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The Estrogen Cost of Cancer Treatment

Evolving Care for AI and ADT-Induced Estrogen Deficiency
in Breast and Prostate Cancer Survivors, Rooted in Whole-Person Medicine

Ksenia Malarkey, ND

Integrative Oncology · Metabolic Health · Hormones

About Dr. Malarkey



Ksenia Malarkey, ND

Naturopathic Physician

Integrative Oncology
Metabolic Health & Hormones

substack.com/@integrativeoncologyinsights
dr.ksenia.malarkey@gmail.com

- **Naturopathic physician specializing in integrative oncology, metabolic health, and hormones;** integrative oncology practice since 2022, working alongside MDs, NDs, and ARNPs on complex cancer cases
- **Education:** ND, Bastyr University
- **Training:** Integrative oncology residency and chief residency, AIMS Institute (2020–2022)
- **Committee Member:** Oncology Association of Naturopathic Physicians (OncANP)
- **Publications:** co-author, "Integrative Oncology's 30-Year Anniversary: A North American Naturopathic Oncology Perspective" (Integr Cancer Ther 2023); lead author, "Triple IV Therapy (Artesunate, Ascorbate, Doxycycline) on Circulating Tumor Cells and DNA: Two Consecutive Cases" (Cancer Ther Oncol Int J 2022)

Disclosures

- **Financial Disclosures:** None
- Content reflects clinical experience and available evidence as of 2026
- Not intended to replace individualized clinical judgment
- **Questions:** welcome in the chat or during the live Q&A

What This Session Covers

- **1. The problem:** why estrogen deficiency in survivors is undertreated
- **2. Shared mechanism:** how AI and ADT both take estrogen away, in both sexes
- **3. Upstream modulators:** estrobolome, circadian signaling, liver phase I/II; our roots, and the foundation everything else sits on
- **4. Breast cancer:** arthralgia, hot flashes, bone, cardiometabolic, cognition, GSM; BCI and a case
- **5. Prostate cancer:** ADT side effects, a case, PATCH and estradiol add-back
- **6. Putting it together:** how fast it moves, what to do when, and a case that shows why

SECTION 1

The Problem

Why estrogen deficiency in cancer survivors is undertreated, and why it is our work

The Survivorship Reality

- 18+ million cancer survivors in the United States (ACS Survivorship Facts & Figures)
- Aromatase inhibitors (AI) and androgen deprivation therapy (ADT) are among the most prescribed long-term oncology therapies
- **Standard duration:** 5–10 years for most; lifelong in advanced or metastatic disease
- **Survivorship is growing —** and the downstream burden of these therapies is just beginning to be fully recognized
- The gap between what patients experience and what gets addressed is wide

Why This Falls to Us

- Oncology appointments are focused on recurrence surveillance — 15 to 30 minutes, labs, imaging
- Symptom burden is documented but rarely addressed in that context
- Only ~half complete 5 years of adjuvant endocrine therapy at full adherence; side effects are a leading driver (Hershman 2010)
- Early discontinuation is linked to higher recurrence and breast cancer-specific death (BIG 1-98; Zuo 2025); all-cause mortality signals (Hershman 2011) partly reflect healthy-adherer bias
- Naturopathic medicine is perfectly equipped to help: longer visits, systems lens, integrative toolkit

~50%

do not complete 5 years of endocrine therapy as prescribed

"I am supporting your patient's tolerance of the treatment you prescribed."

SECTION 2

Shared Mechanism

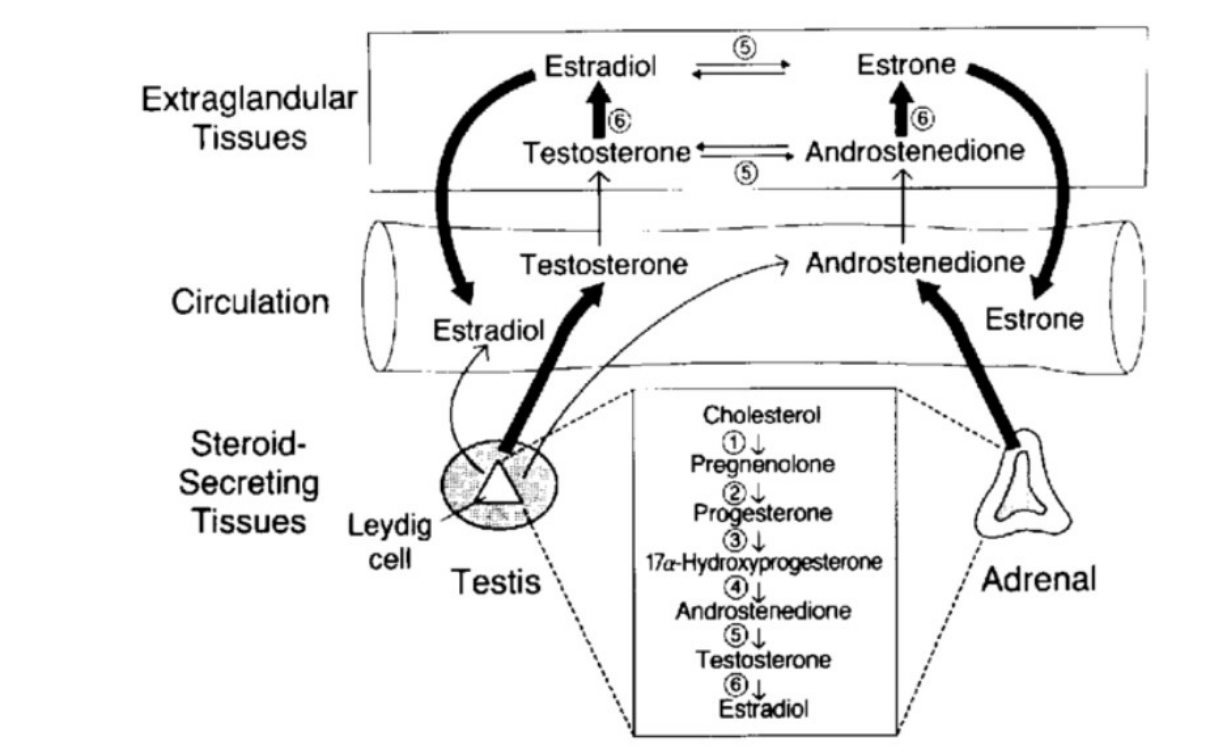
The emerging science: why estrogen is essential in both sexes, and how AI and ADT take it away

Estrogen Is Not Just a Female Hormone

- **Every body runs on estrogen:** bone, brain, heart and blood vessels, joints, and fat all have estrogen receptors, in women and men
- **Men make estrogen too:** about 80% is converted from testosterone by aromatase in fat, bone, and brain; the testes make the rest
- **So both drugs hit the same tissues:** an AI blocks estrogen directly; ADT removes testosterone, the raw material men make it from

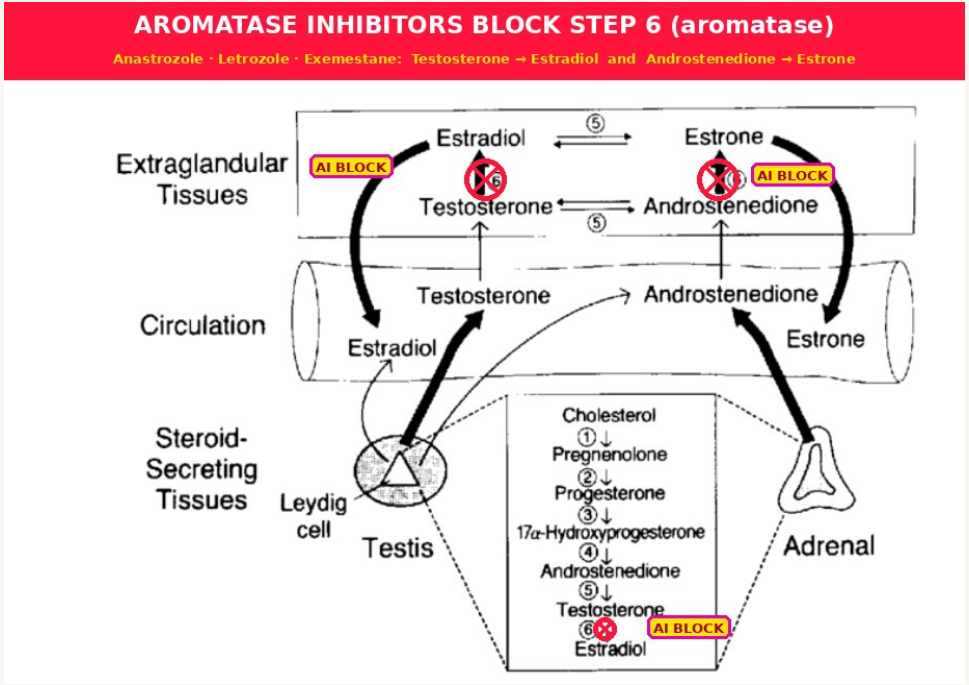
How Aromatase Inhibitor Therapy Works

- Peripheral aromatase converts androgens (androstenedione, testosterone) to estrogens



