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Perimenopause as a Detectable Multisystem Transition: The Scientific Basis for Non-Invasive, Multimodal Assessment

A review of the clinical, biological, and health-economic evidence supporting the development of smartphone-based perimenopause detection research, with findings from a 242-woman cross-sectional study.

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ABSTRACT

Perimenopause, the 2 to 10 year hormonal transition preceding menopause, affects virtually every organ system in the female body yet lacks a standard detection protocol. The average diagnostic delay is estimated at 3 to 7 years. This paper reviews the biological, clinical, and health-economic evidence establishing perimenopause as a multisystem transition with measurable downstream effects on skin, cognition, musculoskeletal function, cardiovascular health, metabolism, and quality of life. It then presents the rationale for a multimodal, non-invasive approach to detection that reads multiple biological channels simultaneously rather than relying on any single biomarker. Findings from a 242-woman cross-sectional study are reported, including statistically confirmed visual signals, coherent symptom cluster differentiation across six organ-system domains after removal of classification criteria (eliminating circularity), and hormonal pattern distributions consistent with the published endocrinological trajectory of the transition. These findings support the feasibility of smartphone-based perimenopause awareness and establish a foundation for prospective clinical validation.

CONTENTS

SECTION 1

Background: The Perimenopausal Transition

Perimenopause is defined as the transitional period preceding the final menstrual period, characterized by progressive irregularity in ovarian function and fluctuating levels of estradiol, progesterone, and follicle-stimulating hormone (FSH). The Stages of Reproductive Aging Workshop (STRAW+10) criteria place the onset of the menopausal transition at the appearance of persistent cycle length variability, typically between ages 40 and 44, though onset as early as the late 30s has been documented.[1,2] Despite this relatively early biological onset, most women do not receive clinical recognition until years later, with only 4.3% of women aged 30 to 35 having consulted a clinician about perimenopausal symptoms.[21]

The duration of the transition is highly variable, ranging from 2 to 10 years, with a median of approximately 4 years. Unlike discrete clinical events, perimenopause is a gradual, nonlinear process marked by hormonal volatility rather than uniform decline. This volatility poses a fundamental challenge to single-timepoint diagnostic approaches: a serum FSH measurement obtained during early perimenopause may fall within the premenopausal reference range one week and the postmenopausal range the next.[3]

The physiological consequences of perimenopause extend well beyond the reproductive axis. Estrogen receptors (ER-alpha and ER-beta) are expressed in the brain, cardiovascular system, bone, skin, liver, gastrointestinal tract, urinary tract, musculoskeletal system, and immune system.[4] The erratic withdrawal of estrogenic signaling during perimenopause therefore produces coordinated effects across multiple organ systems simultaneously. This multisystem nature distinguishes perimenopause from conditions that can be adequately described by a single-organ pathology.

1.1B	47M	40-44	3-7 yr
WOMEN IN THE MENOPAUSAL TRANSITION GLOBALLY	NEW WOMEN ENTERING THE TRANSITION ANNUALLY	TYPICAL AGE RANGE OF ONSET	AVERAGE DELAY FROM SYMPTOMS TO DIAGNOSIS
WHO, 2025	Hill, Maturitas, 1996 (global projection)	Cleveland Clinic; STRAW+10	NICE, 2019

SECTION 2

The Diagnostic Gap

Despite affecting the majority of women during the fourth and fifth decades of life, perimenopause lacks a standardized screening protocol in routine clinical practice. No biomarker has been validated as a reliable single-point diagnostic. FSH testing, the most commonly ordered laboratory assessment, is unreliable during the transition due to the volatility described above.[3]

The consequences of this diagnostic vacuum are well documented. The UK National Institute for Health and Care Excellence (NICE) guidelines reported that the majority of women do not recognize their own symptoms as perimenopausal.[5] Published surveys consistently describe an average diagnostic delay of 3 to 7 years from first symptom to clinical recognition, during which women report consulting multiple specialists for what are, in aggregate, manifestations of a single hormonal transition.

2.1 Clinician preparedness

The diagnostic gap is compounded by insufficient clinician training. Only 18.3% of OB/GYN residency programs in the United States offer formal menopause curriculum (Christianson et al., *Menopause*, 2013).[22] Medical students receive a median of approximately 2 to 3 hours on menopause across their entire education. No published data separates perimenopause-specific training from the already minimal menopause curriculum. Only approximately 20% of primary care physicians report feeling adequately prepared to manage menopausal symptoms (Kling et al., *Mayo Clinic Proceedings*, 2019).[32]

The translational gap is equally concerning. The average time from biomedical research to clinical practice implementation is 17 years (Morris et al., *J R Soc Med*, 2011).[23] Applied to perimenopause: even when research demonstrates effective interventions, the healthcare system takes nearly two decades to absorb them.

