ARTEMIS
Women's Health
Foundation

In collaboration with Catenion

White Paper

Polyendocrine Metabolic Ovarian Syndrome

Mind the Gap(s): Moving Novel Therapies from Bench to Bedside

ARTEMIS Women's Health Foundation

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Note on terminology

This study was originally prepared using the term PCOS, polycystic ovary syndrome. Following an international consensus process, the condition has now been renamed PMOS, polyendocrine metabolic ovarian syndrome. The new terminology more accurately reflects the hormonal, metabolic and ovarian aspects of the condition, while avoiding the misleading focus on "cysts". The content of this study continues to refer to the same condition. The updated terminology is used accordingly throughout.

1 PREFACE

1.1 Background

This White Paper is the result of a series of focused interviews with a broad range of stakeholders involved in the development of new therapies for polyendocrine metabolic ovarian syndrome (PMOS). Participants included leading scientists, patients living with PMOS, clinicians, startup founders and innovators, pharmaceutical and biotech executives, regulatory affairs specialists, drug developers experienced in PMOS trials, and key opinion leaders (KOLs). By bringing together these diverse perspectives, we aim to better define real-world needs, current barriers, and actionable opportunities across the entire landscape of PMOS innovation.

These conversations revealed not only a strong eagerness for coordinated action but also pointed to the urgent need for novel approaches that move beyond short-term symptom relief and target the underlying disease mechanisms experienced by different patient subgroups.

1.2 Overview and Scope

PMOS represents one of the most prevalent yet underserved conditions affecting women, with profound long-term consequences for both health and quality of life. Despite its significant individual and societal impact, there are currently no FDA-approved therapies that address the underlying pathophysiology of PMOS. The only FDA-approved drug for PMOS is clomiphene (Clomid), which targets ovulation induction in the context of PMOS-associated infertility. However, recent advances in science and emerging technologies make it possible for the first time to identify and address the needs of patients most at risk – potentially enabling future targeted, disease-modifying treatments.

This White Paper focuses on the current challenges and new opportunities in PMOS drug development. We analyze barriers and solutions in preclinical research, clinical development, regulatory approval, and market access, informed by interviews across all major stakeholder groups. We do not attempt a comprehensive review of PMOS pathophysiology or existing treatment guidelines; instead, we concentrate on what is needed to transform the field in the decade ahead. Relevant scientific and clinical sources are provided in the “Key References” section.

Our aim is to catalyze collaborative efforts – involving patients, innovators, scientists, clinicians, industry, regulators, and payers – to accelerate the development of evidence-based, mechanism-driven therapies that improve outcomes and quality of life for women living with PMOS.