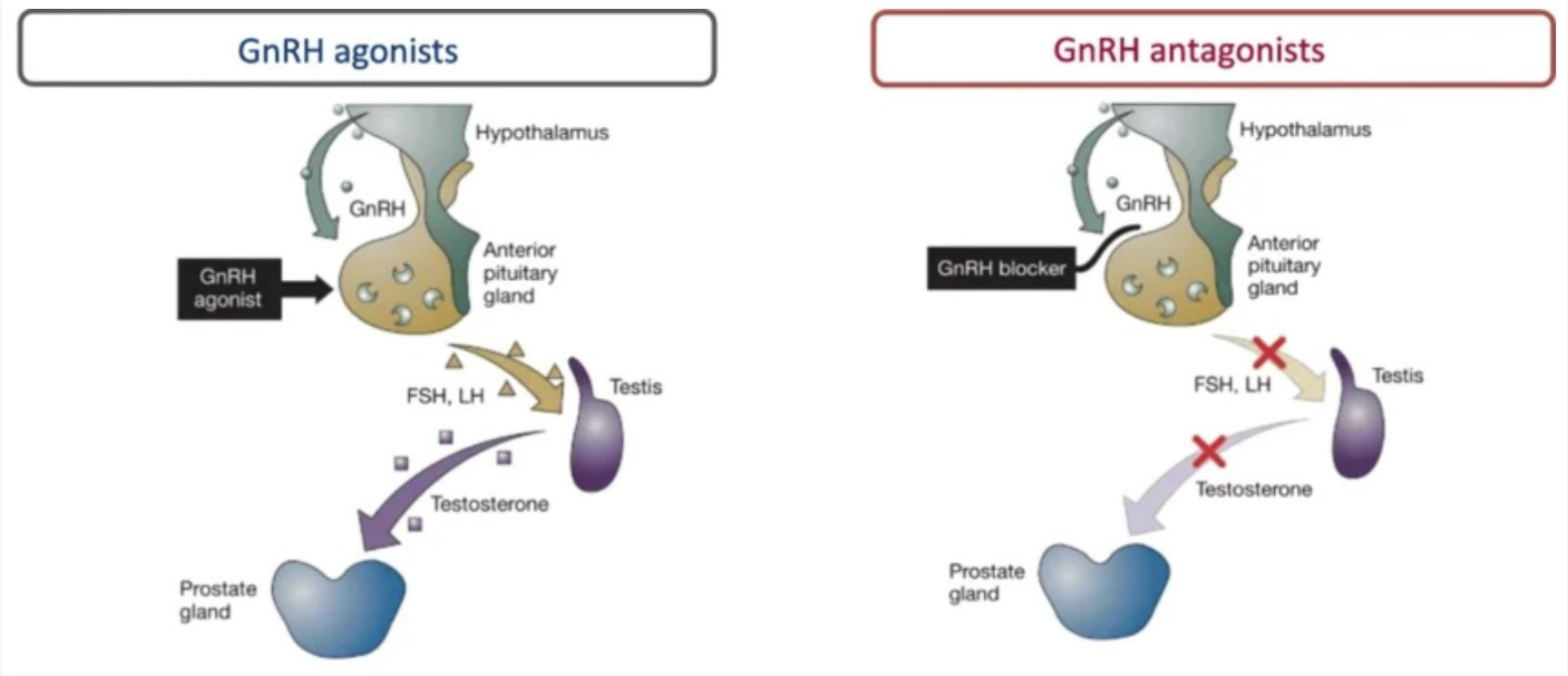
How Aromatase Inhibitor Therapy Works

- **AIs block this conversion — anastrozole, letrozole** (non-steroidal); **exemestane** (steroidal)



- **In postmenopausal women on AI:** estradiol drops to near-zero (≤5 pg/mL)
- In premenopausal women on AI plus ovarian suppression: same near-castrate estrogen levels
- The ovaries are the primary estrogen source in premenopausal women — OFS eliminates that; AI eliminates peripheral backup
- **Result:** profound, sustained estrogen deficiency for 5–10 years

How Androgen Deprivation Therapy Works



- **Agonists (leuprolide, goserelin):** initial surge in LH, FSH, and testosterone (flare) before suppression; microsurges with repeat injections

- **Antagonists (degarelix, relugolix):** immediate suppression of LH, FSH, and testosterone; no flare or microsurges

Figure: Mechanism of action of GnRH agonist and antagonist (ResearchGate)

How ADT Works: Why Estrogen Falls Too

- **Goal:** shut down testosterone to castrate levels (<50 ng/dL; many guidelines now aim for <20)
- Remove the testosterone and you remove the raw material, so estradiol falls with it (numbers on the next slide)
- **Abiraterone goes further:** it also shuts down adrenal androgens, the last raw material, so E2 drops even lower; **enzalutamide**, **apalutamide**, and **darolutamide** block the receptor and don't
- Estrogen loss drives hot flashes, bone loss, and fat gain; testosterone loss drives muscle and strength loss; both drive sexual function (Finkelstein 2013)

The dominant clinical framing of ADT is testosterone loss. But testosterone is not the tissue that gets arthritis, loses bone, or has hot flashes. The tissue that does that needs estrogen.

How Low Is Too Low? Estradiol Reference Points

Men: Normal Range	Postmenopausal Baseline	Clinical Reality
20–40 pg/mL	**< 20 pg/mL**	**Trend matters**
On ADT: **< 10 pg/mL**	Often < 10 by LC-MS/MS. On AI: **< 5 pg/mL**	A single value is a snapshot. **Serial measurement is the tool.**

Use a sensitive estradiol assay (LC-MS/MS preferred; avoid immunoassay in the low-estrogen range). Draw in the morning (7–10 am) and at the same time for every repeat. On vaginal estrogen, draw before the next dose. Postmenopausal women: there is little daily variation, so consistent timing matters more than the exact hour.

Estradiol levels alone do not capture tissue-level estrogen activity. Clinical picture always takes precedence.

The Estrogen Deficiency Syndrome: Shared Consequences

Iatrogenic estrogen deficiency: a predictable syndrome, not a random side effect. AI and ADT produce the same constellation:

Bone	Joints	Cardiovascular	Brain	Sexual Health
Accelerated resorption Fracture risk	Synovial inflammation Arthralgia	Dyslipidemia Endothelial dysfunction	Verbal memory Mood & processing speed	Libido Genital atrophy & pain

These consequences are not unique to one sex or one drug class. Treating them is part of cancer care.

Assessment Baseline: What to Measure

- **Hormonal panel:** Estradiol and total testosterone by LC-MS/MS; free T by equilibrium dialysis or calculated; SHBG; DHEA-S
- **Bone:** DXA at baseline if not done within 12 months; FRAX score
- **Cardiometabolic:** Lipid panel with ApoB and Lp(a), fasting insulin, HOMA-IR, hsCRP, homocysteine; 25-OH **vitamin D** (relevant to arthralgia, bone, and cognitive changes)
- **Neurocognitive:** MoCA or similar validated screen; sleep quality assessment
- **Sexual function:** PROMIS Sexual Function or equivalent validated tool; symptom-specific inquiry
- **Genetics when available:** APOE (cardiometabolic and cognitive risk; clinical testing enters the medical record and can affect life, disability, and long-term care insurance, so discuss first), MTHFR, CYP1B1

SECTION 3

Upstream Modulators

Our roots, tolle causam: estrobolome, circadian signaling, and liver phase I/II, and where women and men differ

Upstream Work: Why It Must Come First

- Upstream modulators are not add-ons; they are the foundation that the breast and prostate protocols build on
- A patient on AI or ADT with significant dysbiosis, poor diet, and chronic sleep disruption will have a partial and unpredictable response to targeted supplements
- Assess gut health and sleep quality before building a supplement protocol; in my experience they explain much of why the same protocol works for one patient and not another

The Estrobolome: Mechanism and Interventions

How It Works

- **1. The liver packages estrogen for disposal:** it attaches glucuronic acid and sends it to the gut in bile
- **2. Some gut bacteria unpack it:** their β-glucuronidase cuts the package open, and the freed estrogen is reabsorbed instead of leaving in stool. These bacteria are the estrobolome (Plottel & Blaser 2011; Kwa 2016)
- **3. More β-glucuronidase, more estrogen back in circulation:** matters most when estrogen is present (**tamoxifen**, premenopausal, after an AI ends)
- **4. It varies by patient:** chemo, antibiotics, and low-fiber diets shift which bacteria dominate

Assessment and Interventions

- **Assessment:** stool β-glucuronidase alone (Doctor's Data), or within a full panel (GI-MAP, GI Effects) if GI symptoms or recent antibiotics; low isn't automatically good
- **Fiber 25–35 g/day:** the best-supported lever; raises diversity and lowers β-glucuronidase
- **Fermented foods:** support Lactobacillus species linked to favorable estrogen metabolism
- **Calcium D-glucarate:** β-glucuronidase inhibitor; for high activity or constipation; no human data in men on ADT
- **Probiotics:** L. acidophilus, B. longum lower fecal β-glucuronidase in small older studies; no survivor outcome data
- Fix the gut before adding more hormonal interventions

Circadian Signaling and Estrogen: Why and How

Why It Matters

- **Melatonin** and estrogen metabolism are linked through clock gene regulation
- Circadian disruption suppresses **melatonin**, impairs estrogen clearance, and alters aromatase expression
- Night shift work is an IARC Group 2A probable carcinogen, with **melatonin** suppression a proposed mechanism
- Hot flashes wake patients on AI and ADT repeatedly, so disruption becomes chronic and self-reinforcing, compounding cognitive and metabolic effects
- Fix circadian alignment first and downstream interventions work better

Protocol

- **Morning light:** 10–30 minutes outdoors within 30 minutes of waking
- **Evening:** reduce blue light after 7–8 pm; filters or blue-blocking glasses
- **Melatonin:** 0.5–1 mg, 30 minutes before sleep; timing matters more than dose, and 10 mg is pharmacologic, not physiologic
- **Meal timing:** 10–12 hour eating window for circadian and cardiometabolic benefit
- **Sleep architecture:** treat hot flashes; they fragment deep and REM sleep

Liver Phase I/II Detoxification and Estrogen Clearance

- **Phase I hydroxylation:** CYP1A1/1A2 → 2-OH; CYP1B1 → 4-OH; CYP3A4 → 16α-OH
- **2-OH estrone:** considered favorable; less estrogenic, anti-proliferative
- **4-OH estrone:** potentially mutagenic via quinone formation; less favorable in estrogen-sensitive cancer
- **16α-OH estrone:** more estrogenic; associated with higher estrogen load
- **DIM and I3C:** shift metabolism toward 2-OH and raise SHBG; individualize. Fits higher estrogen load or 4-OH/16-OH dominance; adds little when E2 is already at the floor; lowers **tamoxifen** metabolites including endoxifen (Thomson 2017)
- **Phase II clears what phase I makes:** methylation, glucuronidation, sulfonation, glutathione; food first, then nutrients (detailed with the breast case)
- **Sulforaphane:** NRF2 activation → phase II upregulation; from cruciferous vegetables, **broccoli sprouts**, or supplements
- **Practical:** Two to three servings of cruciferous vegetables daily is the foundation; supplements are an add-on, not a replacement

Upstream Summary: Same Foundation, Different Targets

Domain	Foundation for Both	Women on AI or Tamoxifen	Men on ADT
Gut / Estrobolome	Fiber 25–35 g/day, fermented foods, targeted **probiotics**; rebuild after chemo and antibiotics; bowel regularity	Estrogen recirculation matters most with **tamoxifen**, premenopausal OFS, obesity, or after AI ends; on an AI little estrogen is left to recirculate. **Calcium D-glucarate** if β-glucuronidase is high	At castrate E2 the gut story is androgens: ADT expands bacteria that make androgens from precursors, linked to castration resistance (Pernigoni 2021); **abiraterone** reshapes the microbiome (Daisley 2020); after pelvic radiation, build fiber slowly
Circadian / Sleep	Morning light; **melatonin** 0.5–1 mg; consistent sleep window; TRE; treat hot flashes	Hot flashes are the main sleep breaker; sleep apnea rises after menopause and often presents as insomnia or fatigue, so it gets missed	Nocturia (BPH, radiation) is a second sleep breaker; sleep apnea is more common and ADT weight gain raises it, so screen (STOP-BANG); with TRE, protect protein against ADT muscle loss
Liver Phase I/II	Cruciferous vegetables, **sulforaphane**, methylation nutrients; **DIM** only when testing supports it; watch for fatty liver	Individualize **DIM**; it lowers endoxifen on **tamoxifen** (Thomson 2017). On **tamoxifen**, avoid strong CYP2D6 inhibitors	Estrogen metabolite work is mostly moot at castrate E2; **DIM** showed no prostate tissue effect (Gee 2016). On **tE2** patches, estradiol is the treatment: skip agents that speed its clearance. **Enzalutamide** and **apalutamide** are strong CYP3A4 inducers, **abiraterone** a CYP2D6 inhibitor: check every supplement

Assess gut and sleep before building a supplement protocol. Same foundation for women and men; the targets differ.