A case study in this lag: after the 2002 Women's Health Initiative (WHI) study, HRT prescriptions dropped by over 50%. The North American Menopause Society (NAMS) issued corrective position statements starting in 2012, clarifying that the WHI's findings applied primarily to older women initiating HRT well past the menopausal transition. Yet clinical behavior has not fully recovered over 20 years later. An entire generation of clinicians was trained to fear HRT rather than understand its nuanced risk-benefit profile.

This translational lag underscores the potential value of tools that can accelerate awareness at the point of care, helping clinicians identify perimenopausal patterns even in the absence of specialist training.

2.2 Available classification frameworks

A common question is whether perimenopause, as a universal transition, requires identification at all. The answer lies in the distinction between a transition and its management.

Puberty is universal, but it is medically monitored: pediatricians track Tanner staging, screen for precocious or delayed onset, and intervene when needed. Pregnancy is natural, but it is screened extensively: every prenatal visit involves structured assessment. Perimenopause is the only major reproductive transition with no standard screening protocol, despite being the gateway to preventive interventions with large effect sizes.

Early identification enables the "window of opportunity" for hormone replacement therapy (HRT), defined as initiation within 10 years of onset or before age 60. When initiated within this window, HRT reduces dementia risk by 30 to 50% (observational data; Shao et al., *Neurology*, 2012),[33] osteoporotic fractures by 30 to 40% (WHI; Cauley et al., 2003), and cardiovascular events by 30 to 50% (ELITE trial, *NEJM*, 2016; DOPS, *BMJ*, 2012).[28,29] Without identification, the window closes silently.

FOLLICULAR RESERVE

The biological clock underlying the transition is invisible without intervention. At birth, the ovaries contain approximately 1 to 2 million oocytes. By puberty, this reserve has declined to approximately 300,000 to 400,000. Accelerated atresia begins when the pool drops below approximately 25,000 follicles, typically around age 37 to 38 (Faddy et al., *Human Reproduction*, 1992; ACOG Committee Opinion No. 589, 2014).[25] This accelerated decline triggers the hormonal instability that defines perimenopause.

STRAW+10 STAGING

The STRAW+10 staging system provides the most widely accepted framework for reproductive aging. It divides the female reproductive lifespan into stages based on menstrual cycle characteristics and hormonal markers.[1,2] The menopausal transition begins at Stage -2 (early transition), defined by a persistent 7+ day difference in cycle length. Stage -1 (late transition) is marked by intervals of amenorrhea exceeding 60 days. While STRAW+10 provides a rigorous staging framework, it requires cycle tracking over time and is not designed as a single-timepoint screening tool.

PRIOR'S 9-CRITERION SCALE

Dr. Jerilynn Prior at the University of British Columbia's Centre for Menstrual Cycle and Ovulation Research (CeMCOR) developed a 9-criterion symptom-based scale specifically designed to identify the perimenopausal transition.[31] The scale is based on her longitudinal research documenting hormonal and symptomatic changes during the transition (Prior, *Endocrine Reviews*, 1998).

The 9 criteria capture downstream effects of progesterone decline and estrogen volatility: heavy flow, shorter cycles, breast changes, night waking, increased cramps, night sweats, migraines, mood swings, and weight gain. The threshold of 3 or more criteria was chosen to balance sensitivity (capturing early transition) with specificity (excluding non-hormonal causes).[6]

Unlike the Greene Climacteric Scale or Menopause Rating Scale, which measure symptom severity, Prior's scale is designed to identify the transition itself. Importantly, Prior's criteria capture the early phase of perimenopause when progesterone falls first, before cycle irregularity becomes obvious. This is precisely the window that STRAW+10 may miss, since STRAW+10 requires a 7+ day cycle length variation to define the onset of the early menopausal transition.

