
3

56-year-old female
PMP
High BMI (39.5)
High Testosterone

A



B



C

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Question 3: Match the description to the correct E2 dial

Polling Question

Game time!

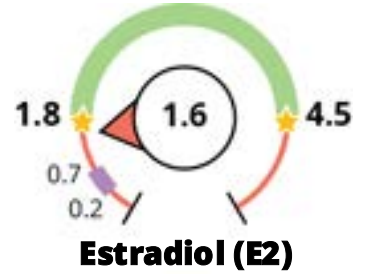
(Problematic, actionable results)

Match the description to the correct dial:

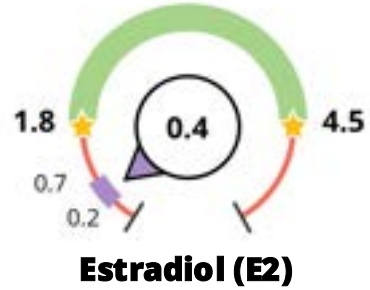
1. 22-year-old female
   Amenorrhea
   BMI 17.5

2. 41-year-old female
   Collected during Ovulation; breast tenderness

3. 56-year-old female
   PMP
   High BMI (39.5)
   High Testosterone



A



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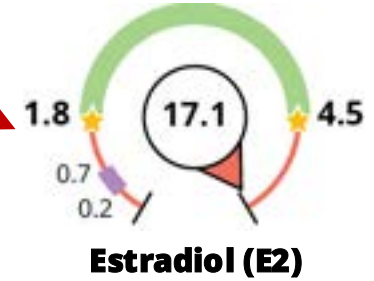

C

Polling Question

Game time!

(Problematic, actionable results)

Match the description to the correct dial:

1

40-year-old female
Cycling regularly
Tamoxifen
Metastatic BR CA
Thickened uterine stripe

Estradiol (E2)

A

2

45-year-old female
Perimenopausal
Chronic menorrhagia

Estradiol (E2)

B

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Question 4: Match the description to the correct E2 dial

Polling Question

Game time!

(Problematic, actionable results)

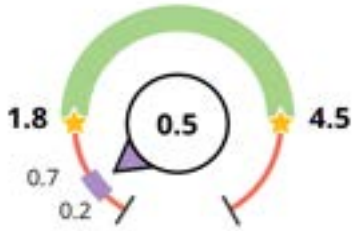
Match the description to the correct dial:

1

40-year-old female
Cycling regularly
Tamoxifen
Metastatic BR CA
Thickened uterine stripe

2

45-year-old female
Perimenopausal
Chronic menorrhagia



Estradiol (E2)

A

Estradiol (E2)

B

Estrogen Treatments

The treatment you choose depends on the cause,
but also the symptoms, treatment goals, and patient preferences.

The DUTCH Treatment Guide: **Low Estrogen**

HPO Axis Support for Low Estrogen *Page 10*	**Ovarian Health Support** ***Page 59***	Hypothyroidism Support *Page 52*	Mood & Cognition Support *Page 57*
HPA Axis Support *Pages 10, 34, 36*	**T and DHEA Support if Low** ***Pages 16, 24***	Stress Support *Page 63*	Hot Flash & Vaginal Dryness Support *Page 13*
Slow CCR Support *Page 39*	Phytoestrogens *Page 59* Estrogen Therapy *Page 72*	**Sleep/Circadian Rhythm Support** ***Page 60***	Cardiovascular Support *Page 50*
Low CAR Support *Page 41*	Hyperprolactinemia Support *Page 52*	**Mitochondrial Support** ***Page 56***	Bone Support *Page 50*

HPO Axis Support · HPA Axis Support · Other Hormone support · OATs Support · Symptom Support · Detox Support · Lifestyle Support · Other Support

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The DUTCH Treatment Guide: **High Estrogen**

HPO Axis Support for High Estrogen *Page 14*	**Estrogen Detox Support *Page 26***	T and DHEA Support if High *Pages 20, 22*	Mood & Cognition Support *Page 57*
HPA Axis Support *Pages 14, 34, 36*	Liver Support *Page 55*	Stress Support *Page 63*	Insulin Resistance Support *Page 54*
Fast CCR Support *Page 39*	GI Support *Indican - page 52* *Phase 3 - page 31*	**Sleep/Circadian Rhythm Support *Page 60***	Obesity (*Weight Loss*) Support *Page 58*
High CAR Support *Page 40*	Phytoestrogens *Page 59*	Slow Aromatase if Low Androgens *Page 19*	Inflammation Support *Page 53*

HPO Axis Support · HPA Axis Support · Other Hormone support · OATs Support · Symptom Support · Detox Support · Lifestyle Support · Other Support

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The DUTCH Dozen
Progesterone

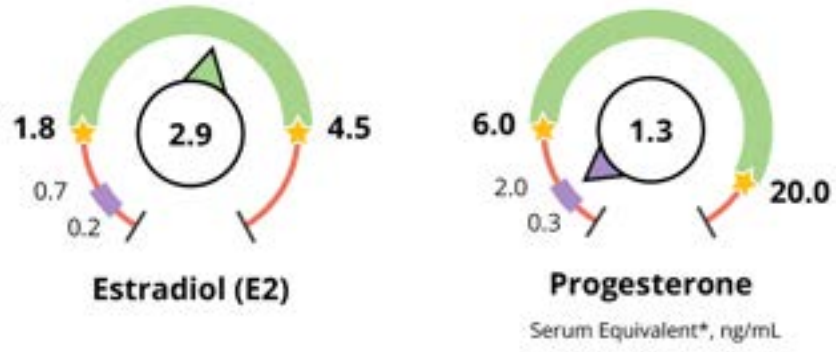
2

The DUTCH Dozen: 2 Progesterone

Estrogen Progesterone

2 Assess progesterone levels given the patient's reproductive status

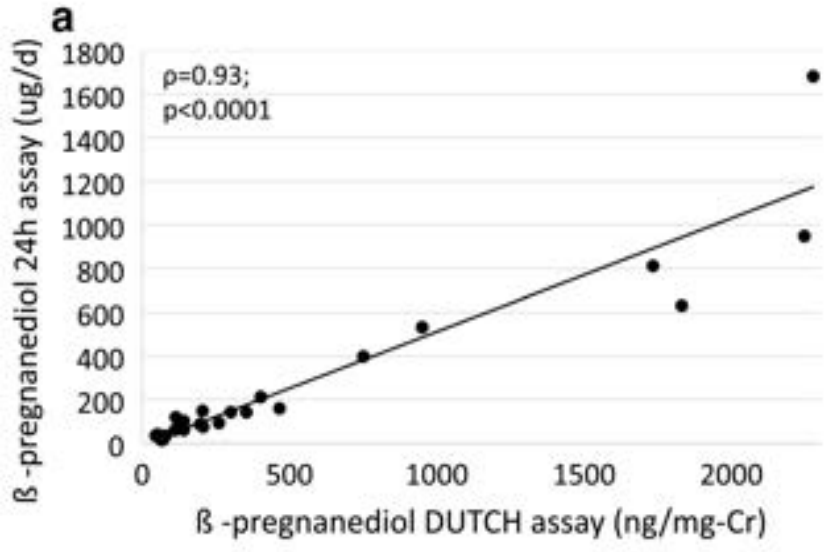
- The **second assessment** checks whether **progesterone levels** are adequate.
- You can also assess for “estrogen dominance” by comparing the Estradiol (E2) and Progesterone (P4) dials.

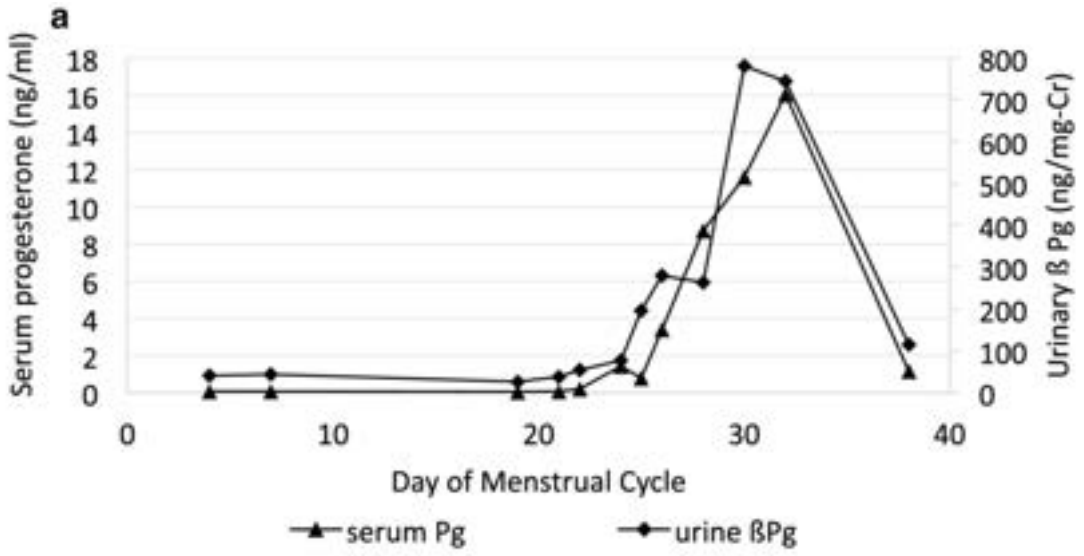


Estrogen dominance pattern

The DUTCH Dozen: 2 Progesterone

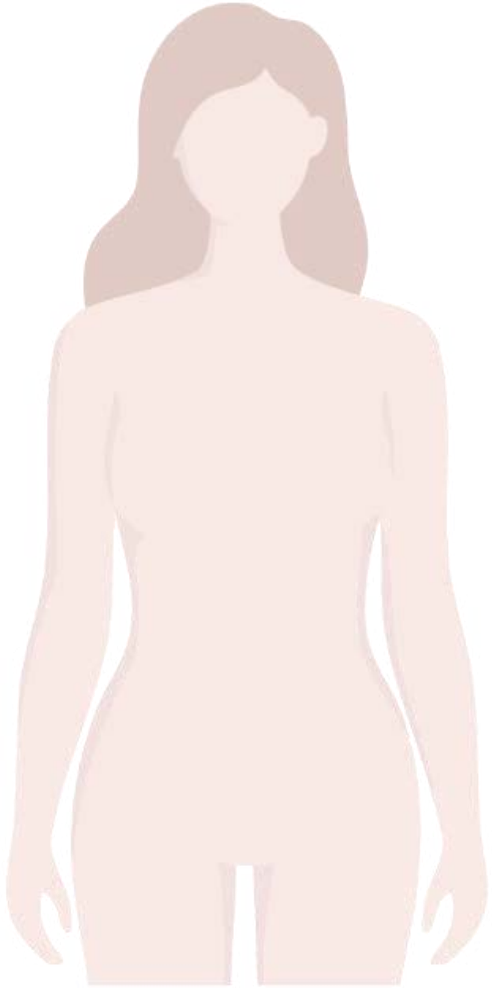
- The DUTCH Test measures progesterone metabolites, **a-pregnanediol** and **b-pregnanediol**. These are used to calculate the Progesterone Serum Equivalent.
- DUTCH dried urine b-pregnanediol correlates with 24-hour liquid b-pregnanediol and serum progesterone.





Newman M, et al. BMC Chem. 2019;13(1):20.

The DUTCH Dozen: 2 Progesterone



Progesterone's Actions

- **Brain:** Potential neuroprotective effects
- **Mood:** GABA agonist, calming
- **Sleep:** GABA agonist, promotes sleep
- **Hair:** Decreases conversion of testosterone to DHT at the hair follicle and suppresses LH, which may reduce androgen-driven hair loss.
- **Metabolism:** Increases metabolic rate (basal body temperature)
- **Bone density:** Promotes bone formation
- **Breast health:** breast cell growth
- **Uterine health:** Stabilizes endometrium
- **Fertility**
- **Balances estrogen:** downregulates ERs and induces enzymes for estrogen metabolism

The DUTCH Dozen: 2 Progesterone

Where **P4** is Made in **Pre-menopausal** Women

ADRENALS

DHEA-S (100%)

DHEA (80%)

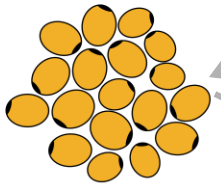
Androstenedione (50%)

Testosterone (25%)

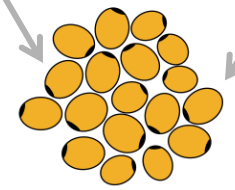
Estradiol (via DHEA)

Progesterone (minimal)

Periphery (including fat tissue)



Periphery (including fat tissue)



Only if ovulation occurs

OVARIES

Estradiol (majority)

Progesterone (majority)

Androstenedione (50%)

Testosterone (25%)

DHEA (20%)

DHEA-S (0%)

Testosterone (50%)

Yesiladali M, et al. Diagnostics (Basel). 2022;12(9).