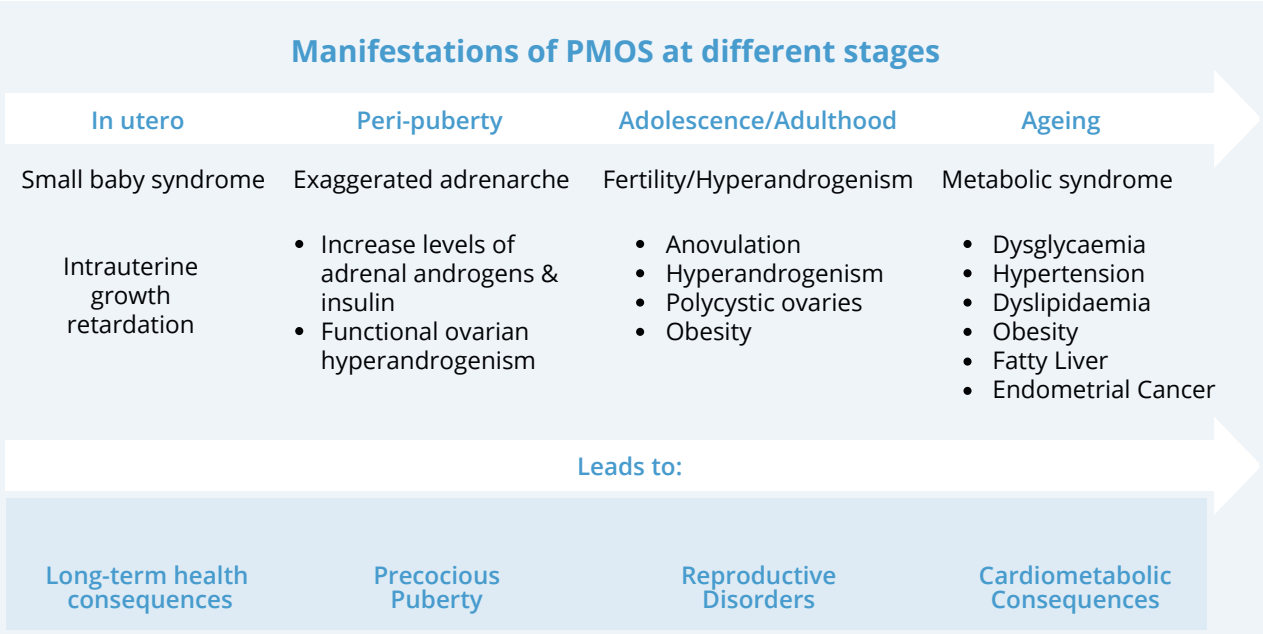
2 INTRODUCTION

2.1 About PMOS

PMOS is the most common endocrine disorder in women of reproductive age, affecting an estimated 6–13% globally. Its clinical presentation is highly variable – spanning reproductive, dermatologic, metabolic, cardiovascular, psychological, and oncologic domains. Importantly, while prevalence estimates often focus on women of reproductive age, PMOS and its health consequences persist well beyond menopause, impacting women across the lifespan. This heterogeneity, together with unpredictable symptom onset and progression, contributes to diagnostic delays and care fragmentation, leaving many patients underserved and at increased risk for long-term health complications.

Domain	Common Features	Common Features
Reproductive	Irregular periods, anovulation, infertility	Persistent subfertility, unopposed estrogen
Dermatologic	Hirsutism, acne, alopecia	Chronic distress, self-esteem issues
Metabolic	Insulin resistance, dyslipidemia, obesity	Type 2 diabetes, fatty liver/MASLD
Cardiovascular	Hypertension, atherosclerosis	Coronary artery disease, stroke
Psychological	Depression, anxiety	Reduced quality of life
Oncologic	Unopposed estrogen effect	Endometrial hyperplasia, cancer

Table 1: PMOS Symptoms and Health Impacts



Graphic 1: PMOS Symptoms change over a woman's lifetime

2.2 Key Pathophysiological Mechanisms

PMOS is a heterogeneous condition rooted in interconnected neuroendocrine, metabolic, and genetic disturbances. A deeper understanding of these underlying mechanisms is essential for advancing diagnostics and developing targeted therapies.

Neuroendocrine Dysregulation

Disruption of the hypothalamic-pituitary-ovarian (HPO) axis is a hallmark of PMOS, particularly among lean hyperandrogenic phenotypes. Increased gonadotropin-releasing hormone (GnRH) pulsatility favors luteinizing hormone (LH) over follicle-stimulating hormone (FSH) secretion, stimulating excess androgen production by ovarian theca cells. Chronic anovulation reduces progesterone feedback, allowing LH levels to remain persistently elevated.

Recent insights highlight the dysregulation of KNDy neurons – central modulators of GnRH secretion – as a key upstream driver. This is further exacerbated by hyperinsulinemia, reinforcing abnormal LH dynamics and androgen excess. These findings support the therapeutic potential of targeting neurokinin receptors to restore hormonal homeostasis.

Metabolic-Hormonal Crosstalk: Adrenal and Ovarian Androgen Pathways

Insulin resistance and compensatory hyperinsulinemia not only drive metabolic dysfunction but also potentiate ovarian androgen production in synergy with LH. Hyperinsulinemia lowers sex hormone-binding globulin (SHBG), increasing the bioavailability of circulating androgens.