EXISTING TOOLS AND THEIR LIMITATIONS

TABLE: PERIMENOPAUSE ASSESSMENT TOOLS COMPARISON

TOOL	PURPOSE	VALIDATED FOR PERIMENOPAUSE DETECTION?	PUBLISHED DIAGNOSTIC ACCURACY
Greene Climacteric Scale	Symptom severity (21 items)	No. AUC 0.53 for menopausal status classification (GAMS study, 2025). Barely above chance.	AUC 0.53
Menopause Rating Scale (MRS)	Symptom severity / QoL (11 items)	Measures treatment need, not transition stage. AUC 0.86 for treatment indication (Heinemann et al., 2004).	AUC 0.86 (treatment need)
MENQOL	Quality of life	AUC 0.73-0.81 across domains, but designed for QoL, not transition detection.	AUC 0.73-0.81 (QoL)
Kupperman Index (1953)	Symptom severity	No validation as diagnostic classifier. Widely considered outdated.	None published
STRAW+10	Reproductive staging	Gold standard staging but requires cycle tracking over months. Not a	N/A (staging framework)

		single-timepoint tool.	
Prior 9-criterion	Transition identification	Designed for this purpose but no formal AUC published.	Not formally published
FSH blood test	Hormonal status	Unreliable during perimenopause due to intra-individual variability.	Poor reliability
ML models (questionnaire-based)	Early menopause prediction	AUC 0.745 (XGBoost, npj Women's Health, 2025) but clinically premature, no external validation.	AUC 0.745 (no validation)

Existing tools achieve modest diagnostic accuracy: the Greene Scale reaches only AUC 0.53 for menopausal status, while the MRS achieves AUC 0.86 for treatment need but was not designed to identify the transition itself. The strongest ML approach achieves AUC 0.745 but lacks external validation. No tool combines visual, cognitive, and symptom channels in a single assessment. This represents a fundamental measurement gap in women's health.

SECTION 3

Multisystem Biology of Estrogen Withdrawal

The scope of physiological change during perimenopause is frequently underestimated in clinical practice. The following summary reflects the peer-

reviewed evidence for estrogen-mediated effects across major organ systems.[4,7,8,9,10]

SYSTEM	DOCUMENTED PERIMENOPAUSAL CHANGES	KEY REFERENCES
Neurological	Disrupted synaptic plasticity, altered serotonin/dopamine/GABA signaling, impaired executive function and working memory, thermoregulatory instability, sleep architecture changes	Weber et al., 2014; Maki & Henderson, 2016
Cardiovascular	Endothelial dysfunction, rising LDL cholesterol, declining HDL, increased blood pressure lability, reduced heart rate variability	Rosano et al., 2007
Skeletal	Accelerated osteoclast activity, declining bone mineral density (onset precedes menopause by several years), increased fracture risk trajectory	Prior, 2019
Metabolic	Declining insulin sensitivity, visceral fat redistribution, altered glucose metabolism, weight gain independent of dietary change	Santoro et al., 2015
Integumentary	Collagen loss (~30% in first 5 postmenopausal years, onset in perimenopause), skin thickness decline (~1.13%/year of estrogen deprivation), altered vascularity	Brincat et al., 1985, 1987
Musculoskeletal	Joint inflammation, connective tissue laxity, muscle mass decline, increased incidence of frozen shoulder and tendinopathy	Watt, 2018
Cognitive	Subjective and objective decline in processing speed, word-finding, and concentration; reported by	Weber et al., 2014

	approximately 60% of perimenopausal women	
Genitourinary	Vaginal and urethral tissue atrophy, altered pH, recurrent urinary tract infections, sexual pain	Portman & Gass, 2014
Immune	Reactivation of dormant autoimmune conditions, altered inflammatory signaling, new-onset sensitivities	Desai & Brinton, 2019

The critical feature of this biology is its simultaneity. These changes do not present sequentially; they co-occur as downstream effects of a single upstream signal disruption. Any approach that evaluates a single organ system in isolation is therefore structurally mismatched to the condition it seeks to detect.

3.1 The neurological transition: Evidence from brain imaging

Lisa Mosconi and colleagues at Weill Cornell Medicine used PET and MRI brain imaging to demonstrate that the menopausal transition produces measurable changes in brain structure and function. Their research represents some of the most compelling evidence that perimenopause is not merely a reproductive event but a whole-body transition with profound neurological consequences.[11,24]

Key findings from Mosconi et al. (*Scientific Reports*, 2021; *Neurology*, 2017):

- Women in perimenopause show decreased brain glucose metabolism (hypometabolism), a biomarker previously associated primarily with early Alzheimer's disease.
- Increased amyloid-beta deposition during the transition.
- Decreased gray and white matter volume.
- These changes occur during perimenopause, not only after menopause.

This challenges the long-held assumption that women's 2:1 higher Alzheimer's risk is simply due to longer lifespan. Mosconi's work suggests that the menopausal transition itself creates a neurological vulnerability that, if unaddressed, may contribute to late-life cognitive decline.

Some brain changes appear to partially stabilize or recover post-transition, suggesting a critical window during which intervention may be most effective.

This aligns with the broader "window of opportunity" concept for HRT: the perimenopausal period is not just when symptoms emerge, but when the neurobiological trajectory may still be modifiable.