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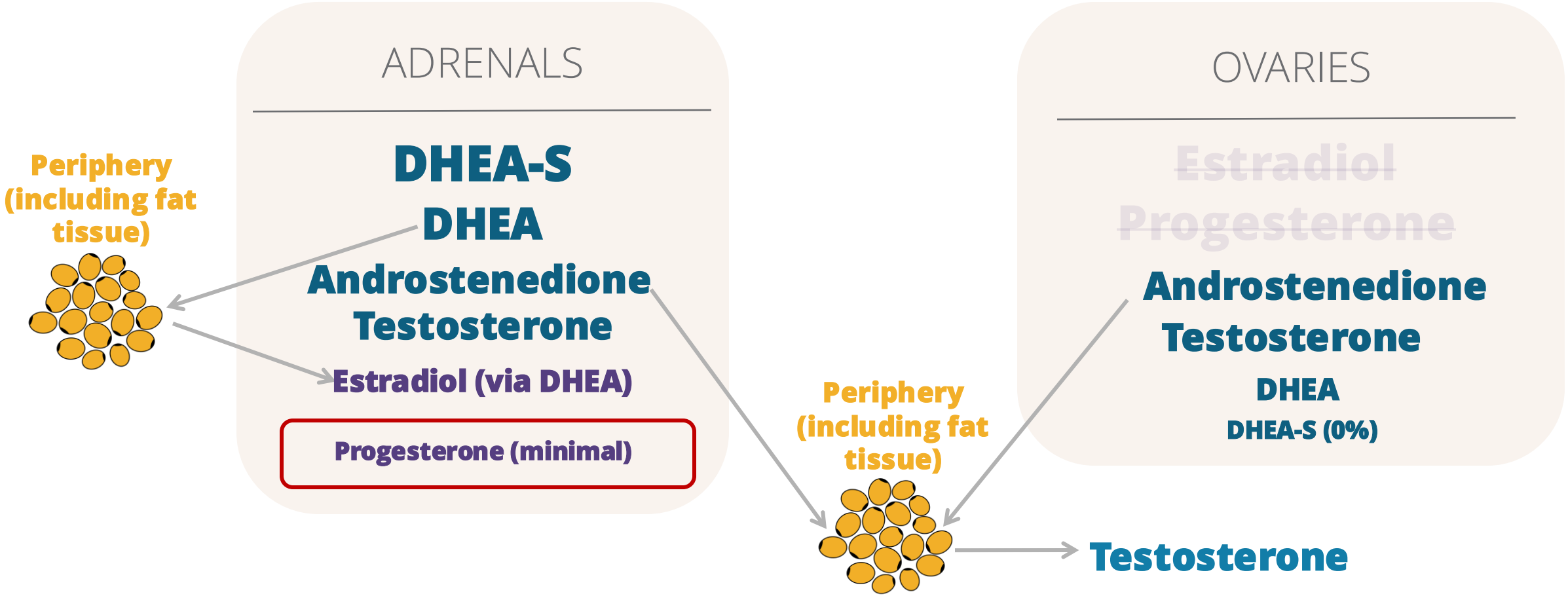
The DUTCH Dozen: 2 Progesterone

Where **P4** is Made in **Post-menopausal (PMP)** Women

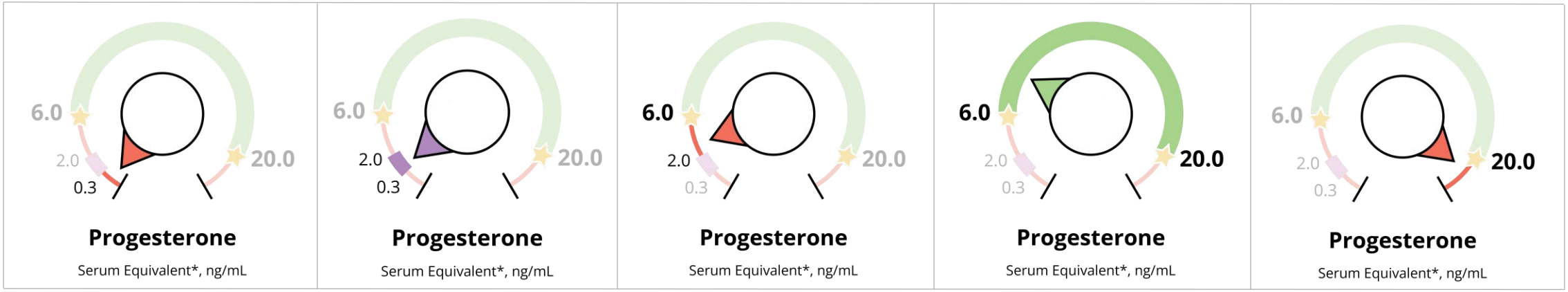


The DUTCH Dozen: 2 Progesterone

Like E2, the patient's **Progesterone (P4)** result will be within **one of these 5 areas on the DUTCH dial**:

Key to Reading the Dial

- Optimal Luteal Range
- Postmenopausal Range



- Below the post-menopausal range
- Within the post-menopausal range
- Above the post-menopausal range but below the luteal range
- Within the luteal range
- Above the luteal range

Pre-Menopausal P4: Causes

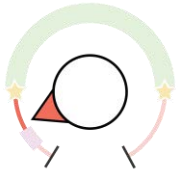
Anovulation
0.3-2.0 ng/mg

Ovaries are NOT Cycling Due To:
- Conditions & medications that suppress the HPO axis, including combo OCPs (1)
- High androgens inhibiting ovulation such as with PCOS
- Diminished ovarian reserve, POI, perimenopause
- Medically induced, as with oophorectomy (3)
- Hypogonadism
- Hypopituitarism

Ovaries are cycling but:
- The patient incorrectly timed the sample collection outside of their luteal phase (7)

Very Low Below PMP
0.0-0.3 ng/mg

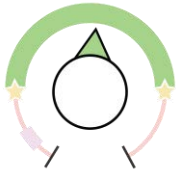
Ovaries are NOT cycling and Subphysiologic P4 Levels:
- Low output of other adrenal hormones, such as cortisol and DHEA, can be associated with very low P4



Sub-optimal
2.0-6.0 ng/mg

Ovaries are Cycling and Ovulation Occurred but P4 Levels are Suboptimal Due To:
- The patient incorrectly timed the sample collection in their early or late luteal phase (not mid-luteal) (27)
- Inadequate ovarian P4 production or luteal phase defect (LPD)
- Conditions that impair (but do not fully suppress) the HPO axis (2)

Ovaries are NOT cycling but P4 levels are above the PMP range due to:
- Elevated adrenal P4 output, typically stress-related (18)



Optimal
6-20 ng/mg

Ovaries are Cycling, Ovulation Occurred and P4 Levels are Optimal:
- Normal ovarian production of P4 during the luteal phase
- P4 >12 ng/mL may be optimal for fertility
- Note that P4 therapy may be bringing P4 levels into the normal range, in the presence of low endogenous corpus luteum P4 production

Oral Progesterone (20)

High
>20 ng/mg

Ovaries are Cycling, Ovulation occurred, but P4 Levels are Elevated Due To:
- Normal robust ovarian P4 production
- Ovarian cysts
- PCOS (some women)
- P4 therapy is increasing P4 on top of endogenous corpus luteum P4 production (20)

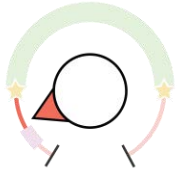
Very High

Supraphysiologic P4 Levels Due To:
- Oral or sublingual P4 or pregnenolone (1st pass affects urine metabolites only, not serum)(19, 20)
- Pregnancy
- Progesterone producing neoplasms (rare)

Ovaries are NOT Cycling but P4 Levels are Above the PMP Range Due To:
- Progesterone (20) and pregnenolone therapy: The degree of elevation in urinary P4 metabolites depends on the route of administration (ROA) and dose. With oral use of progesterone, the Progesterone Serum Equivalent is not a valid concept and will not correlate with serum progesterone. However, the P4 5a-Metabolism may provide insight into its sedating effects. Note that pregnenolone does not increase serum progesterone, but increases progesterone metabolites on the DUTCH Test.(19)

Pre-Menopausal P4: Effects

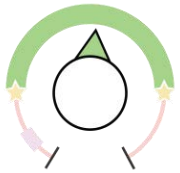
Anovulation
0.3-2.0 ng/mg



Suboptimal
2.0-6.0 ng/mg

When P4 is Low/Suboptimal Relative to E2:
- Abnormal uterine bleeding (AUB)
- Increased endometrial cancer risk
- Breast tenderness
- PMS

When P4 is Low/Suboptimal with Concurrent Low E2:
- Symptoms of low E2
- Insomnia
- Fatigue
- Irritability, Anxiety
- Low bone mineral density (BMD)



Optimal
6-20 ng/mg

Healthy P4 Levels Balanced with E2 are Associated with the Following:
- Regular cycles (25-35 days)
- Cycles are predictable within 1-2 days
- Mild premenstrual symptoms 2-3 days before menses (breast tenderness, fluid retention, bloating) is more consistent with ovulation and healthy progesterone than an absence of symptoms
- Absence of spotting or AUB Levels <12 ng/mg may be suboptimal for fertility

Oral Progesterone (20):
- Laboratory P4 measurement cannot predict endometrial protection

High
>20 ng/mg

High P4 Due to Ovulation is Often Normal & Not Problematic

High progesterone signs & symptoms*:
- Fatigue
- Increased appetite
- Breast tenderness
- Bloating
- More significant symptoms of PMS

*An appropriate dose of oral or sublingual progesterone taken near the time of testing may increase urinary progesterone metabolites due to first-pass metabolism, without reflecting serum progesterone levels or causing symptoms of progesterone excess.

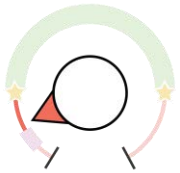
Post-Menopausal P4: Causes

Postmenopausal (PMP)
0.3-2.0 ng/mg

P4 levels are Normal for PMP status:
- Adrenal output supplies all postmenopausal progesterone

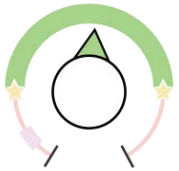
Very Low Below PMP
0.0-0.3 ng/mg

Subphysiologic P4 Levels:
- Low output of other adrenal hormones, such as cortisol and DHEA, can be associated with very low P4, but the difference in P4 is clinically inconsequential



Mildly Above PMP
2.0-6.0 ng/mg

P4 Levels are Above the PMP Range but Below the Luteal Range Due To:
- High adrenal P4 output, typically stress-related (18)
- Transdermal progesterone can result in mild elevations in P4 levels in both urine and serum testing
- OMP skipped on day of testing or lower dose (<100 mg)



Above PMP
6-20 ng/mg

Oral Progesterone:
- When patients report taking oral micronized progesterone (OMP) within 72 hours of collection, adjusted OMP reference ranges are reported (20)

High
>20 ng/mg

P4 levels are Above the PMP Range Due To:
- Progesterone therapy (20) - and secondarily pregnenolone therapy - is the most common cause of urinary P4 metabolites exceeding the PMP range in PMP women. The degree of elevation depends on the route of administration (ROA) and dose. **With oral use of progesterone, the Progesterone Serum Equivalent is not a valid concept and progesterone metabolite levels in urine will not correlate with serum progesterone. However, the P4 5a-Metabolism may provide insight into its sedating effects.** Note that pregnenolone does not increase serum progesterone, but increases progesterone metabolites on the DUTCH Test (19)
- Perimenopause: If not >1.0-1.5 years out from final menstrual period (FMP), consider endogenous ovarian production

Very High

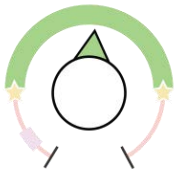
Supraphysiologic P4 Levels Due To:
- Oral or sublingual progesterone or pregnenolone therapy (1st pass affects urine metabolites only, not serum)(19, 20)
- Progesterone producing neoplasms (rare)

Post-Menopausal (PMP) P4: Effects

PMP P4
0.3-2.0 ng/mg

PMP P4 Levels are Considered "Not Clinically Impactful":

- These P4 levels provide no protection against endometrial hyperplasia or cancer in women on estrogen (E2) therapy or with elevated E2 due to obesity.
- Due to progesterone's rapid pharmacokinetics, serum levels may appear low even with oral dosing, depending on the timing of the test relative to administration.