SECTION 4

Breast Cancer

AI-induced estrogen deficiency: advanced diagnostics and whole-person protocols across every domain

Who Is on an Aromatase Inhibitor?

- **Postmenopausal HR+ breast cancer:** standard adjuvant therapy, typically 5–10 years
- **Premenopausal women:** ovarian function suppression (OFS) plus AI is increasingly preferred over **tamoxifen** alone for high-risk disease
- HR+ disease accounts for roughly 70% of breast cancers, so AI users are one of the largest long-term survivorship populations (ACS Breast Cancer Facts & Figures)
- AIs are used in metastatic HR+ disease and as chemoprevention in high-risk postmenopausal women: atypical hyperplasia, LCIS, prior DCIS, strong family history, BRCA2 carriers
- Duration and depth of estrogen suppression are what drive the side effect burden — not just the drug choice

The Three Aromatase Inhibitors: What Matters Clinically

- **Anastrozole and letrozole (non-steroidal):** block the aromatase enzyme while the drug is present; both drive estradiol to near zero in postmenopausal women
- **Exemestane (steroidal):** permanently disables the aromatase enzyme; one of its breakdown products acts as a weak androgen, which in theory may be slightly gentler on bone, though in trials side effects look similar across all three
- **Clinical relevance:** Class effects are shared; all three produce profound (>95%) estrogen suppression
- **Individual tolerability differs:** switching within class is evidence-based for AI-associated arthralgia (ATOLL)
- Patient-level factors (**Vit D** status, baseline joint health, genetics) modify symptom severity more than drug choice

AI-Induced Arthralgia: The Most Common Reason Patients Quit

- **Prevalence:** up to half of patients on AI (Crew 2007: 47%); up to 20% stop AI because of it (Niravath 2013)
- Bilateral, symmetric, small joints; morning stiffness; worsens over first 3–6 months
- Central sensitization component in a subset — pain disproportionate to inflammation markers

Arthralgia is the leading reason women stop their AI, and it is one of the most treatable.

AI-Induced Arthralgia: First-Line Interventions

- **Exercise:** 150 min/week aerobic plus twice-weekly strength training cut worst joint pain 29% vs a 3% rise with usual care (HOPE); recommend first
- **Acupuncture:** Best RCT evidence of any integrative intervention for AIIA (SWOG S1200); clinically meaningful pain reduction vs sham and waitlist; 6-week course as initial trial
- **Vitamin D:** Replete deficiency first; low **Vit D** is associated with worse AIIA, but a 30,000 IU/week RCT missed its primary endpoint (Khan 2017); 60–80 ng/mL is my clinical target, not trial-derived
- **Duloxetine:** Modest benefit vs placebo (SWOG S1202); useful with central sensitization, mood, or sleep disruption; moderate CYP2D6 inhibitor, so caution with **tamoxifen**
- **Switch AI agent:** Most patients tolerate a within-class switch (ATOLL); try before abandoning therapy
- **Alternate dosing: exemestane** 25 mg 3x/week matched daily estradiol suppression (Serrano 2023); **letrozole** Mon/Wed/Fri, even 0.25 mg, matched daily (López 2016). Side effects were similar and there is no recurrence data yet.
- **Planned breaks:** 3-month yearly breaks in extended **letrozole** gave similar 5-year disease-free survival (85.8% vs 87.5%) but no fewer side effects (SOLE)

AI-Induced Arthralgia: Botanicals & Supplements

Targeted: Act on the Pain Mechanism

- **PEA (palmitoylethanolamide):** PPAR-α and mast cell mechanism; strong safety profile; evidence in chronic musculoskeletal pain
- **Boswellia serrata:** 5-LOX inhibition; best-evidenced botanical for joint pain; choose an **AKBA-enriched extract (e.g., 20–30% AKBA)**; most generic products standardize to total boswellic acids with far less AKBA
- **LDN (low-dose naltrexone):** glial modulation, endogenous opioid upregulation; useful when central sensitization is suspected
- **Cannabis / CBD:** modest evidence in cancer-related pain; always check CYP interactions before recommending (**CBD**: primarily 2C19 and 3A4; THC: 2C9 and 3A4)

Supportive: Low-Risk Add-Ons and Contributing Factors

- **Omega-3 fatty acids:** 3.3 g/day did NOT beat placebo in SWOG S0927 (both arms improved); reasonable only as a low-risk add-on
- **Bromelain:** prostaglandin pathway; caution with anticoagulants
- **MSM (methylsulfonylmethane):** modest OA data; safe, inexpensive add-on; low-risk for motivated patients
- **Magnesium:** sleep and pain perception; IV form for short-term relief in refractory cases
- **Alpha-lipoic acid:** better suited to neuropathic overlay than pure joint pain
- **Vitamin B12 (methylcobalamin):** only if deficient or neuropathic component is present

AI-Induced Arthralgia: Refractory and Procedural Options

- **Ketamine infusions:** For centrally sensitized, refractory cases only; refer to a pain management specialist; document rationale clearly
- **IV nutrients:** Empirical; limited AIIA-specific data; selective use in highly motivated patients with significant symptom burden; Myers' cocktail most commonly used
- **When to refer:**
- **Rheumatology:** if inflammatory arthritis cannot be excluded or if joint damage is progressing
- **Pain management:** for central sensitization patterns, refractory pain, or when **ketamine** or nerve blocks are being considered
- **Documentation tip:** Frame all referrals as supporting AI tolerance — this keeps oncology aligned with the goal

AI Therapy and Bone Loss

- **AI-induced bone loss:** **roughly double** the natural postmenopausal rate; **anastrozole** lost ~6% lumbar spine and ~7% hip BMD over 5 years in ATAC
- Fracture rates are higher on AI than **tamoxifen**; adjuvant **denosumab** halved clinical fractures in ABCSG-18
- Estrogen is essential for osteoblast activity and osteoclast suppression; AI removes both signals
- Bone loss is most rapid in the first 2 years of therapy; fracture risk accumulates over the treatment course and is amplified in women with pre-existing low bone density
- **Assessment:** DXA at baseline (lumbar spine and hip) and annually or every 2 years depending on risk
- FRAX score to estimate 10-year fracture probability; incorporate AI use as a risk factor
- Bone turnover markers (CTX, P1NP) can monitor treatment response between DXA scans

Bone Protocol: AI Patients

Foundation

- **Exercise specificity:** Ground reaction force >1.5x body weight is the osteogenic stimulus — loaded resistance training, stair climbing, jumping; cycling and swimming do not qualify; aim 2-3x/week
- **Calcium:** Dietary first (1200 mg/day total); supplement only the gap; avoid large bolus doses — split if supplementing
- **Vitamin D:** Target 60–80 ng/mL; recheck 3 months post-initiation
- **Vitamin K2 (MK-7):** 100–200 mcg/day; carboxylates osteocalcin and matrix Gla protein; reasonable pairing with calcium + **Vit D**, though fracture data are mixed
- **Protein adequacy:** 1.2–1.6 g/kg/day — bone is collagen; women on AI commonly under-eat protein during fatigue; inadequate protein blunts every other intervention

Targeted Additions

- **Magnesium glycinate:** 300–400 mg nightly; cofactor for osteocalcin and bone matrix formation; does double duty on sleep and muscle tension on AI
- **Boron:** 3 mg/day; reduces urinary calcium excretion and enhances **Vit D** utilization; safe, inexpensive, underused
- **Collagen peptides:** 5 g/day raised spine and femoral neck BMD vs placebo over 12 months (König 2018); 5–10 g/day
- **Melatonin:** Osteoblast-stimulating effect in preclinical and small human studies; bone remodeling is circadian; relevant in women already using it for VMS-disrupted sleep
- **Omega-3 (EPA/DHA):** 2–3 g/day; RANKL suppression shown mainly in preclinical work; often already indicated for cardiometabolic risk
- **When to refer:** osteoporosis or high FRAX: **bisphosphonate** or **denosumab** conversation with oncology or PCP (ASCO bone guideline); many AI-specific algorithms act earlier, at T-score below −2.0

AI Therapy and Cardiometabolic Risk

- **Estrogen loss accelerates:** LDL rise, HDL decline, visceral fat accumulation, and insulin resistance
- AI users show higher rates of metabolic syndrome compared to **tamoxifen** users in observational data
- Endothelial dysfunction and increased arterial stiffness documented within months of starting AI
- Cardiac risk is often missed because oncology does not routinely follow lipids in this population
- Premenopausal women on OFS plus AI face a longer window of cardiometabolic exposure than postmenopausal women
- **This is what you all do best:** the gap between oncology visits is where modifiable risk accumulates



Cardiometabolic Protocol: AI Patients

Dietary & Lifestyle

- **Mediterranean dietary pattern:** strongest cardiometabolic evidence in cancer survivors
- **Attention to glycemic load:** insulin resistance is often the primary driver of metabolic shift
- Cardiorespiratory fitness as independent cardiac risk modifier: aerobic exercise 150 min/week
- **Omega-3 (EPA+DHA):** 2–4 g/day; triglyceride lowering, anti-inflammatory
- **CoQ10:** mitochondrial support; modest LDL-oxidation data; especially relevant if **statin** co-prescribed
- **Plant sterols/stanols:** LDL reduction 7–10%; evidence-based; add to food or supplement

Targeted Supplements

- **Red yeast rice (monacolin K):** **statin**-equivalent mechanism; myopathy and rhabdomyolysis risk mirrors **statins**; monitor LFTs and CPK; variable monacolin K content across products; CYP3A4 drug interactions apply
- **Berberine:** AMPK activation; lipid plus insulin data; emerging as a meaningful metabolic agent
- **Magnesium:** insulin sensitivity, blood pressure, cardiometabolic risk reduction
- **B vitamins (B6, B9, B12):** homocysteine reduction; check methylation genetics