SECTION 4

Impact on Quality of Life and Economic Productivity

85%	25-30%	~20%	55% vs 4%
WOMEN WHO EXPERIENCE SYMPTOMS DURING TRANSITION	WHOSE SYMPTOMS SIGNIFICANTLY IMPACT QUALITY OF LIFE	WHO REPORT DEBILITATING, LIFE-DISRUPTING SYMPTOMS	OF WOMEN 30-35 HAVE SYMPTOMS VS. HAVE SEEN A DOCTOR
SWAN; Gold et al., 2006	NAMS	Newson Health survey	Cunningham et al., npj Women's Health, 2025

The human and economic cost of unrecognized perimenopause is substantial. Research published in the last five years has begun to quantify what was previously treated as anecdotal.

1 in 4	10%	$26.6B	14 days/yr
WOMEN WHO CONSIDER LEAVING THE WORKFORCE	WHO ACTUALLY LEAVE EMPLOYMENT	ANNUAL US COST IN LOST PRODUCTIVITY	PRODUCTIVE DAYS LOST PER AFFECTED WOMAN
Fawcett Society, 2022	Fawcett Society, 2022	Mayo Clinic, 2023	Faubion et al., 2023

Downstream chronic disease burden

Beyond immediate quality of life, the perimenopausal window is the period during which the biological foundations for several major chronic diseases are established. Bone density loss that begins in perimenopause manifests as clinical osteoporosis 10 to 20 years later. Cardiovascular risk factors that emerge during the transition contribute to the well-documented post-menopausal increase in

cardiac events. Emerging evidence suggests that the perimenopausal window may also be a critical period for the neurobiological changes that precede late-life cognitive decline.[11]

Early identification of the perimenopausal transition therefore has implications not only for immediate symptom management but for long-term chronic disease prevention. The economic case for early awareness is, in this sense, analogous to the established case for hypertension or dyslipidemia screening: modest investment in early detection yields substantial downstream savings.

The window of opportunity

The "window of opportunity" is defined as the first 10 years after menopause onset, or before age 60. HRT initiated within this window has a fundamentally different risk-benefit profile than HRT initiated after the window closes. After the window, HRT is associated with increased cardiovascular and stroke risk, as demonstrated in the WHI study, whose participants were predominantly over 63. The critical implication: perimenopause must be identified early enough to enable timely intervention.

TABLE: RISK REDUCTION WITH TIMELY HRT (INITIATED WITHIN THE WINDOW OF OPPORTUNITY)

CONDITION	RISK REDUCTION WITH TIMELY HRT	SOURCE
Osteoporotic fractures	~30-40%	WHI, Cauley et al., 2003
Cardiovascular events	~30-50%	ELITE trial (NEJM, 2016); DOPS (BMJ, 2012)
Dementia / Alzheimer's	~30-50% (observational)	Shao et al., Neurology, 2012
Depressive episodes	Significant reduction	Gordon et al., JAMA Psychiatry, 2018

The unrecognized population

A significant proportion of symptomatic women never present to clinical care for perimenopausal complaints. Contributing factors include lack of awareness that symptoms have a hormonal basis, normalization of symptoms as "aging," prior negative clinical experiences, and competing caregiving demands. Any approach that requires a physician visit as the entry point will systematically miss this population.

SECTION 5

Limitations of Symptom-Level Intervention

Current clinical management of perimenopausal symptoms is largely organized around individual complaints rather than recognition of the underlying transition. A woman presenting with insomnia, joint pain, mood disturbance, and cognitive complaints in the same year is likely to be referred to separate specialists and treated with separate interventions for each symptom.

This approach has three structural limitations:

1. **Diagnostic fragmentation.** Each specialist evaluates the complaint within the scope of their specialty. The aggregate pattern, which is diagnostically informative, is never assessed.
2. **Treatment mismatch.** Symptom-level interventions (e.g., SSRIs for mood, sleep aids for insomnia, NSAIDs for joint pain) address downstream effects without engaging the upstream hormonal cause. The result is polypharmacy without root-cause resolution.
3. **Missed prevention window.** Symptom-level treatment does not address the progressive bone, cardiovascular, and metabolic changes occurring concurrently. These changes are modifiable during perimenopause but become increasingly difficult to reverse after the transition completes.