Supplemented P4

Oral Progesterone:

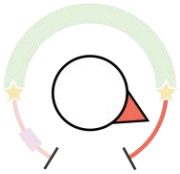
- When patients report taking oral micronized progesterone (OMP) within 72 hours of collection, adjusted OMP reference ranges are reported (20)

Regarding endometrial protection in women with a uterus:
Laboratory P4 measurement cannot predict endometrial protection. Studies performing endometrial biopsies on patients to monitor oral and vaginal micronized progesterone therapy (OMP and VMP) with concomitant E2 therapy have found the following P4 dosing and ROAs to be uterine protective:

- 100 mg OMP nightly or 200 mg OMP 12 consecutive nights per month
- 200 mg OMP nightly may be more uterine-protective with higher dose E2 therapy
- 100 mg VMP 12 consecutive nights per month
- 200 mg VMP 12 consecutive nights per month may be more uterine-protective with higher dose E2 therapy

Adequate P4 Supplementation (See OMP and VMP Dosing Above):

- Protects the endometrium from hyperplasia and cancer with E2 therapy
- May reduce hot flashes, anxiety and irritability, support sleep and bone mineral density



High P4
>20 ng/mg

Too Much P4 Supplementation May Result in High Progesterone Symptoms*:

- Fatigue, drowsiness, dizziness may be resolved by dosing at night (if dosing in the morning)
- Increased appetite
- Breast tenderness
- Bloating

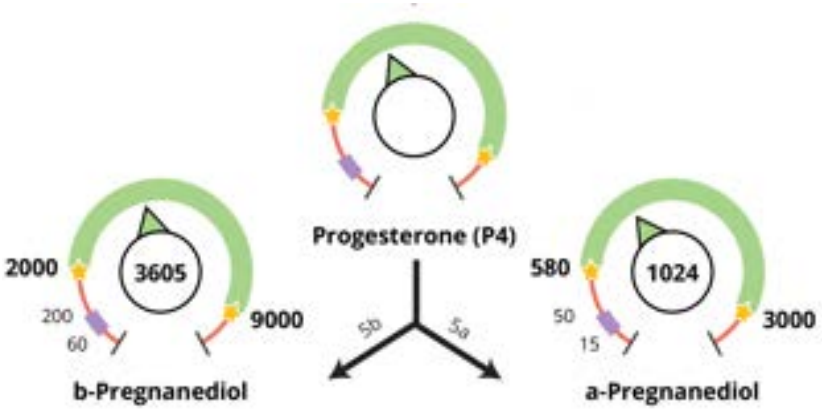
*An appropriate dose of oral or sublingual P4 taken near the time of testing may increase urinary P4 metabolites due to first-pass metabolism, without reflecting serum P4 levels or causing symptoms of P4 excess.

The DUTCH Dozen: 2 Progesterone

Note about OMP:

- When a female patient reports taking OMP within 72 hours of sample collection, the progesterone reference ranges on a female DUTCH report are ***adjusted*** to reflect levels that are typically seen when a standard dose of OMP 100-200 mg is taken during testing.

DUTCH REFERENCE RANGES	α-PREGNANEDIOL	b-PREGNANEDIOL
Luteal	200-740 ng/mg	600-2000 ng/mg
Postmenopausal	15-50 ng/mg	60-200 ng/mg
OMP (typical 100-200 mg dose on day of testing)	580-3000 ng/mg	2000-9000 ng/mg

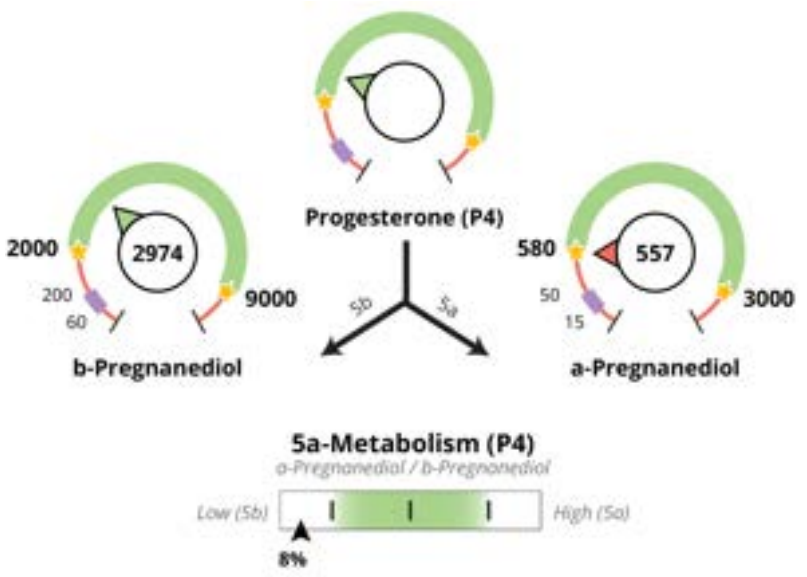


62-year-old PMP female
100 mg OMP

The DUTCH Dozen: 2 Progesterone

- **When a patient takes OMP, DUTCH b-pregnanediol no longer correlates with serum progesterone**. Therefore, we cannot use the DUTCH Test to monitor circulating levels of progesterone with OMP.
- **However, we *can* look at progesterone *metabolism* patterns.** Alpha progesterone metabolites have calming effects and generally support mood and sleep. ***More on this tomorrow!***

- Remember – even if P4 metabolites are within the DUTCH OMP reference ranges, this does **not** ensure endometrial protection when E2 therapy is used concomitantly.



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Polling Question

Game time!

(Problematic, actionable results)

Match the description to the correct dial:

1

34-year-old female
Premature Ovarian Insufficiency (POI)
Very low adrenal function

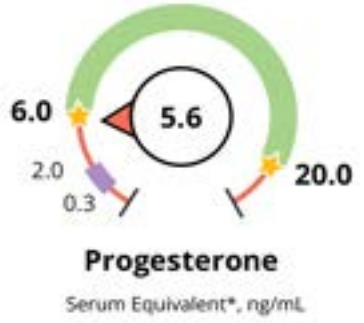
2

35-year-old female
Cycling but low BMI (17.6) and low DHEA

3

55-year-old female
PMP
Chronic Prednisone Use

A



B

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Question 5: Match the description to the correct Progesterone dial

Polling Question

Game time!

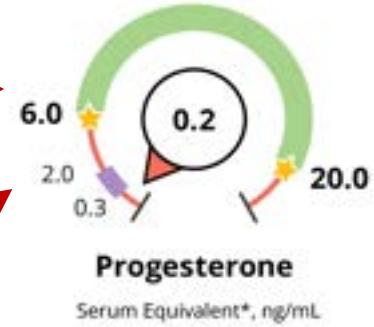
(Problematic, actionable results)

Match the description to the correct dial:

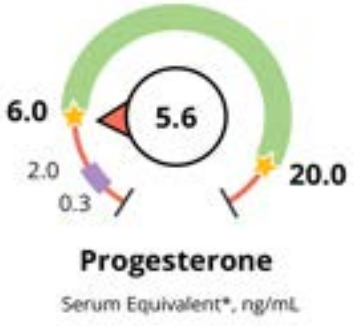
1. 34-year-old female
   Premature Ovarian Insufficiency (POI)
   Very low adrenal function

2. 35-year-old female
   Cycling but low BMI (17.6) and low DHEA

3. 55-year-old female
   PMP
   Chronic Prednisone Use



A



B

Polling Question

Game time!

(Expected, non-actionable results)

Match the description to the right dial:

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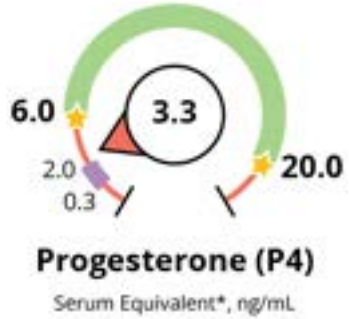
1

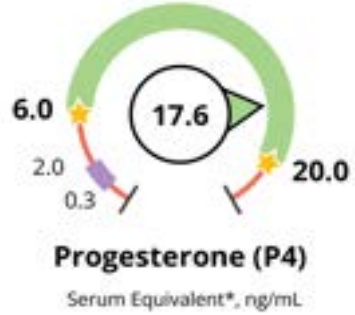
56-year-old female
100 mg oral P4 taken on day of testing
(***DUTCH OMP ranges***)



A

2

54-year-old female
200 mg TD P4 cream during testing



B

Question 6: Match the description to the correct Progesterone dial

Polling Question

Game time!

(Expected, non-actionable results)

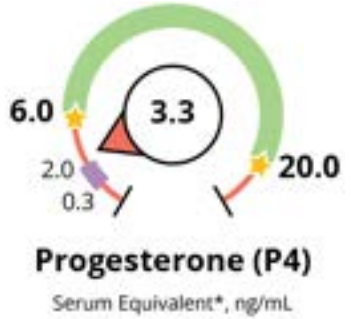
Match the description to the right dial:

1

56-year-old female
100 mg oral P4 taken on day of testing
(***DUTCH OMP ranges***)

2

54-year-old female
200 mg TD P4 cream during testing



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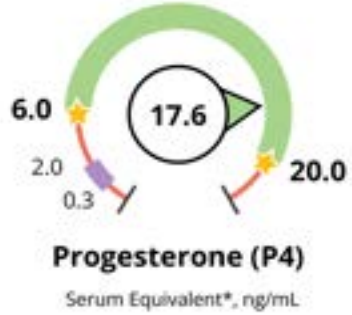


B

Polling Question

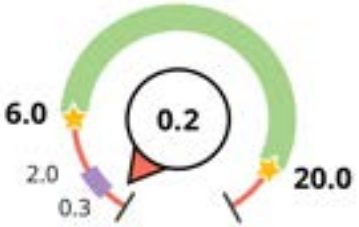
Game time!

(Expected, non-actionable results)

Match the description to the right dial:

1 **39-year-old female**
Oral pregnenolone taken on day of testing

2 **39-year-old female**
36 weeks pregnant



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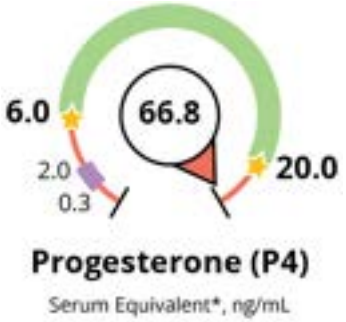

B

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Question 7: Match the description to the correct Progesterone dial

Polling Question

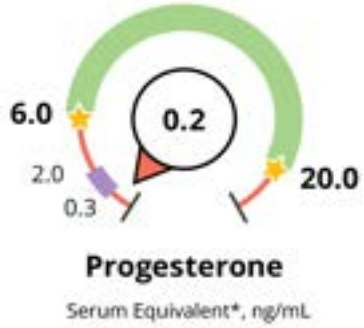
Game time!

(Expected, non-actionable results)

Match the description to the right dial:

1 **39-year-old female**
Oral pregnenolone taken on day of testing

2 **39-year-old female**
36 weeks pregnant



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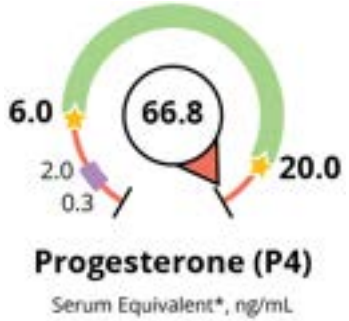

B

P4 Treatments:
Pre-menopausal Women

The treatment you choose depends on the cause,
but also the symptoms, treatment goals, and patient preferences.

The DUTCH Treatment Guide: **Low Progesterone (page 8)**

HPO Axis Support *Page 8*	Ovarian Health Support *Page 59*	Mood & Cognition Support *Page 57*
HPA Axis Support *Pages 8, 34, 36*	T and DHEA Support *Pages 16, 24*	Stress Support *Page 63*
GABA Support *Page 57*	Phytoestrogens & Phytoprogestogens *Page 59*	Sleep/Circadian Rhythm Support *Page 60*
Mitochondrial Support *Page 56*	Estrogen Support *Page 10*	Bone Support *Page 50*

Quiz!

Do you need to treat high P4 in pre-menopausal women?