AI Therapy and Cognitive Function

- **Not chemo brain:** it shows up in women who never had chemo, because it tracks with estrogen loss in the brain's memory centers
- **Controlled data are mixed:** verbal memory and processing speed are the domains most often implicated, yet **anastrozole** showed no effect vs placebo in IBIS-II
- Estrogen depletion plus sleep disruption plus mood effects compounds the clinical picture
- **Often blamed on aging or anxiety:** sort it out with validated tools: MoCA (10-minute objective test), FACT-Cog (patient-reported, built for cancer), and PHQ-9 / GAD-7 for mood and anxiety
- The patient who says "I can't find words" or "I can't think" on AI is describing a real neuroendocrine effect
- APOE4 carriers may be particularly vulnerable; worth identifying early

Neurocognitive Protocol: AI Patients

Primary Interventions

- **Sleep:** address first — nothing else performs well on a broken sleep architecture; assess formally
- **Exercise (aerobic + resistance):** most robust intervention across cognitive domains; aerobic training 3x/week grew hippocampal volume 2% with BDNF rise in an RCT (Erickson 2011); partially offsets estrogen-related hippocampal loss
- **Omega-3 DHA:** structural support for neural membranes; 1–2 g/day
- **Vitamin D:** cognitive function association; replete if deficient; target 60–80 ng/mL

Targeted Support

- **Lion's mane:** NGF stimulation; emerging data; reasonable risk-benefit
- **Acetyl-L-carnitine:** mitochondrial support; some evidence for chemo-related cognitive effects; may generalize to AI
- **Gotu kola:** cerebral circulation, anxiety overlap; historical use with some human data
- **Phosphatidylserine:** modest evidence for age-related cognitive decline; reasonable add-on
- **APOE4 carriers:** lower threshold to act; baseline and annual MoCA; tighter ApoB, BP, and insulin targets; screen for sleep apnea; aerobic exercise and MIND diet as priorities; avoid anticholinergics (including **oxybutynin** for VMS)

Sexual Health: Genitourinary Syndrome with AI

Clinical Context + Lubricants

- **GSM:** vaginal dryness, dyspareunia, urge incontinence, recurrent UTIs; nearly universal on AI; severely undertreated
- **Start non-hormonal, scaled to severity:** lubricants for sex, moisturizers for daily comfort; most patients need both
- **Lubricants:** water-based (Pre-Seed, Slippery Stuff) or silicone-based (Astroglide X, Pjur), which last longest
- **Choose gentle formulas:** low-osmolality; glycerin-, paraben-, and fragrance-free; no warming or tingling types
- **Oil-based (olive, coconut):** fine for some; breaks down latex condoms
- **Moisturizers:** 2–3x/week, not just with sex; polycarbophil (**Replens**) or **hyaluronic acid** (Chen 2013)

Nutrients and Next Steps

- **Vitamin E vaginal suppository:** beat placebo on maturation index, pH, and symptoms in **tamoxifen**-treated survivors (Keshavarzi 2019); matched conjugated estrogen cream for sexual function (Golmakani 2019)
- **How to use:** 30 IU suppository (e.g., Carlson Key-E) or 400 IU gel cap, punctured and inserted; nightly, then taper to comfort
- **Vitamin D vaginal suppository:** similar benefit in the same trial
- **Pelvic floor PT and dilators:** for dyspareunia and pelvic floor guarding
- **If not enough:** vaginal DHEA or testosterone, or ultra-low-dose **vaginal estrogen** with oncology input (next slides)
- **Expect ongoing care:** GSM is chronic and returns when treatment stops

Sexual Health: Genitourinary Syndrome and Localized Estrogen

When Non-Hormonal Options Are Not Enough

- The Menopause Society (2020 GSM statement) and ASCO: low-dose **vaginal estrogen** may be considered after non-hormonal options fail, with oncology input
- **Ultra-low dose preferred: Imvexxy** 4 mcg and **Vagifem** 10 mcg; **Estring** ~7.5 mcg/day continuous release; cream at 0.5 g more commonly used
- **Women currently on AI:** small systemic E2 rise within 2–3 weeks is a theoretical concern for AI efficacy; oncology must be looped in; most will agree
- Document the conversation regardless of outcome

Absorption and Recurrence Data

- **Vagifem 10 mcg:** peak serum E2 ~5 pg/mL at first dose; stabilizes at postmenopausal baseline within 2–3 weeks
- **Imvexxy 4 mcg:** serum E2 remains consistently below 5 pg/mL
- **Estring:** transient rise at insertion, then stable in postmenopausal range
- No RCT for recurrence. Le Ray 2012 (13,479 on ET): no increased recurrence; AI subgroup too small to estimate
- Cold 2022 (Danish, 8,461): no overall increase in recurrence or mortality, BUT recurrence RR 1.39 in the AI subgroup (mortality not increased)
- Melisko 2017 (AI users, LC-MS/MS): **Estring** 7.5 mcg caused no persistent E2 rise
- HABITS: systemic MHT raised recurrence; not topical, not applicable here
- **I believe:** benefit outweighs risk in most women with significant GSM; stratify by time since diagnosis, concurrent AI use, and patient preference

Sexual Health: Vaginal Testosterone, DHEA, and Non-Hormonal Options

Agents and Rationale

- **Compounded vaginal testosterone:** Androgen receptors in vulvovaginal tissue; evidence for GSM and libido — dual mechanism; some local aromatization to E2 (discuss with oncology)
- Often preferred when patient or oncologist hesitant about **vaginal estrogen**
- **DHEA (prasterone / Intrarosa):** Converts locally to androgens and estrogens; FDA-approved for dyspareunia; serum hormone levels remain within postmenopausal range at standard dose
- **Ospemifene:** oral SERM for GSM; antiestrogenic in breast tissue. EU label (Senshio) allows use in survivors only after all treatment, including adjuvant ET, is complete; not with an AI or **tamoxifen**. US label advises against use with a history of breast cancer

Practical Dosing

- **Vaginal testosterone (compounded):** 300–500 mcg/g in a water-soluble base (hydroxypropyl cellulose or similar); 0.5–1 g applied intravaginally or to vulvar tissue 3x/week; titrate to symptom response
- Monitor total and free testosterone and sensitive E2 at 6–8 weeks; keep within female physiologic range; Witherby 2011 and Melisko 2017 (AI users) support safety; 12% had persistent E2 rise in Melisko
- **Prasterone (Intrarosa):** 6.5 mg intravaginally at bedtime (Labrie 2016); survivor data are mixed (N10C1); discuss with oncology in HR+ disease
- **Hyaluronic acid:** 1 suppository (typically 5 mg) intravaginally daily to 3x/week; OTC; safe to use without oncology sign-off; good bridge while awaiting consultation

Herbal & Nutraceutical Options for Hot Flashes: AI and Tamoxifen

Non-Estrogenic — Preferred in HR+ Context

- **Magnesium glycinate (300–400 mg/day):** Small RCT data for VMS; strong evidence for sleep architecture and anxiety — these alone justify its use; start here for essentially every patient
- **Pollen extract (120 mg/day):** Non-estrogenic; placebo-controlled RCT in menopausal women (Winther 2005); survivor-specific data are limited; option when phytoestrogen avoidance is the priority
- **Black cohosh (isopropanolic extract, 20 mg BID):** not estrogenic; small benefit in a 22-trial meta-analysis (Sadahiro 2023), rated moderate certainty by the IMS (2026); but no better than placebo in survivors (N01CC)
- **Acupuncture: Electroacupuncture** beat **gabapentin** at 24 weeks with fewer side effects in survivors (Mao 2015); integrates naturally with arthralgia management
- **Hypnosis:** 68% drop in hot flash score in survivors (Elkins 2008); self-administered audio 53% vs 41% sham (Elkins 2025); no cost, no interactions
- **CBT for hot flashes:** reduced hot flash burden in breast cancer patients (MENOS 1); pairs with any other option

ER-Active and Hormone-Modulating Herbs — Use With Context

- **Soy isoflavones (40–80 mg/day):** estrogenic (weak, SERM-like, prefers ERβ); dietary soy linked to lower recurrence (Shanghai cohort); modest, inconsistent VMS effect
- **Red clover isoflavones:** estrogenic, same isoflavone mechanism; less breast data; more caution in HR+; reasonable in prostate cancer
- **Rhapontic rhubarb extract (ERr 731):** estrogenic via ERβ, little ERα activity; RCT benefit for climacteric symptoms (Heger 2026); no survivor data, so discuss with oncology in HR+
- **Maca (gelatinized):** probably not estrogenic; helped mood and sexual symptoms without changing hormones (Brooks 2008), but one small trial reported an E2 rise (Meissner 2006); caution on an AI
- **Why it matters more on an AI:** with E2 near zero, even a weak phytoestrogen is the strongest signal left at the receptor; **tamoxifen** blocks the receptor directly
- **DIM: mostly avoid in postmenopausal women.** Not estrogenic; it shifts estrogen metabolism. It lowers already-low E2 further, may act on ERα at the floor (preclinical), and has no VMS benefit

Hot Flash Management: Pharmacological Options on an AI

SNRIs, SSRIs, and Gabapentinoids

- **Venlafaxine 37.5–75 mg/day:** best-evidenced SNRI in survivors (Loprinzi 2000); **desvenlafaxine** is an alternative; also helps mood and sleep
- **Paroxetine 7.5 mg:** the only FDA-approved non-hormonal SSRI for VMS (Simon 2013); fine on an AI, avoid with **tamoxifen**
- **Escitalopram 10–20 mg or citalopram:** reduced hot flash frequency vs placebo (MsFLASH, Freeman 2011); good fit when anxiety or low mood co-exist
- **Gabapentin 900 mg/day:** cut severity ~46–49% (Pandya 2005); dose heavier at bedtime for night sweats and sleep
- **Pregabalin 75 mg BID:** modest benefit (Loprinzi 2010); option if **gabapentin** is poorly tolerated

Other Options and Cautions

- **NK receptor antagonists: fezolinetant**, **elinzanetant**; the most targeted non-hormonal option (next slide)
- **Oxybutynin 2.5–5 mg BID:** beat placebo (ACCRU SC-1603); anticholinergic, so caution with cognitive complaints
- **Clonidine 0.1 mg/day:** modest benefit (Pandya 2000); limited by dry mouth, low BP, and rebound on stopping
- **Progestins (megestrol):** ~80% reduction (Loprinzi 1994) but generally avoided in HR+ disease; oncology's call
- **If on tamoxifen instead:** avoid strong CYP2D6 inhibitors (**paroxetine**, **fluoxetine**, **bupropion**; FDA); prefer **venlafaxine**, **desvenlafaxine**, **citalopram**, **escitalopram**