Approximately 25 to 30% of perimenopausal women with mood symptoms are prescribed antidepressants as first-line treatment. General SSRI non-response rates are 30 to 40%. For hormonally driven mood disturbance, the underlying

mechanism is estrogen-related, not serotonin-related, suggesting that antidepressant monotherapy addresses the wrong target in many cases. Gordon et al. (*JAMA Psychiatry*, 2018) demonstrated that transdermal estradiol was significantly more effective than placebo for preventing depressive episodes during perimenopause.[27]

TABLE: TREATMENT EFFICACY COMPARISON FOR PERIMENOPAUSAL MOOD SYMPTOMS

APPROACH	REMISSION / RESPONSE RATE	SOURCE
Transdermal estradiol (HRT)	68% remission vs 20% placebo	Soares et al., Arch Gen Psychiatry, 2001
Transdermal estradiol (prevention)	17.3% depressive episodes vs 32.3% placebo	Gordon et al., JAMA Psychiatry, 2018
Escitalopram + HRT (combination)	Greatest reduction across all measures ($p<0.001$)	Liu et al., Frontiers in Physiology, 2026
SSRIs alone (meta-analysis, 7 RCTs)	Significant but modest improvement vs placebo	Xu et al., Scientific Reports, 2020
Venlafaxine (SNRI) alone	81.3% response, 75% remission (open-label)	Unclear if replicable in RCT

The clinical implication is clear: when the underlying driver is hormonal, hormone-directed treatment substantially outperforms antidepressant monotherapy. Correct identification of perimenopause as the root cause is the critical first step that determines which treatment pathway the patient enters.

For vasomotor symptoms, the contrast is even sharper: HRT reduces hot flash frequency by 50 to 100%, while the most effective SSRI (paroxetine) achieves approximately 40 to 50% reduction.

How many symptoms does a typical clinician assess? Standard menopause consultations use tools like the Greene Climacteric Scale (21 items) or the MRS (11 items). These cover a fraction of the perimenopausal symptom landscape. MARKABLE's 60-symptom assessment across six biological clusters represents a more comprehensive mapping of the transition's multisystem footprint.

FIGURE 1. FRAGMENTED PATHWAY VS. INTEGRATED RECOGNITION

CURRENT: FRAGMENTED SYMPTOM PATHWAY	INTEGRATED: ROOT-CAUSE RECOGNITION
Joint pain → Orthopedic referral Insomnia → Sleep specialist or sedative Mood changes → Psychiatry or SSRI Fatigue → Thyroid panel (normal) Brain fog → "Probably stress" Skin changes → Dermatology consult **Result: 3+ specialists, 3+ prescriptions, 0 root-cause identification. Patient returns repeatedly.**	Multimodal assessment flags coordinated pattern across systems → Single recognition of perimenopausal transition → Woman may share her wellness profile with her clinician → Integrated treatment plan addressing the hormonal cause → Longitudinal tracking of response **Result: Faster diagnosis, reduced specialist referrals, improved patient outcomes and retention.**

The published literature on hormone therapy (HT) demonstrates that systemic treatment addressing the root hormonal cause can simultaneously resolve symptoms across multiple domains while providing protective effects against bone loss and possibly cardiovascular and cognitive decline, particularly when initiated during the perimenopausal window ("timing hypothesis").[12] This evidence supports the clinical value of root-cause identification over symptom-level management.

Rationale for a Multimodal Approach

The biological characteristics of perimenopause suggest specific requirements for an assessment approach:

1. **Multimodal.** Because the transition produces simultaneous effects across multiple organ systems, an awareness tool that reads multiple biological channels concurrently is better matched to the biology than any single-channel approach.
2. **Non-invasive and accessible.** Because a substantial proportion of symptomatic women do not present to clinical care, the tool must reach women outside the clinical setting. Smartphone-based approaches satisfy this requirement.
3. **Longitudinal capability.** Because the transition unfolds over years, single-timepoint assessment is inherently limited. A platform that enables repeated assessment and trajectory tracking offers additional clinical value.
4. **Pattern-based rather than threshold-based.** Because no single biomarker has been validated as a reliable standalone indicator, the assessment logic should integrate signals across channels rather than depending on any one measurement exceeding a fixed threshold.

MARKABLE was developed on this rationale. The platform captures data across three independent channels: (1) visible biological signatures derived from facial image analysis, (2) functional cognitive measurements, and (3) structured self-reported symptom profiling across six biological clusters. The convergence of signals across these independent channels provides the basis for pattern-level detection that individual channels cannot achieve alone.

In practice, the assessment takes under ten minutes. The woman takes a smartphone selfie, completes a brief set of cognitive tasks, and answers a structured symptom questionnaire. The platform integrates these inputs and generates a multimodal profile that can be shared with her clinician or tracked over time.