HPO Axis Support · HPA Axis Support · Other Hormone support · OATs Support · Symptom Support · Detox Support · Lifestyle Support · Other Support

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The DUTCH Treatment Guide: **Low Progesterone (page 8)**

HPO Axis Support *Page 8*	Ovarian Health Support *Page 59*	Mood & Cognition Support *Page 57*
HPA Axis Support *Pages 8, 34, 36*	T and DHEA Support *Pages 16, 24*	Stress Support *Page 63*
GABA Support *Page 57*	Phytoestrogens & Phytoprogestogens *Page 59*	Sleep/Circadian Rhythm Support *Page 60*
Mitochondrial Support *Page 56*	Estrogen Support *Page 10*	Bone Support *Page 50*

Quiz!

Do you need to treat high P4 in pre-menopausal women?

Most likely no!

However, if they are experiencing symptoms of high progesterone, manage symptoms ***(page 9 of Treatment Guide)***, and consider assessing contributors of higher progesterone.

HPO Axis Support · HPA Axis Support · Other Hormone support · OATs Support · Symptom Support · Detox Support · Lifestyle Support · Other Support

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The DUTCH Dozen
2-OH Preference (Phase 1)

3

The DUTCH Dozen: 3 2-OH Preference (Phase 1)

Estrogen Progesterone

3 Assess 2-OH preference in phase 1 estrogen metabolism

- The **third assessment** focuses on phase 1 of estrogen metabolism, specifically, the preference for the protective **2-OH pathway**.

You make estrogen (or take ET).

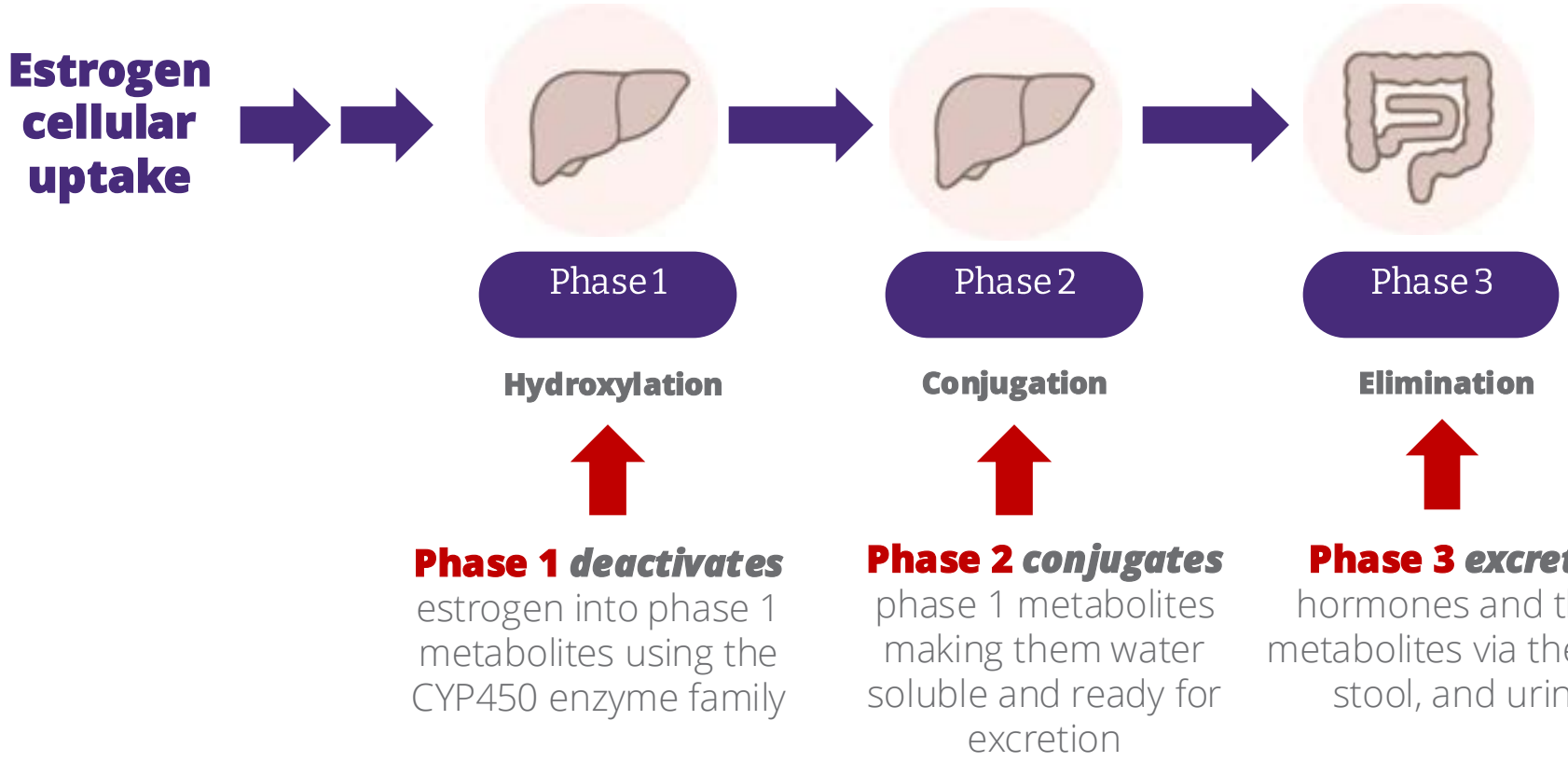
Your body uses the estrogen.

You no longer need the estrogen.

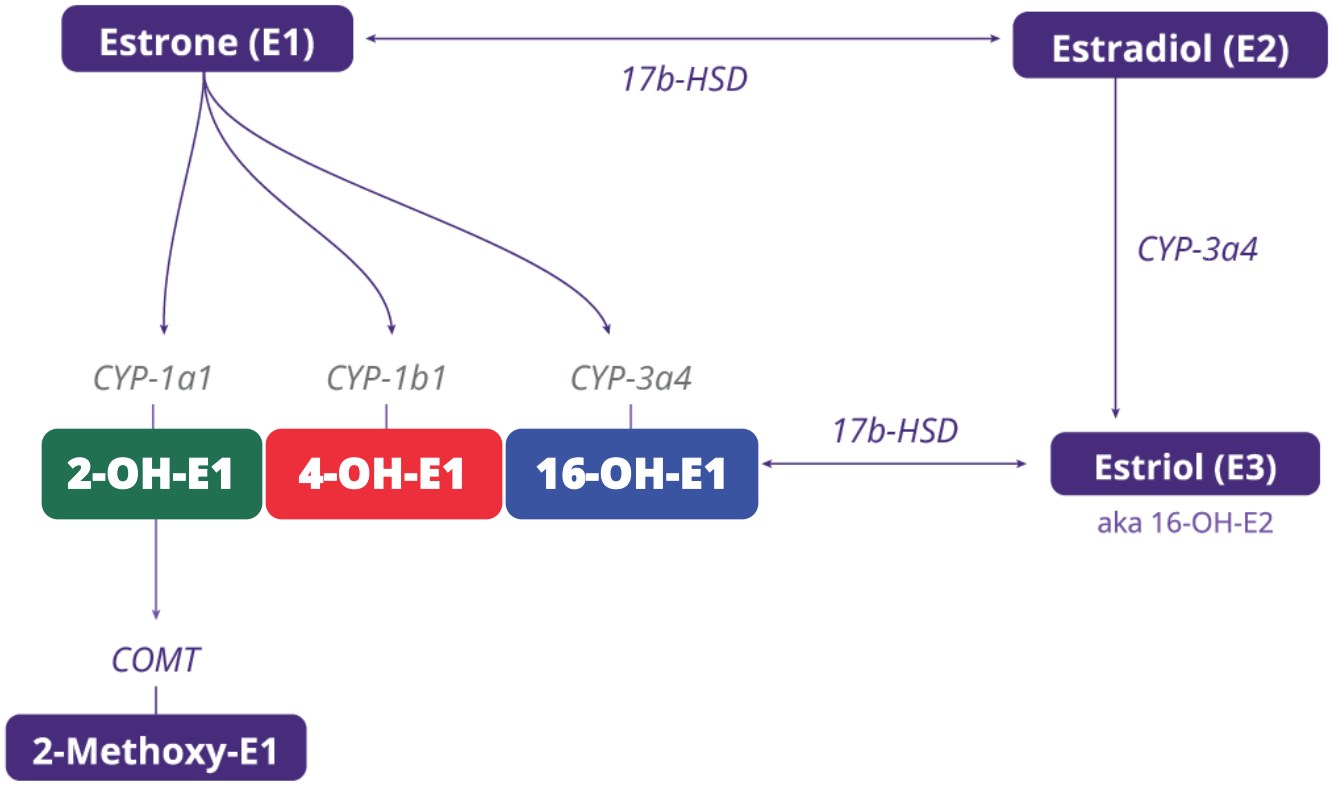
Where does the estrogen go?

The DUTCH Dozen: 3 2-OH Preference (Phase 1)

- There are 3 phases of estrogen detoxification:



The DUTCH Dozen: 3 2-OH Preference (Phase 1)



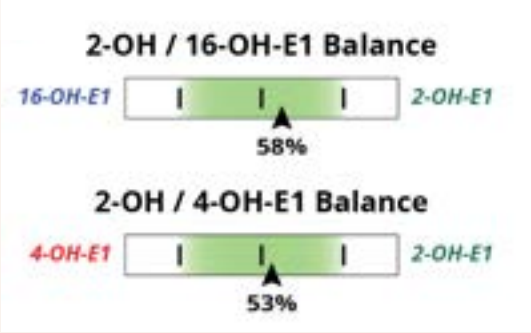
In phase 1, parent estrogens (E1 and E2) are broken down via 3 main pathways.

- **2-OH** is the **protective** pathway
- **4-OH** is the **genotoxic** pathway
- **16-OH** is the **estrogenic** pathway

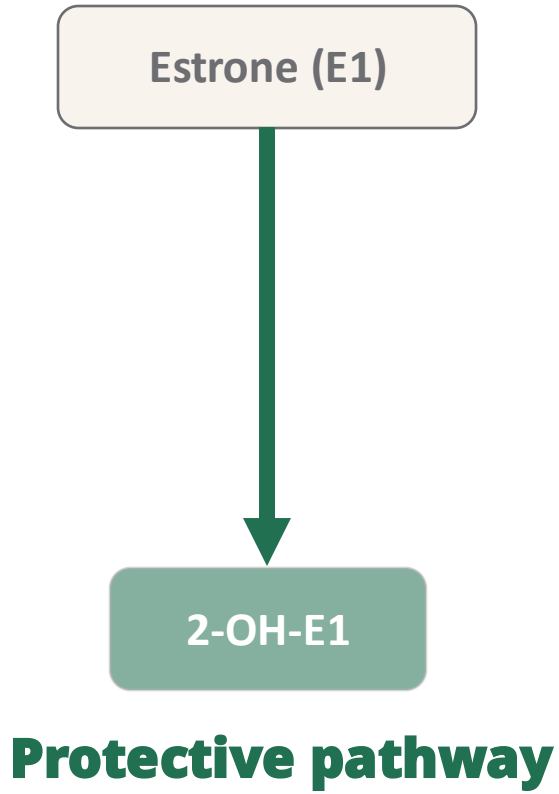
The DUTCH Dozen: 3 2-OH Preference (Phase 1)

2-OH Estrogen Metabolites: **Protective**

- Antiestrogenic, anti-carcinogenic
- More stable than 4-OH metabolites
- The 2-OH pathway is associated with lower breast cancer risk, and we refer to it as the **"protective" pathway.**



A 2/16 and 2/4 balance >20%-30% is ideal for many patients.



Protective pathway

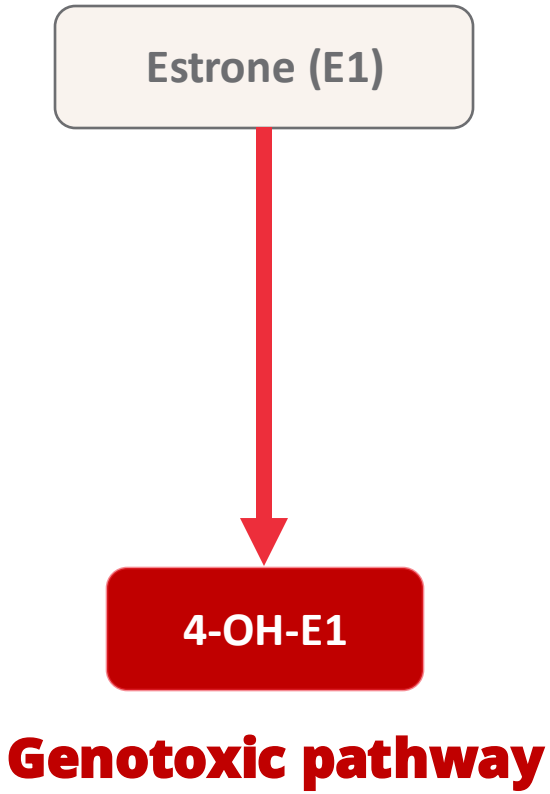
Tsuchiya Y, et al. Cancer Lett. 2005;227(2):115-124.