NK Receptor Antagonists for VMS: What's Available and When to Choose

The Three Options

- **NK3 selective — Fezolinetant (Veozah):** FDA-approved 2023 (SKYLIGHT 1); 45 mg/day; boxed warning Dec 2024 for rare serious liver injury: LFTs baseline, monthly x3, then months 6 and 9; contraindicated with CYP1A2 inhibitors and cirrhosis
- **NK1+NK3 dual — Elinzanetant (Lynkuet):** Approved Oct 2025 for menopausal VMS; 120 mg at bedtime (label); OASIS-4 in HR+ patients on endocrine therapy (**tamoxifen** or AI): 3.4–3.5 fewer moderate-severe episodes/day vs placebo. Label warnings: somnolence/CNS effects; transaminase elevation (LFTs baseline and 3 months)
- **NK1 selective — Aprepitant:** FDA-approved for CINV only; no controlled VMS data; not a VMS option

When to Choose Which

- **Choose fezolinetant when:** VMS is isolated without sleep or mood burden; LFTs normal; no CYP1A2 inhibitors; longest post-market experience
- **Choose elinzanetant when:** VMS plus sleep disruption or mood burden; HR+ patients on endocrine therapy (OASIS-4 was run in exactly this population; use during endocrine therapy is off-label)
- **Interactions: Elinzanetant** is a CYP3A4 substrate and inhibitor: avoid strong CYP3A4 inhibitors and strong/moderate inducers (rifampin, St. John's wort); 60 mg with moderate inhibitors
- **HR+ safety note:** Neither agent is estrogenic; no CYP2D6 interaction with **tamoxifen**

CASE

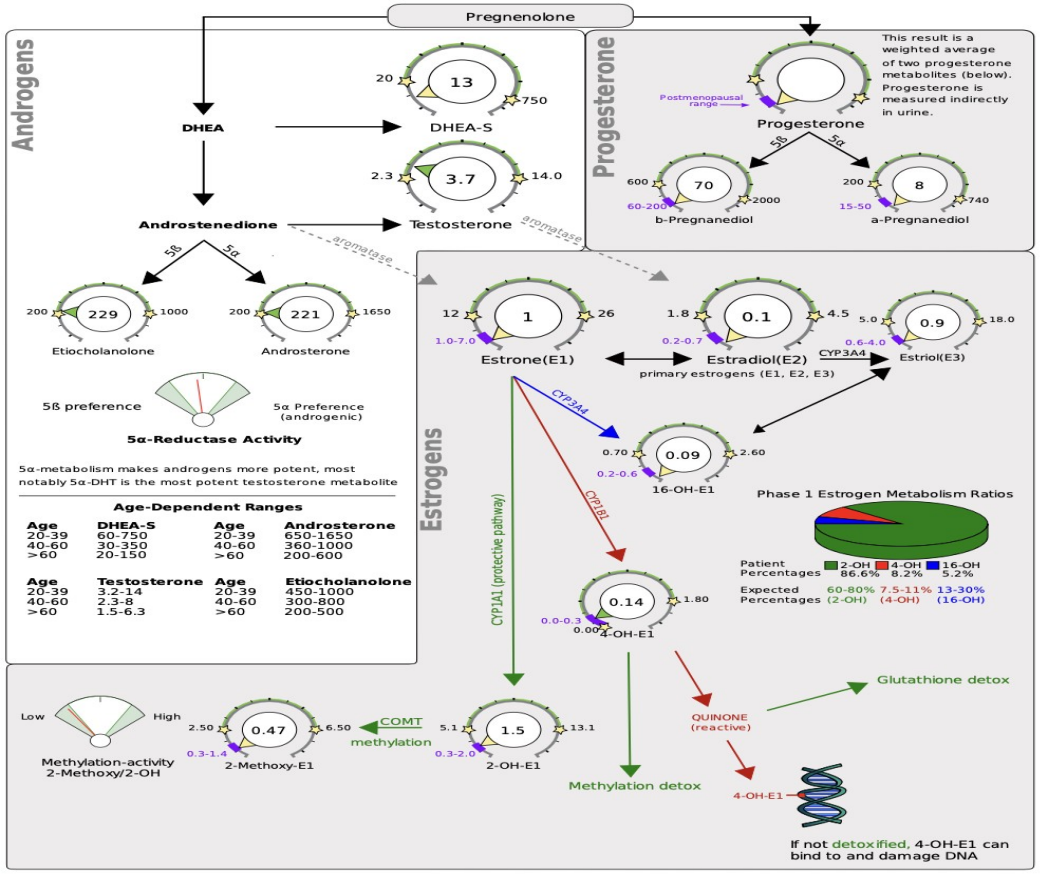
Extreme Refractory VMS in HR+ Breast Cancer: 9 Years

Background

- **66F, bilateral mastectomy 4/2017; right stage IIB (T2 N1a) grade 3 IDC ER 75% PR 75% HER2−; left stage 0 high-grade DCIS ER 99%; 4 cycles TC, post-mastectomy XRT right** Anastrozole 2017–2020, self-discontinued for insomnia; BCI: late recurrence risk 12.7%, no predicted benefit from extended ET; firmly declines further antiestrogen therapy
- **Extreme severity: several hot flashes per hour, day and night, with drenching night sweats and insomnia**; 9 years at presentation and currently untreated
- Onset 2017, triggered by abruptly stopping her highest-dose estradiol patch at diagnosis, then **anastrozole** on top
- **Failed pharmacological: venlafaxine**, **clonidine**, **gabapentin**
- **Failed botanical: black cohosh**, St. John's wort, wild yam, phenylalanine
- On **DIM** for 1 year with no VMS benefit; DUTCH test ordered prior to this visit
- T1DM x 30 years (Omnipod 5 with Dexcom); BRCA1/2 negative; LDL 188 rising, stage 2 HTN, CAC 10

CASE

Refractory VMS: Hormone Metabolite Profile



What the DUTCH Showed

- **E2 = 0.1 (ref 0.2–0.7)** Estradiol below postmenopausal reference range; off **anastrozole** since 2020, so this is her own postmenopausal floor, not drug effect
- **2-OH: 86.6% of metabolite ratio (expected 60–80%)** 2-hydroxy pathway is the dominant and protective route, but here it is already above the expected ceiling with very little substrate driving it
- **4-OH: 8.2% (expected 7.5–11%)** The genotoxic hydroxylation pathway is within normal range; no evidence of elevated quinone-forming activity
- **16-OH: 5.2% (expected 13–30%)** Well below expected range — the proliferative metabolite is not a concern here
- **COMT methylation: adequate** 2-Methoxy-E1 = 0.47 (ref 0.3–1.4); methylation capacity is not the limiting factor

Estrogen Metabolism in Survivors: Support Clearance, Don't Push E2 Lower

Why Not Lower E2 Further

- **E2 is already at the floor:** on an AI, and in most postmenopausal women and men on ADT
- **The AI does the cancer work:** adding estrogen-lowering supplements brings no proven extra protection
- **Lower E2 has a cost:** worse bone loss, hot flashes, joint pain, cognition, and GSM
- **The real concern is reactive metabolites:** 4-OH catechol estrogens can form quinones that damage DNA, whatever the total amount
- **So the goal shifts:** help the body neutralize and excrete what estrogen remains (phase II), rather than suppress it

Phase II Focus: Food First, Then Nutrients

- **Methylation (COMT):** converts 2-OH and 4-OH catechols to inert methoxy forms; **folate** (**5-MTHF**), B12, B6, **riboflavin**, **magnesium**, **choline/betaine**
- **Glucuronidation (UGT):** packages estrogens for stool excretion; fiber 25–35 g/day, cruciferous vegetables, limit alcohol; **calcium D-glucarate** only if β-glucuronidase is high
- **Sulfonation (SULT):** inactivates estrogens and needs sulfur; adequate protein, allium and cruciferous vegetables
- **Glutathione conjugation:** neutralizes quinones; **sulforaphane** (**broccoli sprouts**), **NAC**, **glycine**
- Evidence is largely mechanistic; outcome data in survivors are limited. Food first, targeted nutrients second.

CASE

Extreme Refractory VMS in HR+ Breast Cancer: Protocol

Protocol

- **Stopped DIM:** E2 at the floor, 2-OH dominant, 4-OH normal — no substrate to redirect, no genotoxic signal to suppress
- **Elinzanetant (Lynkuet):** phase 3 data in HR+ patients on endocrine therapy (OASIS-4); started 60 mg x 3 weeks, then 120 mg at bedtime
- **Acupuncture**, oncology-experienced, 10 sessions over 10 weeks
- **Hypnosis** audio nightly (Elkins protocol): high compliance, no cost, no interaction
- **Magnesium glycinate** 400 mg QHS