> **Note on intellectual property:** The specific algorithms, feature engineering, and model architecture underlying MARKABLE's multimodal analysis constitute proprietary intellectual property. While the precise algorithmic architecture is not disclosed here, the model relies on biologically interpretable features grounded in published physiology. Clinicians can trust that generated insights reflect known mechanisms of estrogen-mediated change rather than opaque statistical associations. Technical details are available under appropriate agreements with clinical and scientific partners.

SECTION 7

Study Design and Findings

7.1 Study design

Cross-sectional observational study with case-control structure. 264 women enrolled; 242 included after exclusion of surgical menopause (n=6), age below 30 (n=4), and absent image data (n=1). Primary analysis conducted within the 35 to 50 age window (n=216; 125 perimenopausal, 91 controls) to align with the STRAW+10 definition of the transition window.[1]

Perimenopause classification was based on Dr. Prior's 9-criterion scale, with a threshold of three or more criteria.[6] Age distributions between groups were comparable (peri mean 41.0, control mean 42.4; p=0.28, not significant), and all key findings were verified using partial correlation controlling for age.

For the visual analysis, n=215 women had usable image data. For the multimodal analysis combining visual, cognitive, and symptom channels, n=51 women had complete data across all three modalities. Sample sizes for individual analyses are reported alongside each finding below.

7.2 Key finding: Circularity-free symptom differentiation

To ensure independence from the classification criteria, all symptom indices were reconstructed after removing the nine Prior criteria. The remaining non-classification symptoms were verified to have no semantic or clinical overlap with the nine classification criteria. The remaining symptoms were grouped into six biological clusters. All six clusters differentiated perimenopausal from control women with large effect sizes (Cohen's d ranging from 0.65 to 1.10), confirming that the multisystem symptom pattern is fully independent of the classification system.

TABLE 1. SYMPTOM CLUSTER DIFFERENTIATION AFTER REMOVAL OF CLASSIFICATION CRITERIA

CLUSTER (NON-PRIOR SYMPTOMS ONLY)	COHEN'S D	P VALUE
Overall non-Prior symptom burden	1.10	0.0004
Musculoskeletal	1.02	0.0009
Cognitive	0.87	0.003
Mood	0.86	0.009
Sleep	0.84	0.006
Vasomotor	0.84	0.006
Genitourinary	0.65	0.011

N=51. Effect sizes are Cohen's d. All clusters significant at $p<0.05$.

FIGURE 2. EFFECT SIZES (COHEN'S D) FOR CIRCULARITY-FREE SYMPTOM CLUSTERS. N=51.

All clusters statistically significant ($p<0.05$). Classification criteria excluded from all indices.

CLINICAL HIGHLIGHT

Musculoskeletal symptoms (d=1.02) are the strongest circularity-free differentiator in the dataset.

Joint pain, stiffness, and muscle complaints in women aged 35 to 50 are commonly attributed to overuse, aging, or rheumatological conditions. The present data suggest that these symptoms, particularly when co-occurring with cognitive, mood, or sleep changes, may be consistent with the perimenopausal transition and could inform further clinical evaluation.

7.3 Key finding: Exploratory visual signal

Within the visual analysis channel, one specific facial parameter distinguished perimenopausal from control women at the Bonferroni-corrected significance threshold (p_{Bonf}=0.046, n=215). This represents the most stringent multiple-comparison correction applied in the study, testing against all measured parameters simultaneously. The finding survived image quality correction, cosmetic confound exclusion (e.g., lipstick: p remained significant after excluding subjects with detected cosmetic confounds), and partial correlation for age.

A secondary visual feature showed a consistent group difference ($p<0.01$) but did not survive Bonferroni correction at this sample size.

> The specific parameters and their biological interpretation are described in restricted technical documentation. In summary, detailed parameter descriptions are available in restricted technical documentation.[13,14]

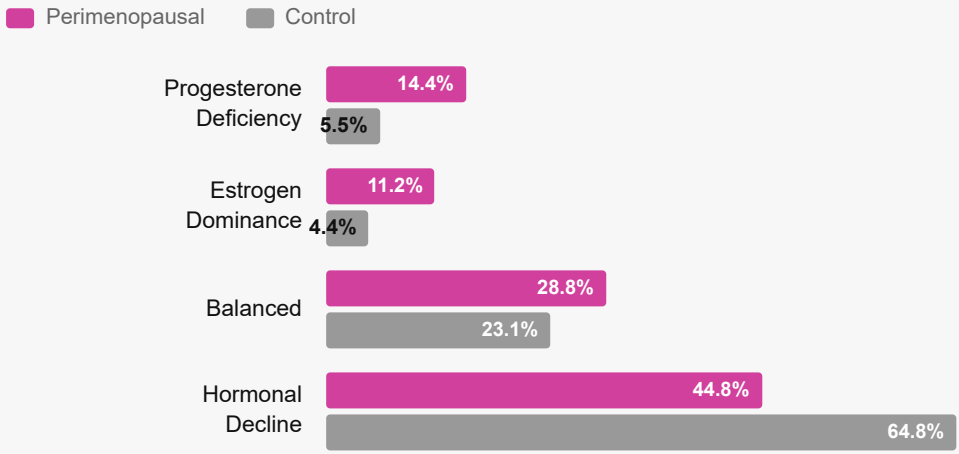
7.4 Key finding: Hormonal pattern distributions