The DUTCH Dozen: 3 2-OH Preference (Phase 1)

4-OH Estrogen Metabolites: **Genotoxic**

- Formed in the liver, breasts, uterus
- 4-OH-E1 is **unstable** and forms **"reactive"** quinones that cause **DNA damage** and increase **breast cancer risk.**

A low 2/4 balance (below 20%–30%) may signal a need for intervention.

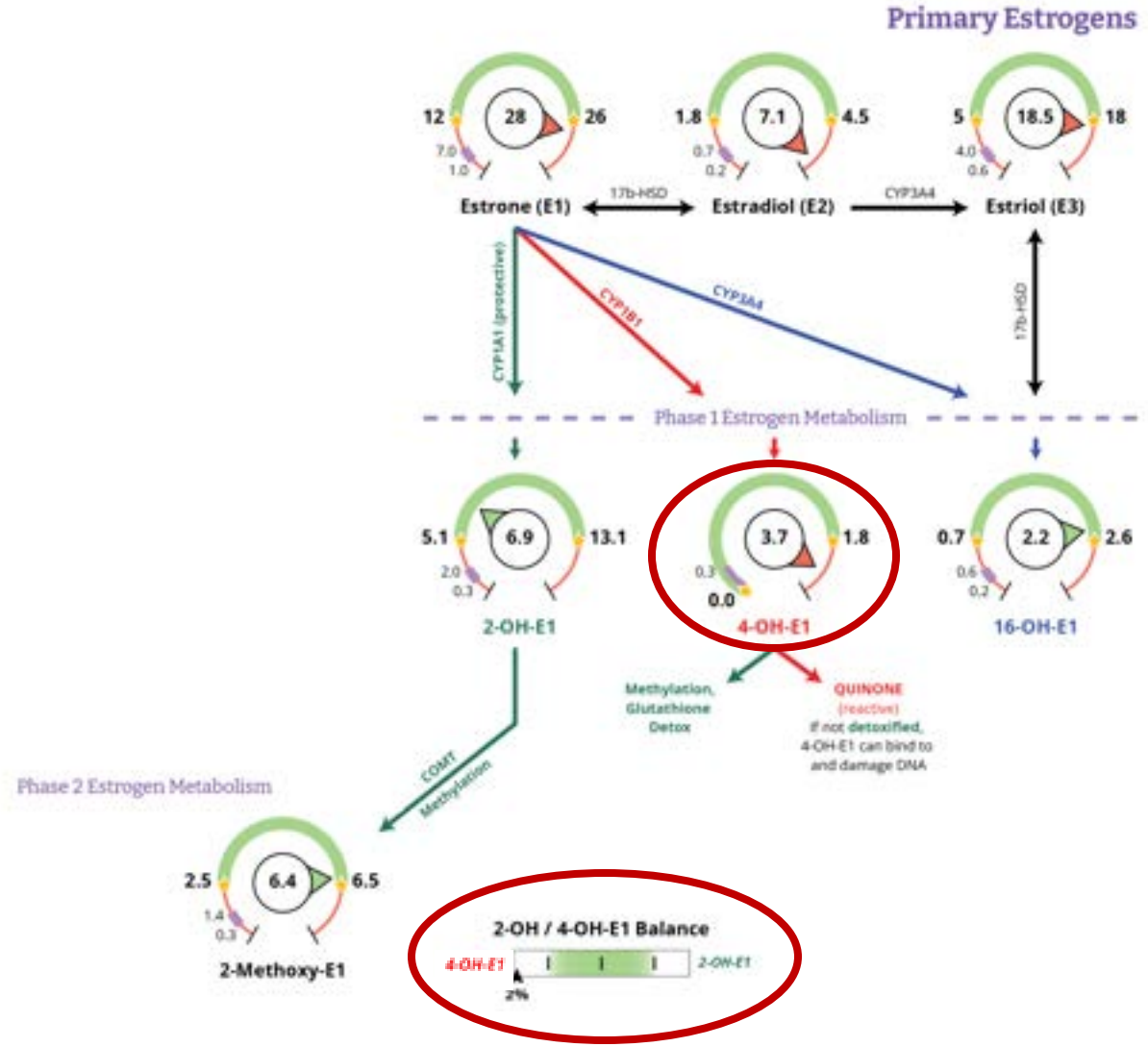


Liehr JG, Ricci MJ. 1996;93(8):3294-3296.
Tsuchiya Y, et al. Cancer Lett. 2005;227(2):115-124.

The DUTCH Dozen: 3 2-OH Preference (Phase 1)

- DUTCH Report of a **36-year-old** female diagnosed with **ER/PR+ breast cancer** 5 years prior. Recurrence in lymph node 2 years prior. Taking Tamoxifen during testing

- Note that Tamoxifen, being a SERM, lowers risk for breast cancer recurrence by blocking estrogen receptors (ERs) in the breast tissue. It does not block ***potential 4-OH genotoxic actions*** in the breast tissue.



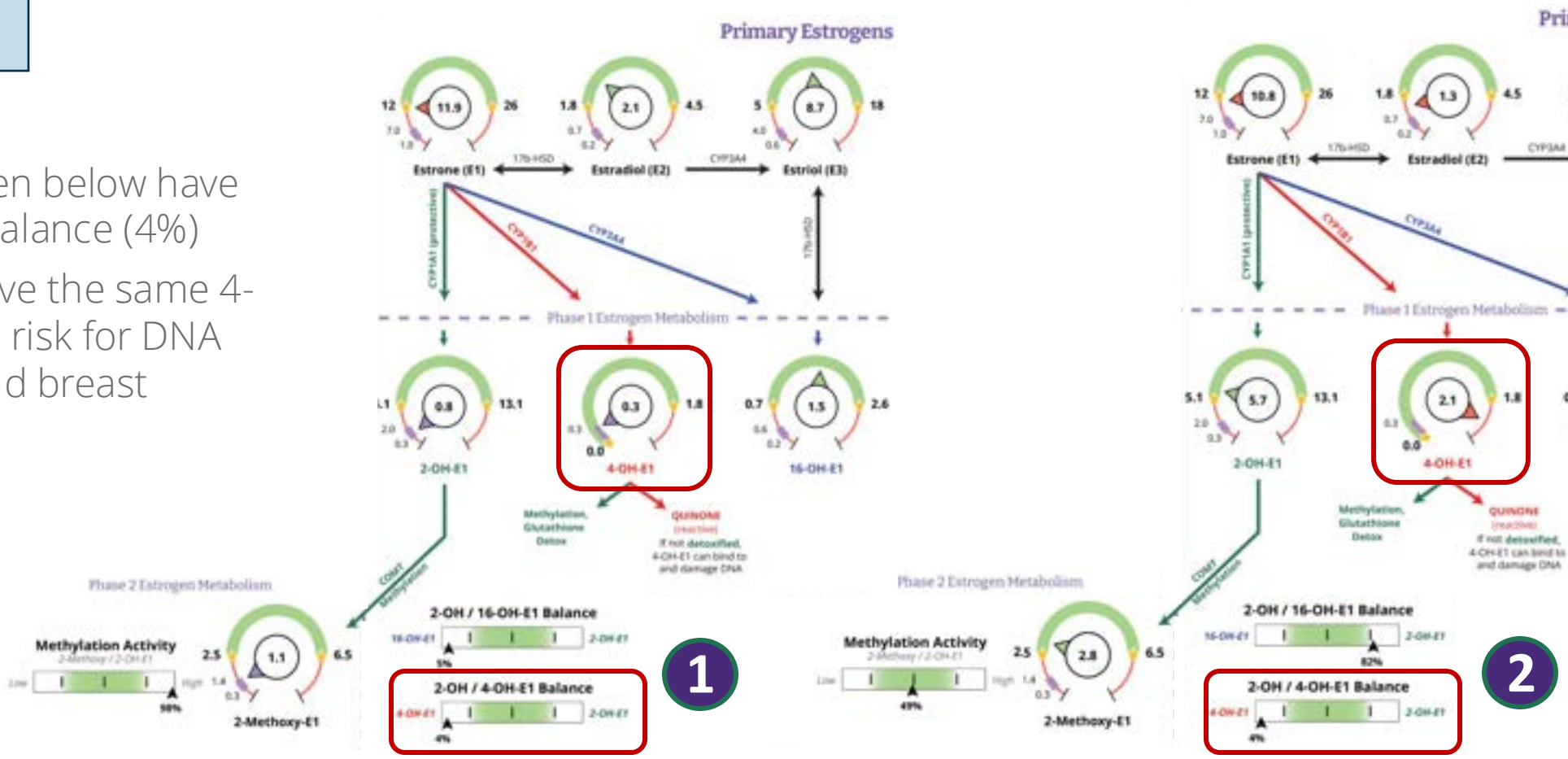
The DUTCH Dozen: 3 2-OH Preference (Phase 1)

Think about it!

Game time!

4-OH-E1 *levels* matter! The 2/4 balance should always be evaluated ***in conjunction with*** 4-OH-E1(E2) levels.

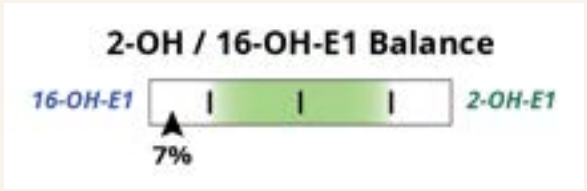
- Both women below have a low 2/4 balance (4%)
- Do they have the same 4-OH related risk for DNA damage and breast cancer?



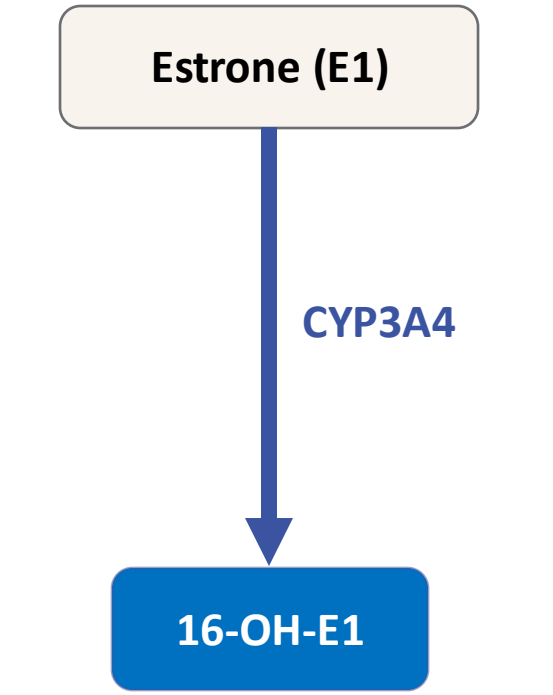
The DUTCH Dozen: 3 2-OH Preference (Phase 1)

16-OH Estrogen Metabolites: Estrogenic

- Significant estrogenic activity, though less than E2.
- Associated with **estrogen-related conditions**
  - Heavy bleeding, breast tenderness, uterine fibroids, endometriosis
  - Increased breast cancer risk. ***It does not appear to have DNA damaging or carcinogenic properties, but it is proliferative (causes tissue growth).***
- Other associated conditions: RA, SLE
- CYP3A4 inducers: obesity, alcohol, smoking, etc.



A low 2/16 balance (below 20%–30%) may signal a need for intervention.