CASE

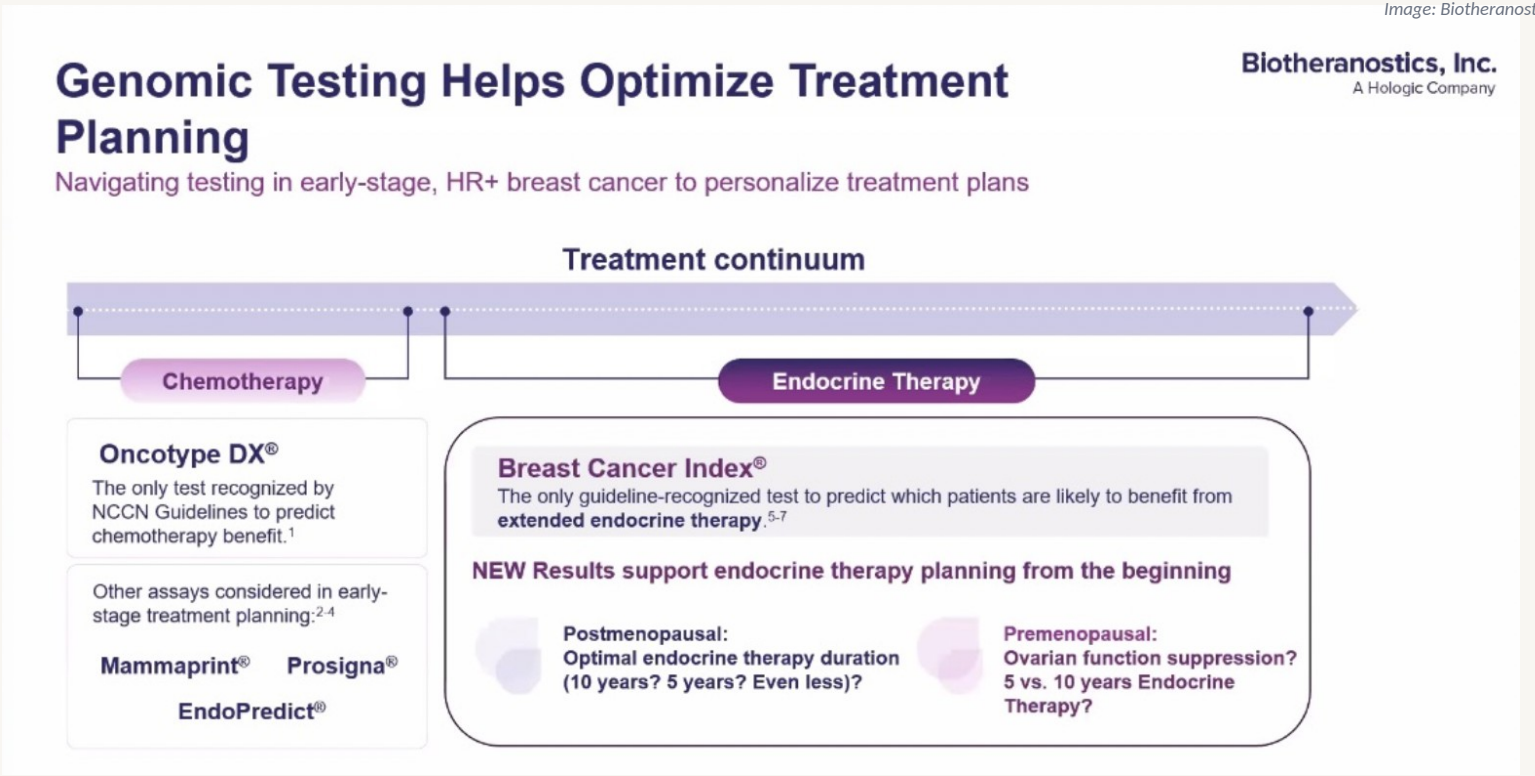
Extreme Refractory VMS in HR+ Breast Cancer: Outcome

Outcome — 1 Month

- **Hot flashes 60–70% better** Frequency and severity both improved; patient reports sleeping through the night for the first time in years
- **Dizziness first 3 weeks** Dizziness is a labeled CNS effect; resolved with slower escalation. The label starts at 120 mg with no titration; I now start at 60 mg for 3 weeks as a clinical choice
- **Remaining protocol:** **Acupuncture** started week 3 (delayed by scheduling); **hypnosis** audio compliance was high; **magnesium** unchanged
- **CV risk co-management:** **statin** conversation with PCP initiated; DEXA ordered (last 2019)

Where BCI Fits: Genomic Testing Across the Treatment Continuum

Image: Biotheranostics, Inc. (Hologic)



Oncotype DX answers "chemo or not?" BCI answers "how long, and in premenopausal women, OFS or not?"

Breast Cancer Index (BCI): Extended Endocrine Therapy Decision Tool

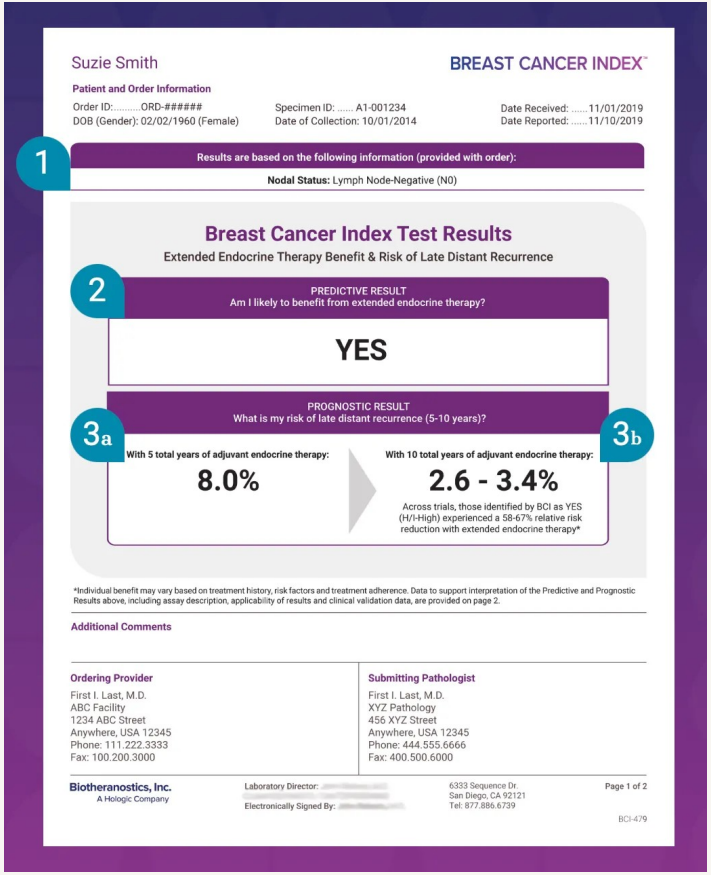
Postmenopausal

- **Full 0–10 Year Report** Overall recurrence risk (years 0–10) to guide primary adjuvant endocrine therapy; late recurrence risk (years 5–10); prediction of extended endocrine therapy (ET) benefit
- **5–10 Year Report** Late distant recurrence risk and extended ET benefit prediction for patients already on 5 years of ET; validated for late recurrence in Sgroi 2013
- **Medicare LCD covered when:** ER+ and/or PR+, HER2-, stage T1-3 pN0-N1 M0, no distant metastasis, results inform chemo or ET management

Premenopausal

- **Same two reports, plus:** the 0–10 year report informs whether to add OFS (ovarian function suppression) to primary adjuvant ET
- **Test eligibility (both):** ER+ (and/or PR+), HER2-, N0 or N1 (up to 3 nodes), T1–3 M0, non-relapsed, FFPE primary untreated invasive breast tissue
- **Clinical pearl:** A patient who stops AI because of side effects may have BCI data supporting truncation — use it to support the conversation, not bypass it

Reading a BCI Report



Suzie Smith

BREAST CANCER INDEX™

Patient and Order Information

Order ID: .....ORD-######
DOB (Gender): 02/02/1960 (Female)

Specimen ID: A1-001234
Date of Collection: 10/01/2014

Date Received: 11/01/2019
Date Reported: 11/10/2019

1

Results are based on the following information (provided with order):

Nodal Status: Lymph Node-Negative (N0)

Breast Cancer Index Test Results

Extended Endocrine Therapy Benefit & Risk of Late Distant Recurrence

2

PREDICTIVE RESULT
Am I likely to benefit from extended endocrine therapy?

YES

PROGNOSTIC RESULT
What is my risk of late distant recurrence (5-10 years)?

3a

With 5 total years of adjuvant endocrine therapy:

8.0%

3b

With 10 total years of adjuvant endocrine therapy:

2.6 - 3.4%

Across trials, those identified by BCI as YES (H/I-High) experienced a 58-67% relative risk reduction with extended endocrine therapy*

*Individual benefit may vary based on treatment history, risk factors and treatment adherence. Data to support interpretation of the Predictive and Prognostic Results above, including assay description, applicability of results and clinical validation data, are provided on page 2.

Additional Comments

Ordering Provider
First I. Last, M.D.
ABC Facility
1234 ABC Street
Anywhere, USA 12345
Phone: 111.222.3333
Fax: 100.200.3000

Submitting Pathologist
First I. Last, M.D.
XYZ Pathology
456 XYZ Street
Anywhere, USA 12345
Phone: 444.555.6666
Fax: 400.500.6000

Biotheranostics, Inc.
A Hologic Company

Laboratory Director:
Electronically Signed By:

6333 Sequence Dr.
San Diego, CA 92121
Tel: 877.886.6739

Page 1 of 2

BCI-479

Sample report, fictitious patient. Image: Biotheranostics, Inc. (Hologic)

- **1. Input:** nodal status (N0 vs N1) sets the risk model
- **2. Predictive (H/I ratio):** will extended ET help? YES or NO. This is the treatment decision
- **3a. Prognostic:** late distant recurrence risk, years 5–10, if ET stops at 5 years
- **3b. With 10 years of ET:** projected risk for YES patients. Here 8.0% drops to about 3%, roughly 5 points absolute
- **Read 2 and 3 together:** high risk + NO benefit means more years of AI won't close the gap; that is where our risk-reduction work matters most
- **Evidence:** validated in MA.17, Trans-aTTom, IDEAL; in NSABP B-42 the primary endpoint interaction was not significant, but H/I-High patients gained distant recurrence benefit after year 4

Breast Cancer Protocol Summary (1 of 2)

Domain	First Line	Add-On / Escalate	Monitor
Arthralgia	Exercise 150 min/wk + strength 2x/wk (HOPE); **acupuncture**, 6-week trial (S1200); replete **Vit D**; switch AI within class before stopping (ATOLL)	**Duloxetine** (S1202); **PEA**; AKBA-enriched **boswellia**; **LDN** if central sensitization; **omega-3** as add-on only (S0927 negative); alternate AI dosing or planned breaks are oncology's call; refer rheum/pain if refractory	Pain score; morning stiffness; **Vit D** level; ANA/RF if inflammatory features
Hot Flashes	**Acupuncture** (Mao), **hypnosis** (Elkins), **CBT** (MENOS 1); **magnesium** for sleep; **venlafaxine**, **paroxetine** 7.5 mg (AI only), or **escitalopram**; **gabapentin** 900 mg, heavier at bedtime	**Elinzanetant** 120 mg qHS if sleep/mood burden (OASIS-4) or **fezolinetant** 45 mg; **oxybutynin** (not with cognitive complaints or APOE4); **pollen extract** or **black cohosh** as adjuncts; **DIM** has no VMS benefit	Hot flash diary; sleep; LFTs: **fezolinetant** baseline, monthly x3, then 6 and 9 mo; **elinzanetant** baseline and 3 mo
Bone	Loaded resistance + impact exercise 2–3x/wk; Ca 1200 mg/day diet-first; **Vit D** 60–80 ng/mL; K2 (**MK-7**); protein 1.2–1.6 g/kg	**Collagen peptides** 5–10 g (König); **magnesium glycinate**; **boron**; **bisphosphonate** or **denosumab** for osteoporosis or high FRAX, via oncology or PCP (ASCO)	DXA at AI start, then every 1–2 years; FRAX; CTX and P1NP between scans

Breast Cancer Protocol Summary (2 of 2)

Domain	First Line	Add-On / Escalate	Monitor
Cardio-metabolic	Mediterranean diet; aerobic exercise 150 min/wk; lower glycemic load or TRE for insulin resistance; **omega-3** 2–4 g/day for triglycerides	**Berberine**; **plant sterols**; **red yeast rice** (**statin**-like risks, check LFTs/CPK); **CoQ10** if on a **statin**; **statin** via PCP if LDL/ApoB rising	ApoB, Lp(a), fasting insulin, HOMA-IR, hsCRP, homocysteine; lipids yearly
Neuro-cognitive	Treat hot flashes and sleep first; aerobic + resistance exercise (Erickson); **DHA** 1–2 g/day; replete **Vit D**	**Lion's mane**; **acetyl-L-carnitine**; **gotu kola**; **phosphatidylserine**; APOE4: act earlier, tighter vascular targets, avoid anticholinergics	MoCA at baseline and yearly; screen for sleep apnea; review anticholinergic burden
GSM / Sexual Health	Lubricants for sex; moisturizers 2–3x/wk (**hyaluronic acid**, polycarbophil); vaginal **vitamin E** or D (Keshavarzi); **pelvic floor PT** and dilators	Vaginal DHEA 6.5 mg or **vaginal testosterone**; ultra-low-dose **vaginal estrogen** with oncology input (Cold: AI caveat); systemic estrogen not advised	Symptom score or PROMIS Sexual Function; sensitive E2 if on vaginal hormones; document the oncology conversation

Across every domain: sleep and gut first; support estrogen clearance, don't push E2 lower; loop in oncology and document

SECTION 5

Prostate Cancer

ADT-induced estrogen deficiency: the overlooked mechanism, and what transdermal estradiol is teaching us

Who Is on Androgen Deprivation Therapy?