To evaluate whether the platform's multimodal assessment captures biologically meaningful patterns, we examined the distribution of algorithmically derived hormonal profiles across groups. Because MARKABLE is positioned as a wellness and awareness tool rather than a diagnostic device, the ability to generate outputs consistent with established endocrinology serves as independent validation of the assessment's biological grounding.

HORMONAL PATTERN	PERIMENOPAUSAL (N=125)	CONTROL (N=91)	RATIO

Progesterone Deficiency	14.4%	5.5%	2.6x
Estrogen Dominance	11.2%	4.4%	2.5x
Hormonal Decline	44.8%	64.8%	0.7x
Balanced	28.8%	23.1%	1.2x

FIGURE 3. HORMONAL PATTERN DISTRIBUTION BY GROUP. N=216.



Progesterone deficiency and estrogen dominance are 2.6x and 2.5x more prevalent in the perimenopausal group, consistent with the established hormonal sequence of the transition.

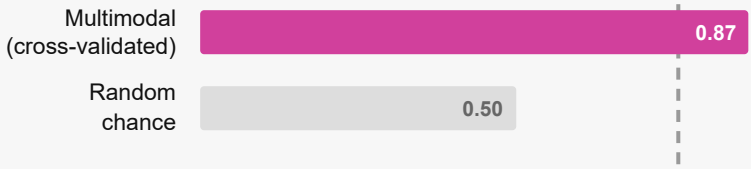
The 2.6-fold overrepresentation of progesterone deficiency and 2.5-fold overrepresentation of estrogen dominance in the perimenopausal group align with the established hormonal sequence of the transition: progesterone declines first, producing relative estrogen dominance before estrogen itself becomes erratic.[6,15] These patterns were not pre-specified; they emerged from the multimodal analysis. Their concordance with published endocrinology provides independent validation of the analytical approach.

7.5 Multimodal performance

When visual, cognitive, and symptom channels were combined in a cross-validated multimodal model, the area under the receiver operating characteristic curve (AUC) reached 0.87 (n=51). This represents a feasibility-stage estimate from a small but rigorously validated sample. The reported AUC reflects conservative, bias-corrected cross-validation. No single channel achieved

comparable performance, confirming that the multimodal combination is essential.

FIGURE 4. AREA UNDER THE ROC CURVE: MULTIMODAL MODEL VS. CHANCE. THE MULTIMODAL APPROACH SUBSTANTIALLY OUTPERFORMS RANDOM CHANCE.



Dashed line indicates chance level (AUC = 0.50). Cross-validated multimodal combination (AUC = 0.87). N=51.

Existing perimenopause assessment tools achieve limited diagnostic accuracy: the Greene Climacteric Scale, the most widely used, reaches only AUC 0.53 for menopausal status classification. The MRS achieves AUC 0.86, but for treatment need rather than transition identification. The strongest published ML model achieves AUC 0.745 but lacks external validation and uses questionnaire data only. MARKABLE's multimodal approach (AUC 0.87, cross-validated) addresses a measurement gap by combining channels that no existing tool integrates.

> The validation methodology was designed to prevent the performance inflation common in health-AI literature. The corrected AUC of 0.87 reflects this rigorous approach.

SECTION 8

Clinical Implications

These findings have several implications for clinical practice and research:

For perimenopause awareness

These findings suggest the potential feasibility of a multimodal, non-invasive approach to perimenopause awareness. A smartphone-based platform combining visual, cognitive, and symptom channels achieved an AUC of 0.87 in a cross-

sectional feasibility study (n=51), suggesting the potential of a multimodal approach. These exploratory findings require prospective validation.

For clinical recognition of underdiagnosed symptoms

The finding that musculoskeletal symptoms (d=1.02) are the strongest circularity-free differentiator has direct clinical relevance. Joint pain, muscle aches, and stiffness in women aged 35 to 50 are commonly attributed to overuse, aging, or rheumatological conditions. The present data suggest that clinicians should consider perimenopause in the differential diagnosis when these symptoms present in the relevant age window, particularly when co-occurring with cognitive, mood, or sleep complaints.