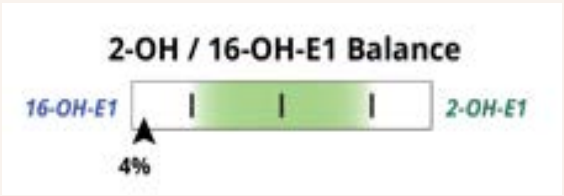
Estrogenic pathway

For references, please see "16-OH-E1 References" at the end of the presentation

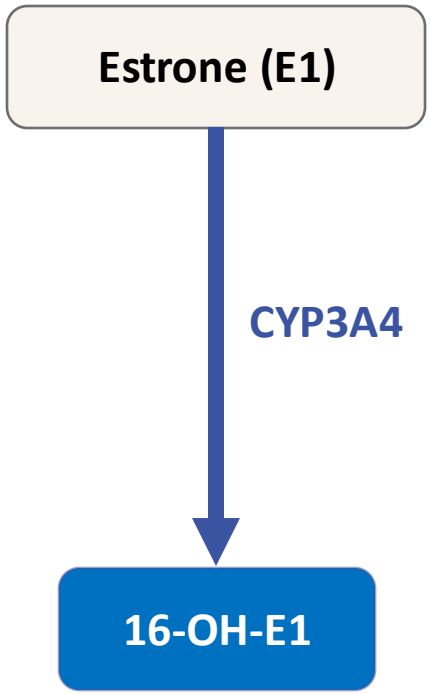
The DUTCH Dozen: 3 2-OH Preference (Phase 1)

16-OH Estrogen Metabolites: Estrogenic

- 16-OH-E1 is associated with greater PMP bone mineral density (BMD); **BUT it is not recommended to push 16-OH for bone protection (E2 therapy is).**
- Therefore, while this pathway is associated with more overall estrogenic activity, keep in mind this isn't always bad.
- However, this woman would likely benefit from improving her 2/16 balance, however, **remember that 2-OH/16-OH-E1 sliders should always be evaluated in conjunction with 16-OH-E1 levels!** For example, if her 16-OH-E1 level on page #2 was in the PMP range, we likely wouldn't intervene.



24-year-old female
Breast tenderness
Heavy bleeding

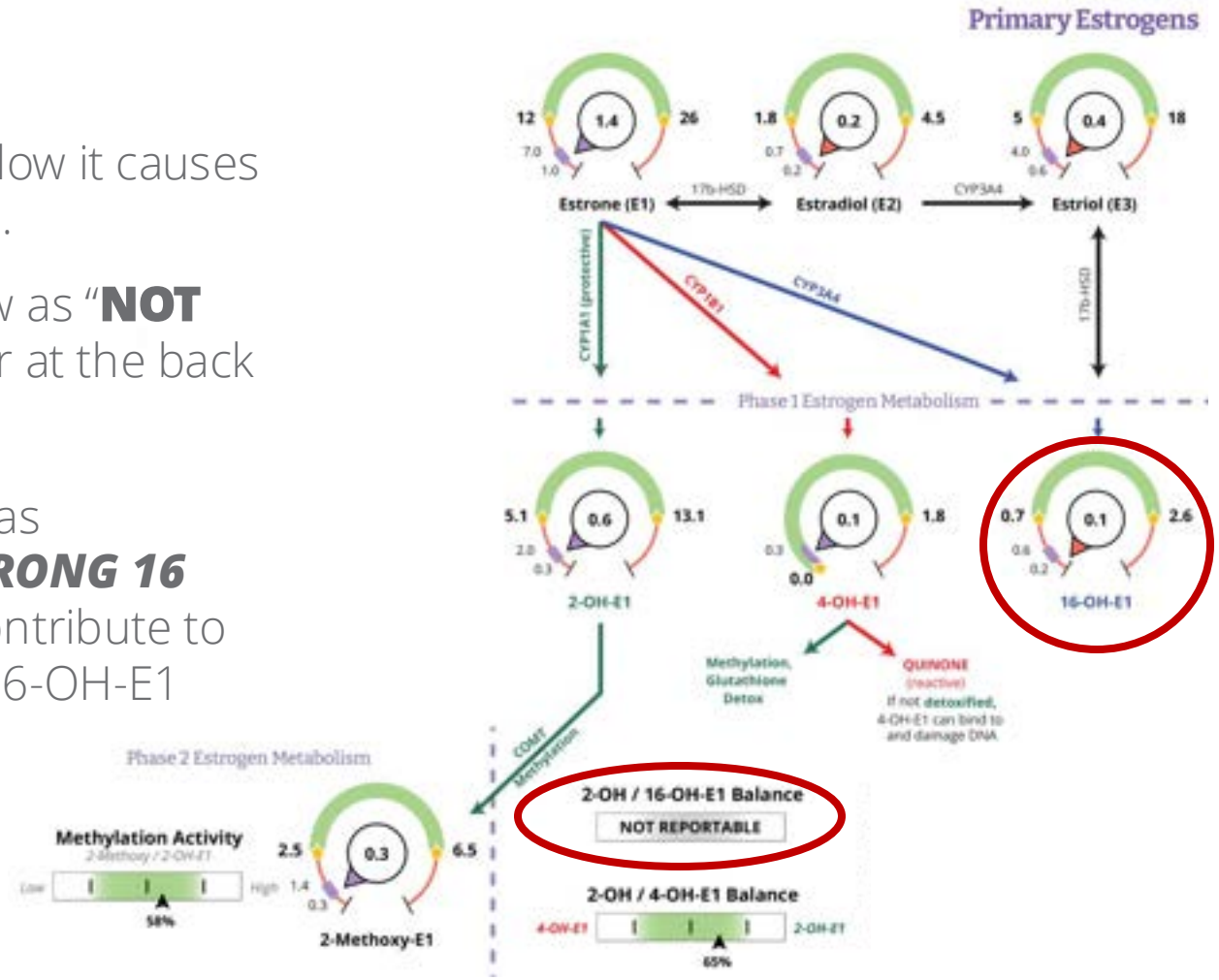


Lim SK, et al. J Clin Endocrinol Metab. 1997;82(4):1001-1006.

The DUTCH Dozen: 3 2-OH Preference (Phase 1)

Low Ratio Reliability

- When estrogen metabolite levels are ***very*** low it causes the ratios between them to be less reliable.
- When this happens, the slider bar will show as "**NOT REPORTABLE**", and a comment will appear at the back of the report.
- In this example, even if the 2/16 balance was reportable (***let's pretend it showed a STRONG 16 preference***), this preference would **not** contribute to estrogen excess symptoms as the overall 16-OH-E1 value is very low at 0.1 ng/mg.



The DUTCH Treatment Guide: **Phase 1 Treatments**

Lower 4-OH-E1 Preference:

Lower Estrogen, if High* *Page 28,14*	Support Methylation *Page 30*
Use CYP1B1 Inhibitors *Pages 28*	**Minimize DNA Damage *Pages 28 Pyroglutamate – p 24***
Avoid CYP1B1 Inducers *Page 28*	Support the 2-OH Pathway *Page 30*

Lower 16-OH-E1 Preference:

Lower Estrogen, if High* *Page 28,14*	Support Sulfation & Glucuronidation *Page 29*
Use CYP3A4 Inhibitors *Pages 29*	Lower Beta-Glucuronidase *Pages 31*
Avoid CYP3A4 Inducers *Page 29*	Support the 2-OH Pathway *Page 30*

*If estrogen levels are low, consider avoiding or using caution with supplements that lower estrogen levels, such as diindolylmethane (DIM), indole-3-carbinol (I3C), and calcium-d-glucurate (CDG).

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The DUTCH Dozen
Methylation Activity (Phase 2)

4

The DUTCH Dozen: 4 Methylation Activity (Phase 2)

Estrogen Progesterone

4 Assess methylation of 2-OH estrogens

- The **fourth assessment** evaluates phase 2 estrogen detoxification, focusing on **methylation**.

The DUTCH Dozen: 4 Methylation Activity (Phase 2)

- COMT is the enzyme that methylates (and thus deactivates) the catechol estrogens (2-OH and 4-OH metabolites).

2-OH

2-OH-E1 → 2-Methoxy-E1

2-OH-E2 → 2-Methoxy-E2

4-OH

4-OH-E1 → 4-Methoxy-E1

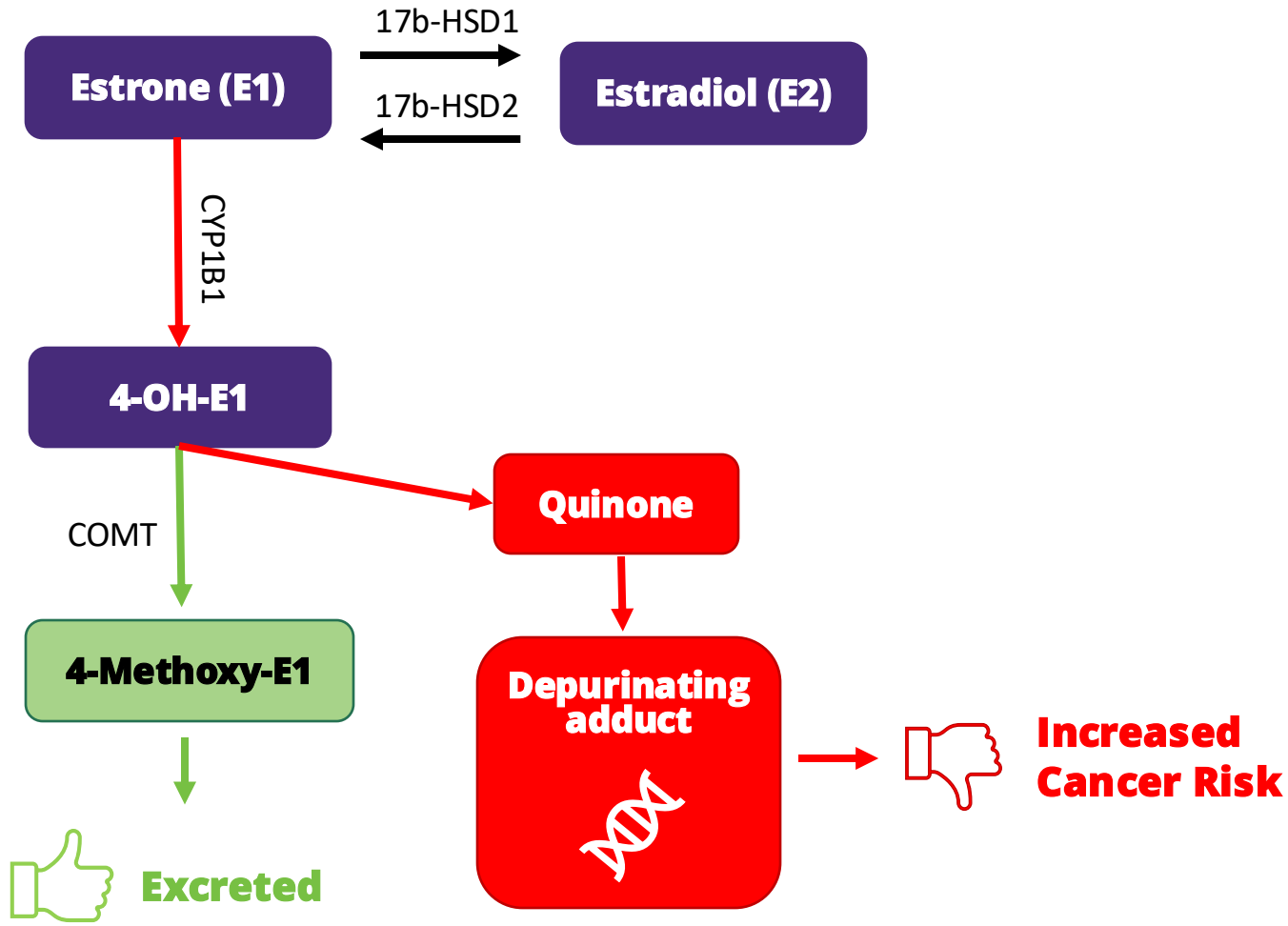
4-OH-E2 → 4-Methoxy-E2

Why doesn't DUTCH measure 4-Methoxy?

4-Methoxy concentrations are typically ***very low***, resulting in poor accuracy and results that are not clinically meaningful enough to report.

The DUTCH Dozen: 4 Methylation Activity (Phase 2)

By deactivating the 4-OH metabolites (via methylation), COMT prevents them from causing DNA damage!