- High-risk localized, locally advanced, and metastatic prostate cancer
- Biochemical recurrence (rising PSA) post-surgery or radiation
- Duration ranges from 6 months (short-course with radiation) to lifelong in metastatic disease
- About 45% of men with prostate cancer receive ADT at some point (Gilbert 2009); among 3.5 million US survivors (ACS 2025), that is over a million men exposed, and hundreds of thousands on it at any time (Cetin 2012)
- The side effect burden scales with duration — a patient on 3-year ADT faces a different picture than one on 18 months

ADT Side Effect Burden

80–89%	19%	>50%	78–88%	42%
Hot Flashes	Fracture by 5 Years	Metabolic Syndrome	Severe ED / Loss of Libido	Gynecomastia

- **Sources:** hot flashes Vitolins 2013 and PATCH; fracture 19% vs 13% without ADT (Shahinian 2005); metabolic syndrome Braga-Basaria 2006; sexual function King 2012 (small ADT subgroup); gynecomastia any grade on LHRH agonists in PATCH
- **Cognition:** patients report it often, but controlled data are mixed; a meta-analysis found no significant association (Sun 2018). Screen and treat, but don't promise a number
- Each of these domains is treatable. Most men on ADT receive no targeted management.

Bone Loss in ADT Patients

What Happens

- **Fast loss:** 2–4% of bone density per year, steepest in year one
- **Fractures:** 19% vs 13% by 5 years without ADT (Shahinian 2005)
- **Often missed:** baseline DXA is frequently never ordered
- **Falls:** most fractures follow a fall; hot flashes and nocturia wake these men at night

What We Do

- **Load the bone:** resistance + impact training 2–3x/week, plus balance work
- **Build the matrix:** calcium diet-first, **Vit D** 60–80 ng/mL, K2 (**MK-7**), **magnesium**, **boron**, protein 1.2–1.6 g/kg, **collagen peptides**
- **Drug when indicated:** **denosumab** cut new vertebral fractures 62% (Smith 2009) or **zoledronic acid**, via oncology or PCP; dental check first
- **Monitor:** DXA at ADT start, then every 1–2 years; FRAX

Cardiometabolic Risk in ADT Patients

What ADT Does, and How Fast

- **12 weeks:** fasting insulin +26%, insulin sensitivity −13%, before glucose moves (Smith 2006)
- **1 year:** fat mass +9%, lean mass −3%: more fat, less muscle to clear glucose (Smith 2002)
- **Long-term:** metabolic syndrome in >50% (Braga-Basaria 2006)
- **Hard outcomes on GnRH agonists:** diabetes HR 1.44, coronary disease 1.16, sudden cardiac death 1.16 (Keating 2006); FDA label warning since 2010
- **Relugolix:** fewer cardiac events than **leuprolide** in HERO, not confirmed for **degarelix** in PRONOUNCE; worth raising, not settled

What We Do

- **Baseline before the first injection:** fasting insulin/HOMA-IR, A1c, ApoB, Lp(a), BP, waist; recheck at 3 months
- **Resistance training first:** reversed ADT muscle loss in an RCT (Galvão 2010); add aerobic
- **Food:** protein 1.2–1.6 g/kg, Mediterranean, low glycemic load; TRE only if protein holds
- **Insulin resistance:** **berberine** 500 mg BID–TID, **magnesium**, inositol; metformin + lifestyle helped in a pilot RCT (Nobes 2011)
- **Lipids:** psyllium 10 g/day, **plant sterols** 2 g/day, **omega-3** 2–4 g/day for triglycerides; **CoQ10** if on a **statin**
- **Known CAD or rising ApoB:** same-week call to cardiology; **statin** first, supplements add on (case ahead)
- **Whole load:** screen for sleep apnea, BP to goal

Hot Flashes in Men on ADT

~80% of men on ADT get hot flashes, often severe and sleep-disrupting (Vitolins 2013; 89% on LHRH agonists in PATCH)

Tested in men

- **Progestins work best: medroxyprogesterone** 20 mg/day cut hot flashes 84% vs 47% for **venlafaxine** (Irani 2010); **megestrol** 20 mg BID cut them 85%, men included (Loprinzi 1994). Oncology prescribes
- **Oxybutynin 2.5–5 mg BID:** beat placebo in men on ADT, about 7 vs 2 fewer hot flashes/day at 5 mg (A222001); avoid with cognitive complaints or urinary retention
- **Gabapentin 900 mg:** modest benefit (N00CB); lower doses no better than placebo
- **Venlafaxine and soy:** no better than placebo in men (Vitolins 2013). What works in women doesn't automatically work here

Borrowed from women's data

- **Acupuncture:** small, uncontrolled studies in men; low risk, reasonable for men avoiding another drug (Mao 2015)
- **Sleep first: melatonin** and sleep hygiene, since night sweats fragment sleep
- **Micronized progesterone:** no data in men; 300 mg qHS helped VMS and sleep in women (Prior 2012). My practice: compounded 10–25 mg oral, or 10% cream 1/8 tsp (~60 mg) to the perineum; loop in oncology
- **Stellate ganglion block:** refractory cases only; sham-controlled RCT in women (Walega 2014), no male data

Neurocognitive Effects in ADT Patients

What Happens

- **Domains hit:** verbal memory, spatial ability, executive function
- **Mixed data:** overlaps with normal aging; a meta-analysis found no significant association (Sun 2018)
- **Underreported:** men rarely raise it; partners notice first

What We Do

- **Screen:** MoCA at baseline and yearly, PHQ-9, sleep apnea (STOP-BANG)
- **Move:** aerobic + resistance exercise, the strongest lever we have
- **Sleep first:** treat hot flashes and nocturia that break sleep
- **Nutrients:** **DHA** 1–2 g/day, replete **Vit D**; **lion's mane**, **acetyl-L-carnitine**, **gotu kola** as add-ons
- **Protect:** cut anticholinergic load (including **oxybutynin**); APOE4 carriers act earlier

Sexual Health in Men on ADT

What Happens

- **Libido:** loss is near universal; testosterone and estrogen both drive desire
- **Erections:** disuse leads to smooth muscle atrophy and penile shortening
- **The couple:** partner distress is often as high as his; most men won't bring it up

What We Do

- **Ask directly, include the partner:** IIEF-5 at baseline
- **Preserve tissue:** vacuum erection device most days; **PDE5 inhibitor** (blunted at castrate T), coordinate with urology
- **Escalate:** intracavernosal injections via urology; **pelvic floor PT** for climacturia or leakage
- **Redefine intimacy:** sex therapy or couples counseling; pleasure without penetration
- **Ask oncology:** intermittent ADT preserves more sexual function in selected men

Gynecomastia on LHRH Agonist ADT

Mechanism and Timing

- **Pathophysiology:** relative estrogen excess at castrate testosterone; distinct from **tE2**-patch gynecomastia (direct estrogen effect, see **tE2** section)
- **Oncology prevention:** **tamoxifen** 20 mg/day or breast-bud radiation, ideally before starting; evidence mainly from bicalutamide monotherapy (review)
- **Timing is everything:** first 6–12 months is active, tender glandular growth that still responds to **tamoxifen**; after ~12 months it turns fibrotic and only surgery changes it
- **Our job:** ask and examine early; men rarely raise it, and a missed window is permanent

Naturopathic Considerations

- **Remove contributors:** 5-alpha reductase inhibitors (finasteride, dutasteride), spironolactone, cimetidine, opioids, **cannabis**, alcohol; estrogenic supplements (soy isoflavone concentrates, hops, red clover, dong quai, licorice); topical lavender and tea tree oil
- **Atypical picture:** check LFTs, TSH, prolactin
- **Do not lower estrogen further:** skip **DIM**, **I3C**, **chrysin**, **zinc** as an aromatase inhibitor; E2 is already <10 pg/mL and lower worsens bone, VMS, cognition
- **Tenderness:** topical **diclofenac**, compression garment, cold packs
- **Body composition:** weight loss reduces the fatty component, not the gland; chest resistance training helps contour and body image
- **Refer:** tender or growing tissue back to oncology early; surgery if established and bothersome

CASE

tE2 Patch as Primary ADT: A Physician's Case

Background

- **59M physician, locally advanced prostate cancer with bony metastases** 2018: started **Trelstar** (LHRH agonist) — hot flashes, night sweats, severe sleep deprivation, secondary depression; discontinued within weeks
- Off ADT for years; T recovered to 518 ng/dL
- PSA risen to 762 ng/mL; treatment urgently needed
- Would not tolerate conventional ADT again

Approach & Outcome (Day 29)

- **tE2:** 4 x 0.1 mg/day patches, changed twice weekly
- **Prophylactic breast irradiation:** 15 Gy (5 Gy x 3 days) before starting patches
- **PSA:** 762 → 77.4 ng/mL (89.8% reduction)
- **Testosterone:** 518 → 60 ng/dL (88.4% reduction, approaching castrate)
- No hot flashes. Normal sleep. No depression.
- **Sole side effect:** mild nipple tenderness resolved with topical **diclofenac**

The PATCH Trial: tE2 vs. LHRH Agonist in Prostate Cancer (NEJM 2026)