Operational value for healthcare providers

Beyond scientific interest, multimodal perimenopause assessment has direct operational implications for clinics and health systems:

- **Reduced diagnostic workup time.** A structured, pre-visit multimodal profile reduces the clinical burden of differentiating perimenopausal symptoms from other conditions. The platform performs the cross-system pattern recognition that currently requires multiple specialist consultations.
- **Fewer unnecessary referrals.** When the underlying perimenopausal transition is identified early, the cascade of single-system specialist referrals (orthopedics, sleep medicine, psychiatry) can be avoided or redirected, reducing system costs and patient frustration.
- **Improved patient retention.** Women who feel their symptoms are recognized and attributed to a coherent cause are more likely to remain engaged with a clinic. Conversely, repeated inconclusive visits are a documented driver of patient attrition in this population.
- **Longitudinal monitoring.** For clinics offering hormone therapy or other interventions, the platform provides a standardized, repeatable measurement of treatment response across multiple domains, complementing clinical follow-up with additional self-tracked wellness data.

For the root-cause treatment paradigm

The coherent differentiation across all six symptom clusters supports the biological rationale for treating perimenopause as a systemic transition rather

than a collection of independent complaints. This aligns with published evidence on the efficacy of appropriately timed hormone therapy across multiple domains simultaneously.[12]

SECTION 9

Limitations

The following limitations are acknowledged and inform the roadmap for subsequent research:

LIMITATION	IMPACT	PLANNED MITIGATION
Small complete-data sample (n=51)	Symptom and cognitive findings are underpowered for Bonferroni correction	Expand to n=150+ in prospective pilot
Cross-sectional design	Cannot establish causation or track temporal progression	Longitudinal arm in development
No hormonal blood confirmation	Classification based on validated symptom criteria, not serum levels	FSH/estradiol correlation in next cohort
Self-referred sample	Possible selection bias toward symptom-aware women	Clinic-recruited validation cohort planned
Limited ethnic diversity	Predominantly Fitzpatrick 3-5; limited FP 1-2 validation	Broader recruitment; ethnic calibration built into platform
Visual channel alone: limited	Single-channel visual assessment is insufficient	Multimodal combination addresses this directly

Peer review pending	Independent validation in progress	Manuscript in preparation for submission to peer-reviewed journal

These limitations define the boundaries of the current evidence. They do not undermine the central finding: that multimodal, non-invasive assessment of perimenopause is feasible, scientifically grounded, and clinically warranted.

SECTION 10

Conclusions and Next Steps

Perimenopause is a multisystem hormonal transition that affects virtually every organ system in the female body. It is experienced by every woman who reaches natural menopause. It lacks a standard detection protocol, is diagnosed with an average delay of 3 to 7 years, and is treated, when treated at all, at the level of individual symptoms rather than the underlying cause.

The present data demonstrate that this transition produces a coherent, detectable pattern across multiple biological channels: visual, cognitive, and symptomatic. No single channel is sufficient. The multimodal combination achieves clinically meaningful assessment performance (AUC=0.87, cross-validated).

The next steps in the clinical development of this approach are:

1. Prospective validation in a clinic-recruited cohort (target n=150 to 300), including comparison to clinical diagnosis by menopause specialists
2. Peer-reviewed publication of the full methodology and results
3. Assembly of a clinical advisory panel comprising menopause medicine specialists, endocrinologists, and epidemiologists
4. Longitudinal follow-up to characterize signal trajectory across the transition
5. Multi-site validation across diverse populations
6. Regulatory pathway exploration toward FDA clearance as a clinical decision-support tool, with the long-term goal of enabling any primary care physician to identify and manage perimenopausal transitions with the same confidence as a menopause specialist

Collaborate with MARKABLE

We are actively seeking partners across three domains:

ENGAGEMENT TYPE	WHAT IT INVOLVES	WHO THIS IS FOR
Clinical Pilots	Pilot integration of the MARKABLE wellness platform	Menopause clinics, OB/GYN practices,

	alongside clinical practice to explore whether multimodal wellness insights may support clinician awareness of perimenopausal patterns	health systems
Scientific Advisory	Clinical and methodological guidance on study design, validation protocols, and interpretation of findings. Advisory board positions available.	Menopause medicine specialists, reproductive endocrinologists, epidemiologists
Research Collaboration	Collaborative analysis opportunities and co-authored publications under appropriate data governance agreements	Academic researchers, clinical investigators

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