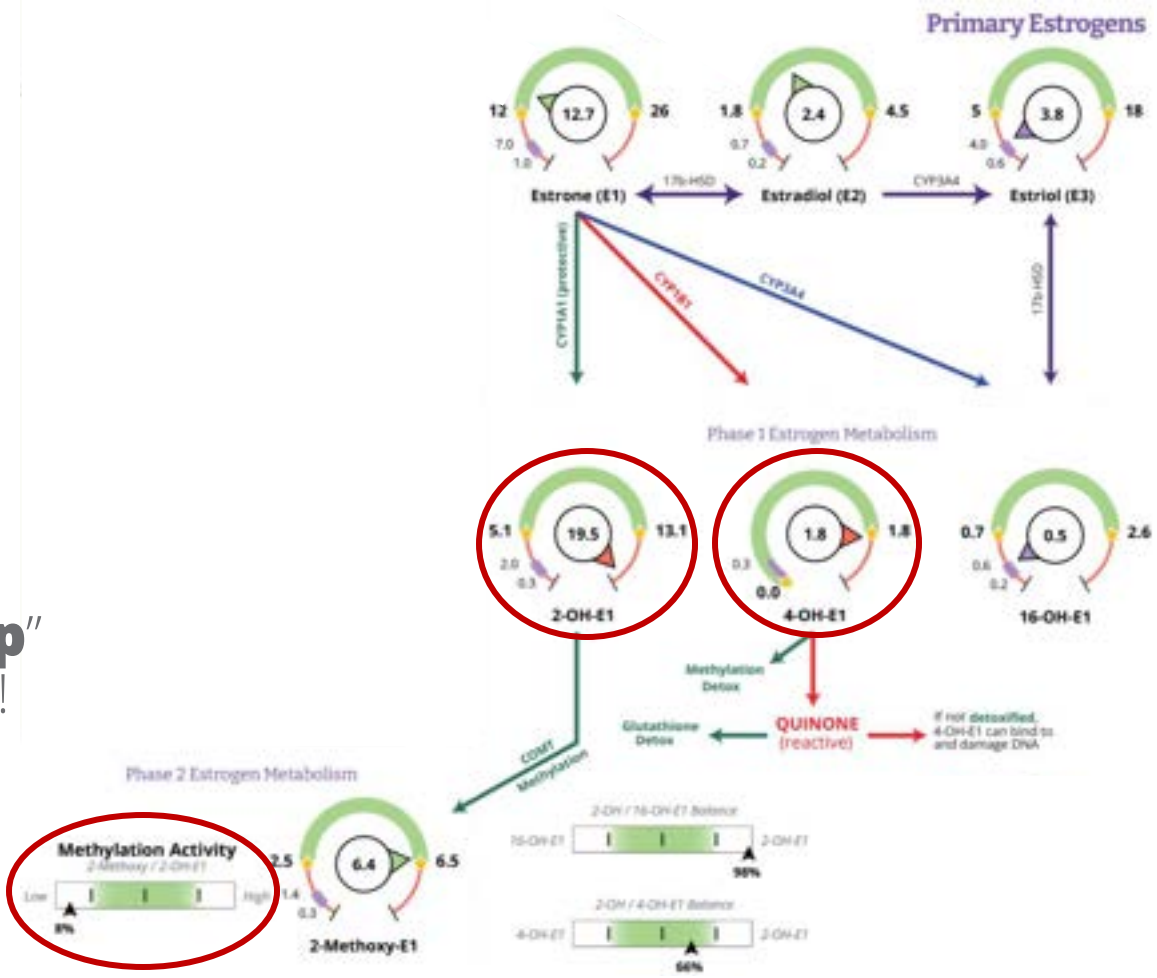


Samavat H, et al. Cancer Lett. 2015;356(2 Pt A):231-243.

The DUTCH Dozen: 4 Methylation Activity (Phase 2)

- Slow COMT activity has been linked to:
  - Endometriosis
  - Endometrial cancer
  - Breast cancer
  - Uterine fibroids (mixed data)
- Fast COMT activity has not been associated with estrogen-related health issues.

- Therefore, it's not ideal that this 45-year-old woman's 2-OH-E1 and 4-OH-E1 are "**backing up**" in phase 1 due to **slow methylation activity**!



Samavat H, et al. Cancer Lett. 2015;356(2 Pt A):231-243.

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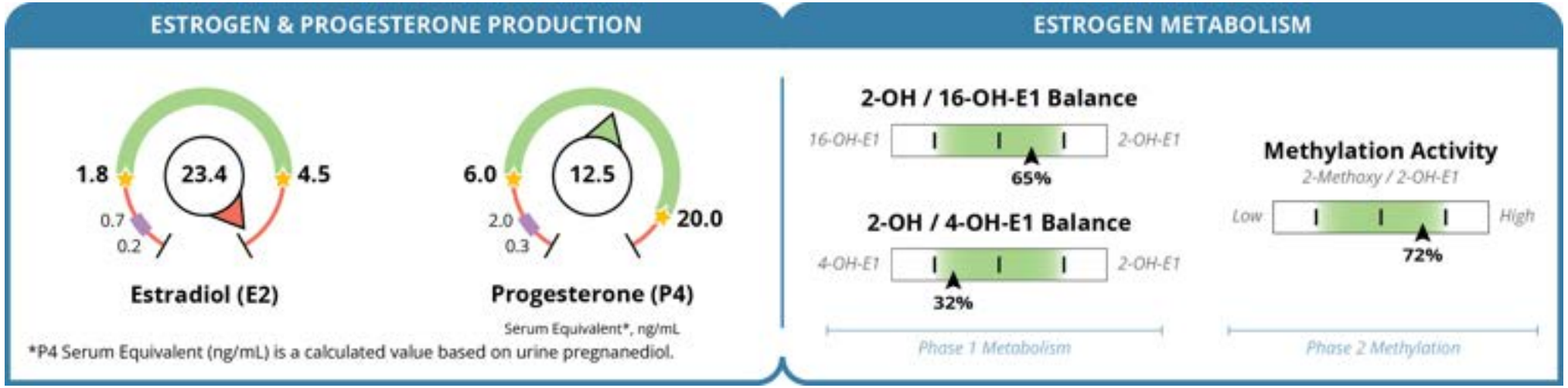
The DUTCH Dozen: 4 Methylation Activity (Phase 2)

- Methylation activity below 20% usually indicates suboptimal detoxification.
- Methylation activity between 20-30% may benefit from intervention especially if paired with high estrogens or estrogen-related conditions.

- **For example, it's likely advantageous for this 37-year-old female's methylation activity to be >20% due to her high baseline estrogen and *slight* 4-OH preference:**



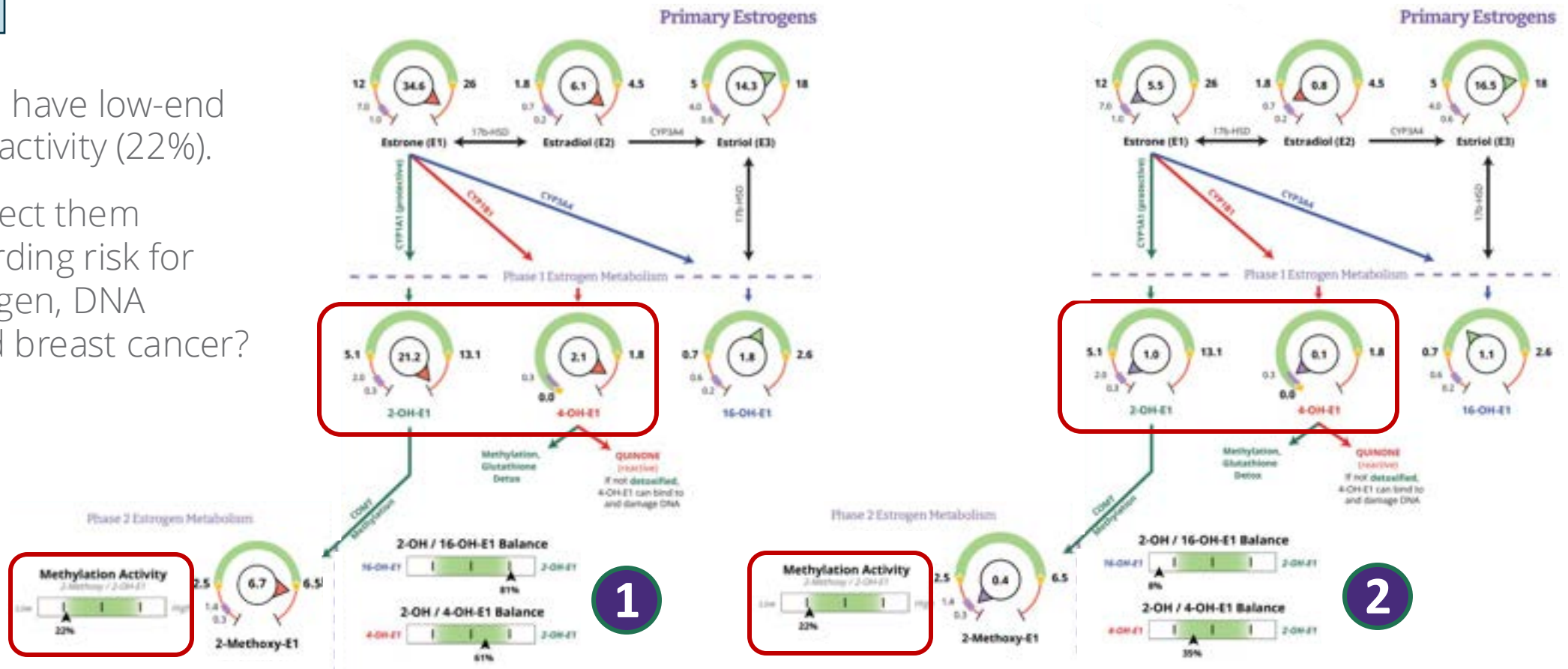
The DUTCH Dozen: 4 Methylation Activity (Phase 2)

Think about it!

Game time!

Metabolite levels matter! Methylation Activity should always be evaluated ***in conjunction with*** estrogen levels.

- Both women have low-end methylation activity (22%).
- Does this affect them equally regarding risk for excess estrogen, DNA damage, and breast cancer?

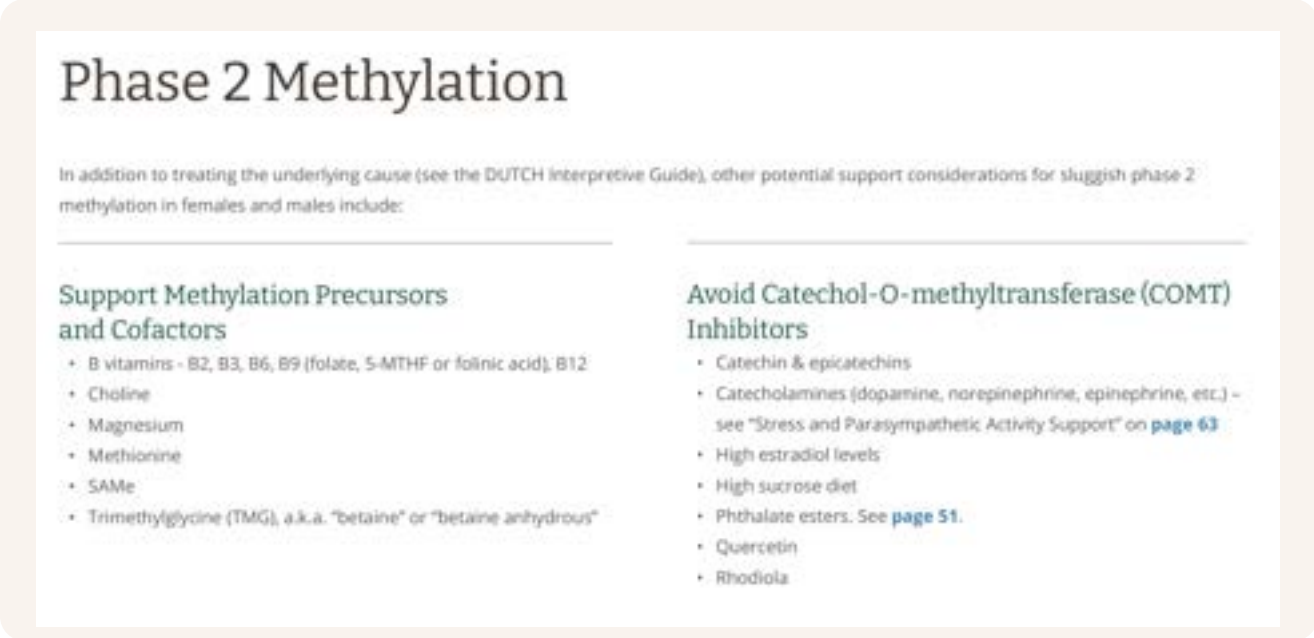


The DUTCH Treatment Guide: **Phase 2 Treatments**

Support Methylation Precursors & Cofactors
Page 30

Avoid COMT Inhibitors
Page 30

◯ Detox Support



Phase 2 Methylation

In addition to treating the underlying cause (see the DUTCH Interpretive Guide), other potential support considerations for sluggish phase 2 methylation in females and males include:

Support Methylation Precursors and Cofactors

- B vitamins - B2, B3, B6, B9 (folate, 5-MTHF or folinic acid), B12
- Choline
- Magnesium
- Methionine
- SAMe
- Trimethylglycine (TMG), a.k.a. "betaine" or "betaine anhydrous"

Avoid Catechol-O-methyltransferase (COMT) Inhibitors

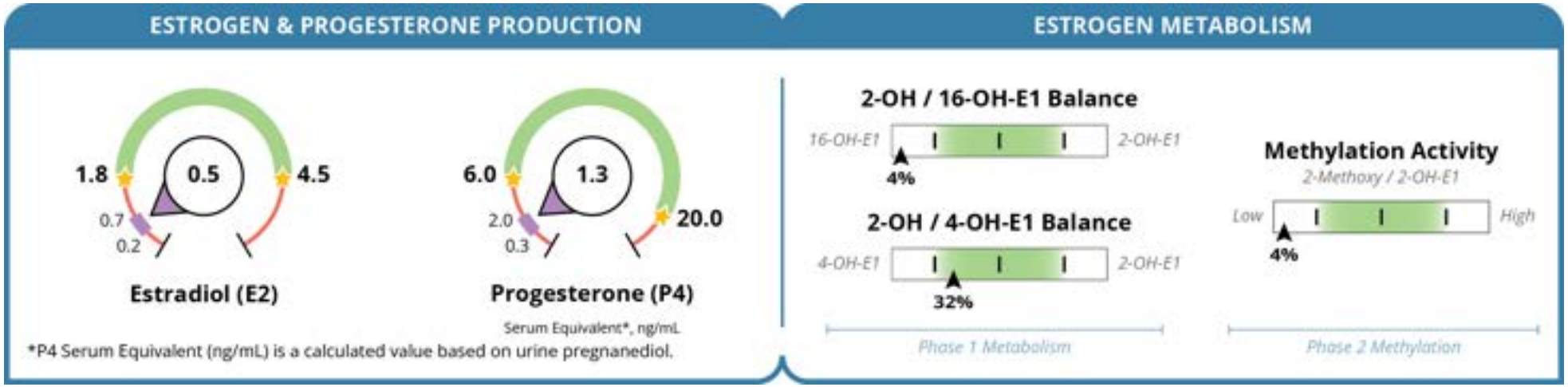
- Catechin & epicatechins
- Catecholamines (dopamine, norepinephrine, epinephrine, etc.) – see "Stress and Parasympathetic Activity Support" on page 63
- High estradiol levels
- High sucrose diet
- Phthalate esters. See page 51.
- Quercetin
- Rhodiola

Page 30 of the DUTCH Treatment Guide

Putting it All Together!

The DUTCH Dozen: Putting it all together!

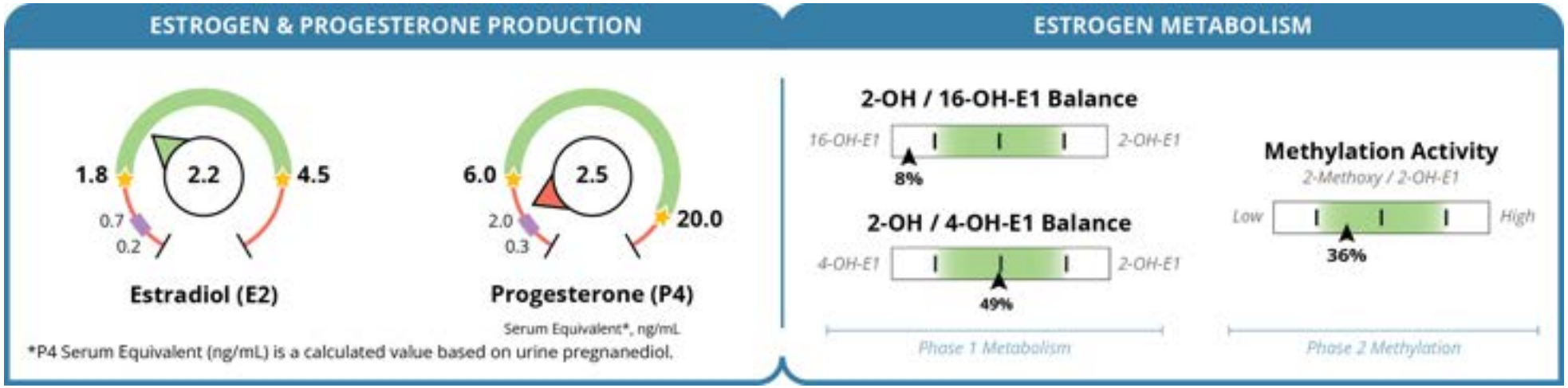
- **24-year-old female** diagnosed with Premature Ovarian Insufficiency (POI). Complains of fatigue, low libido, and stressful roommate situation (doesn't like to be home). BMI 21.3.



- Would her low 2/16 balance be more significant if her estrogen was within the luteal range?
- What if this was the result of a woman on a combination oral contraceptive pill? Does she need bioidentical estrogen therapy?

The DUTCH Dozen: Putting it all together!

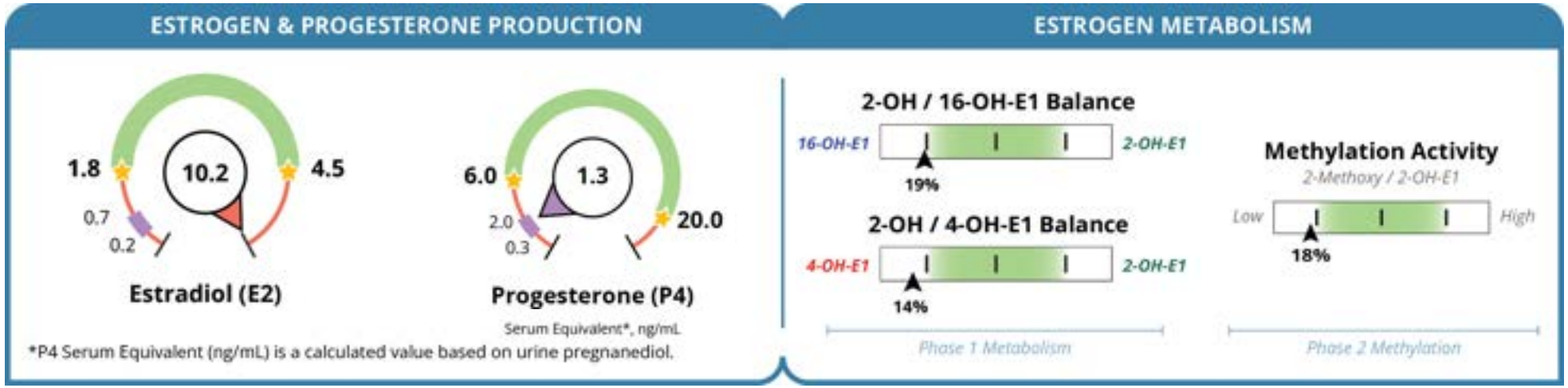
- **29-year-old female** diagnosed with PCOS. Complains of irregular cycles, high stress, facial hair, and breast tenderness. BMI 29.3.



- Did she ovulate?
- What symptoms could be impacted (made worse) by her low 2/16 balance?

The DUTCH Dozen: Putting it all together!

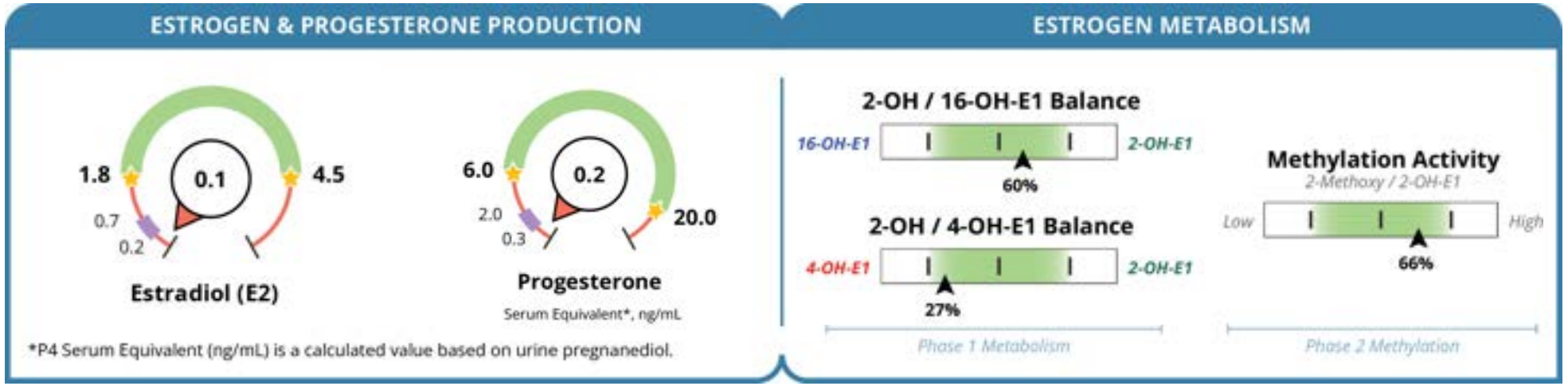
- 39-year-old female with suspected endometriosis. Complains of dysmenorrhea, heavy bleeding, and frequent night wakings. BMI 26.6.



- Why would it be important to improve her estrogen metabolism?
- What if she collected during ovulation (E2 reference range 4-12 ng/mg). Would that change your assessment and treatment plan?

The DUTCH Dozen: Putting it all together!

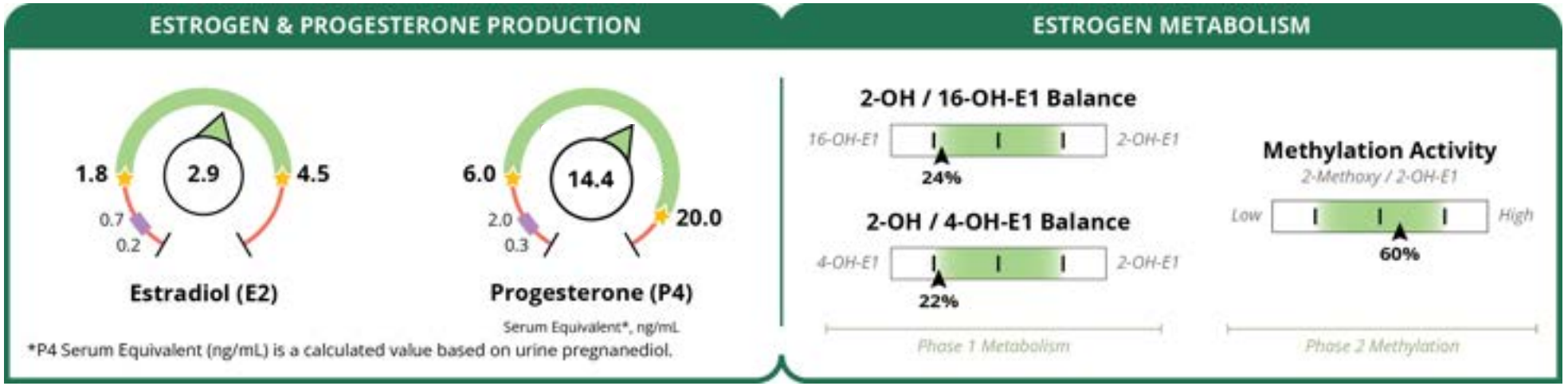
- **55-year-old PMP female** on 15 mg prednisone for the past month. She has not been able to taper below 15 mg without her ulcerative colitis flaring up. Complains of hair loss, hot flashes, irritability, and sleep issues. BMI 28.1.



- Why is her E2 and P4 below the PMP range?
- Could her estrogen and progesterone levels change once she's able to come off prednisone?

The DUTCH Dozen: Putting it all together!

- **58-year-old PMP female** on 100 mg OMP, 0.075 E2 patch, 5 mg transdermal T cream, and 1.0 mg vaginal E3. Complains of acne, occasional bothersome hot flashes, and weight loss resistance. BMI 30.1.



- True or False - Her progesterone serum equivalent is within the OMP reference range – this ensures her OMP is protecting her uterus from hyperplasia and cancer.
- She is still experiencing occasional hot flashes. Would you increase her E2 patch dose?

References

References

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Thank You!

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