Study Design

- Randomized, phase 3 non-inferiority trial; Langley et al., N EJM 2026
- n = 1,360 men, locally advanced M0 PCa, 75 UK centers
- **tE2:** four 100 mcg/24h patches changed twice weekly, reduced to three if castrate at 4 weeks, INSTEAD OF LHRH agonist; estradiol as the primary ADT mechanism, not add-back
- Estradiol suppresses testosterone via HPG negative feedback without eliminating estradiol itself
- **Castrate testosterone sustained through year 1:** 85% in both arms

Outcomes

- **3-yr metastasis-free survival: tE2** 87.1% vs. LHRHa 85.9% (noninferior; HR 0.96)
- **5-yr overall survival: tE2** 81.1% vs. LHRHa 79.2% (HR 0.90)
- **Hot flashes:** 44% vs. 89% any grade; grade ≥2: 8% vs. 37%
- **Bone:** lumbar spine BMD +7.9% on **tE2** vs. −3.0% on LHRHa at 2 yr (BMD substudy)
- Metabolic parameters improved with **tE2** (PATCH programme update)
- **Cardiovascular events:** no difference, HR 1.11 (Lancet 2021)
- **Gynecomastia:** 85% vs. 42% any grade; grade ≥2: 37% vs. 9%

Managing Gynecomastia with tE2 Patch ADT

- **Expect it:** most men on **tE2** develop some breast growth (PATCH, previous slide); it is the trade-off for sparing bone and hot flashes
- **Plan before the first patch:** prophylactic breast-bud radiation works best given up front
- **The evidence:** breast-bud RT prevents gynecomastia with bicalutamide (review); not yet proven for **tE2**
- **Skip tamoxifen and DIM here:** **tamoxifen** brings hot flashes back, and blocking estrogen defeats the point of **tE2**
- **Tenderness:** topical **diclofenac** to the breast buds

The Other Option: Low-Dose Estradiol Add-Back

- **Different from PATCH:** keep the standard ADT drug and add a low-dose patch to restore normal male E2; testosterone stays suppressed. Not guideline-endorsed
- **Who:** men with severe hot flashes, bone loss, or cognitive effects who want it
- **Dose:** 0.025–0.05 mg/day patch; target E2 20–40 pg/mL
- **Monitor:** E2 and testosterone at 4–6 weeks, then every 3 months; PSA per oncology
- **With oncology:** frame it as risk reduction; PATCH cardiovascular data is supportive but indirect; document, and respect a no

ADT Protocol Summary (1 of 2)

Domain	First Line	Add-On / Escalate	Monitor
Bone	DXA at ADT start; loaded resistance + impact exercise 2–3x/wk; Ca 1200 mg/day diet-first; **Vit D** 60–80 ng/mL; K2 (**MK-7**); protein 1.2–1.6 g/kg; **magnesium glycinate**	**Collagen peptides**; **boron**; **denosumab** (Smith 2009) or **zoledronic acid** for osteoporosis or high FRAX, via oncology or PCP; dental check before starting	DXA every 1–2 years; FRAX; **Vit D**; CTX and P1NP between scans
Hot Flashes	Sleep first, **melatonin**; **acupuncture** (low risk, data mostly from women); **gabapentin** 900 mg, modest benefit in men (N00CB)	**Medroxyprogesterone** 20 mg/day via oncology, best tested option (Irani 2010); **oxybutynin** 2.5–5 mg BID (A222001); **venlafaxine** and soy no better than placebo in men (Vitolins); **stellate ganglion block** if refractory	Hot flash diary; sleep quality; night sweats
Cardio-metabolic	Mediterranean diet; aerobic 150 min/wk + resistance training; TRE; insulin resistance is the primary target	**Berberine**; **omega-3** for triglycerides; **plant sterols**; **statin** via PCP if ApoB rising; **relugolix** is an open question for oncology (HERO vs PRONOUNCE)	Fasting insulin, HOMA-IR, A1c; ApoB, Lp(a); BP; waist; baseline and every 3–6 months in year one

ADT Protocol Summary (2 of 2)

Domain	First Line	Add-On / Escalate	Monitor
Neuro-cognitive	Ask directly and include the partner; sleep first, screen for sleep apnea; aerobic exercise; **DHA**; replete **Vit D**	**Acetyl-L-carnitine**; **gotu kola**; **lion's mane**; cut anticholinergic burden; neuropsych testing if decline is significant	MoCA at baseline and yearly; mood screen (PHQ-9); partner report
Sexual Health	Ask directly; **PDE5 inhibitor** (coordinate, blunted at castrate T); vacuum erection device for tissue preservation; involve the partner	Intracavernosal therapy via urology; sexual medicine or couples counseling referral	IIEF-5 (SHIM); relationship and mood check-in
Gyneco-mastia	Ask and examine in the first 6–12 months; remove contributors (5-ARIs with urology, spironolactone, alcohol, **cannabis**, estrogenic supplements); **diclofenac**, compression	**Tamoxifen** or breast-bud RT via oncology while still active; surgery once fibrotic; skip **DIM**, **I3C**, **chrysin**	Breast exam each visit in year one; LFTs, TSH, prolactin if atypical

Across every domain: don't push E2 lower; ask directly, men won't volunteer; tE2 and E2 add-back are an oncology conversation

Key Takeaways

- AI and ADT cause a predictable, treatable estrogen deficiency syndrome in women and men
- Breast and prostate cancer share the mechanism, so the protocols overlap
- Start upstream: fix the gut and the sleep before adding the eighth supplement
- Evidence-based options exist in every domain: joints, bone, heart, brain, and sexual health
- You don’t need to be an oncologist to do this well; you need to document well and communicate clearly
- Treating side effects is cancer treatment, and this is how naturopathic medicine evolves without losing its roots

SECTION 6

Putting It Together

Prevention in practice: how fast it moves, and what to do when

When a Patient Wants to Stop

Work Through It Together

- **1. Find the driver:** ask “What’s driving this?” Usually one symptom, and usually fixable
- **2. Know their real risk:** BCI, Oncotype, stage, and years already completed
- **3. Offer real options:** treat the symptom, switch drugs, alternate dosing, planned breaks, intermittent ADT
- **4. Respect the choice:** if they still stop, it’s informed; keep caring for them

With Oncology

- Document supplements, referrals, and adherence talks, with adherence as the rationale
- “I’m seeing [patient] for [symptom] from their AI/ADT. Here is my plan; I’ve checked it against your treatment and will keep you updated.”
- Call for urgent issues; send notes for routine ones

The Treatment Timeline: How Fast It Moves, What to Do When

At the Start

Both: DXA, ApoB, fasting insulin, sensitive E2, MoCA; start loaded exercise

Women: replete Vit D; baseline joint and GSM symptoms

Men: flare cover; gynecomastia plan before the first dose

Weeks to 3 Months

Women: hot flashes surge; arthralgia builds over 3–6 months, the peak window for quitting

Men: fasting insulin +26% by 12 weeks, before glucose moves; hot flashes

Both: 3-month recheck: symptoms, insulin, lipids, adherence

3–12 Months

Women: bone loss fastest in years 1–2; GSM worsens

Men: fat +9%, lean mass −3% by 1 year; gynecomastia treatable only in months 6–12

Both: act on rising labs now, not at the next annual

Years 1–5

Women: cognition, GSM, cardiometabolic drift

Men: metabolic syndrome in >50%; diabetes and cardiac events rise

Both: DXA every 1–2 yrs; labs every 6–12 mos; MoCA yearly

Extend, Stop, After

Women: BCI informs years 5–10; off the AI, E2 returns to baseline and joints often ease

Men: intermittent ADT in selected men; testosterone can take a year or more to recover

Both: bone and heart risk outlast the drug

It moves in weeks, not years. See these patients long enough and you will see a fracture, new bone pain, a cardiac event, rapid cognitive decline.

CASE

The Signal Was in the Labs: ADT and a Cardiac Event

What Happened

- **75M, Gleason 9, post-prostatectomy,** on **relugolix**, PSA undetectable; known CAD with a prior stent
- **Also on the chart:** severe sleep apnea (AHI 47), off CPAP for months; BP above goal; no **statin**
- **Already doing a lot:** baby aspirin, irbesartan, **omega-3**, ubiquinol, hawthorn, **magnesium**, modified citrus pectin, quercetin, methylated B vitamins; hs-CRP 1.1, A1c 4.7
- **One quarter on ADT:** LDL 117 → 168, total cholesterol 199 → 260, fasting insulin 8.3 → 12.6, while A1c stayed 4.7
- **My plan:** out-of-state patient, so I couldn't prescribe; cardiology referral for a **statin**, supplements for lipids, recheck next quarter
- **Two weeks later:** chest and arm pain; troponin negative, cath found 70% LAD stenosis, new stent; EF preserved

What I Would Do Differently

- **Treat it as urgent:** a 44% LDL jump in known CAD is a same-week call to cardiology, not a referral in the plan
- **Adjuncts aren't enough:** a long, well-chosen list didn't hold his LDL; supplements add to a **statin**, they don't hold its place
- **Treat the whole load:** CPAP back on, blood pressure to goal, alongside the lipids
- **Verify "intolerance":** the chart said he failed two **statins**; family later said he may never have tried one
- **Read the trend, not the A1c:** insulin moved first
- **Relugolix is not a shield:** the antagonist with the favorable HERO signal didn't prevent this

Shameless Plugs

OncANP

Oncology Association of Naturopathic Physicians

- **Where naturopathic oncology lives:** NDs, students, and allied providers across North America, working alongside conventional oncology
- **Learn:** annual conference, lectures, webinar archive
- **Grow:** FABNO board certification in naturopathic oncology
- **Be found:** Find an ND directory for patients and referring oncologists

oncanp.org

KNOW Database

Knowledge Network for Oncology Wellness

- **What it is:** a clinical evidence database built for integrative oncology providers
- **How it works:** AI-powered, human-curated; search by diagnosis, intervention, mechanism, or the clinical question in front of you
- **Access:** included with OncANP membership, or subscribe on its own

oncanp.org/know-database

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CLINICAL TOOLS & LABS

FRAX Fracture Risk Assessment Tool.

MoCA: Montreal Cognitive Assessment.

PROMIS Sexual Function Measures.

DUTCH Hormone Metabolite Testing.

GI-MAP: stool β-glucuronidase and microbiome.

HOMA-IR Calculator (MDCalc).

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Thank You

Questions are welcome in the chat or during the live Q&A.

Dr. Ksenia Malarkey, ND

Integrative Oncology · Metabolic Health · Hormones

Substack: substack.com/@integrativeoncologyinsights

Email: dr.ksenia.malarkey@gmail.com

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Q&A

15 minutes

Please type your questions in the chat.