Adipose tissue inflammation – driven by overnutrition, obesity, and gut dysbiosis – amplifies insulin resistance and disrupts normal ovarian signaling through the release of pro-inflammatory cytokines and immune cell infiltration.

While classic androgens (testosterone, androstenedione) are largely ovarian in origin, a distinct class – 11-oxygenated androgens – is predominantly produced by the adrenal glands. Elevated in PMOS, these androgens (e.g., 11-ketotestosterone) are synthesized via enzymes such as 11β-HSD2 and AKR1C3, and act as potent androgen receptor agonists. Importantly, 11-oxy androgens contribute to hyperandrogenism independently of ovarian hormone production and are strongly linked to adverse metabolic and reproductive outcomes.

Therapeutic Targeting of 11-Oxy Androgen Pathways

Key enzymes involved in 11-oxygenated androgen biosynthesis – AKR1C3 and 11β-HSD1– are emerging as therapeutic targets. AKR1C3 catalyzes the final step in 11-oxy androgen synthesis in both adrenal and peripheral tissues (e.g., adipose), while 11β-HSD1 contributes to local glucocorticoid activation and insulin resistance. See more about AKR1C3 inhibitors in section 2.5.

Genetic and Epigenetic Factors

While not following a monogenetic inheritance, PMOS tends to run in families, with genetic variants affecting both neuroendocrine and metabolic pathways. Reproductive-dominant subtypes often present with elevated LH and SHBG levels and are linked to specific genetic loci, while metabolic subtypes are associated with insulin resistance, obesity, and distinct genetic profiles.

Epigenetic and environmental influences – including prenatal androgen exposure, early-life nutrition, and lifestyle factors – further shape phenotypic expression. Notably, even modest weight loss (5–10%) can significantly improve ovulatory function and hormonal balance in many women, underscoring the interplay between environment and gene expression.

In Summary, PMOS Is Characterized by:

- Dysregulated GnRH/LH secretion driving androgen excess
- Multiple androgen sources – ovarian and/or adrenal and/or adipose tissue – particularly elevated 11-oxyandrogens
- Metabolic dysfunction driven by insulin resistance, adipose inflammation, and hormonal feedback loops
- A complex interplay of genetic, epigenetic, and environmental factors influencing disease expression

2.3 Diagnosis and the Evolution of PMOS Subtypes

Diagnosis of PMOS is based on the Rotterdam criteria, i.e. the presence of at least two of the following three features: a) oligo/anovulation, b) clinical or biochemical hyperandrogenism, and c) polycystic ovaries on ultrasound. Recent international guidelines (2023) provide age-specific recommendations and endorse AMH as an alternative to transvaginal ultrasound in adults where appropriate. However, AMH testing should be used only as one component of the diagnostic workup due to variable sensitivity and specificity across populations.

While these standardized criteria remain invaluable, they do not capture the full biological diversity of PMOS.

Advances in genetics, metabolomics, and data science are revealing new mechanistic subgroups—highlighting the syndrome's complexity and pointing toward a future where molecular subtyping informs therapy and new targets for treatment. A recent large-scale study by Gao et al. identified four reproducible, data-driven PMOS subtypes—HA-PMOS, OB-PMOS, SHBG-PMOS, and LH-PMOS—through unsupervised clustering of clinical variables from over 11,900 women. These subtypes demonstrated distinct long-term (6.5-year) reproductive and metabolic trajectories, with differing risks for complications such as dyslipidemia, diabetes, and ovarian hyperstimulation syndrome (OHSS). Notably, by the study's end, many participants no longer met the Rotterdam criteria, underscoring the dynamic nature of PMOS and the potential for personalized, subtype-based risk stratification and management.

Subtype Class	Defining Features	Status/Notes	Proportion
Hyperandrogenic	High androgens, hirsutism, acne, irregular cycles	May be lean or overweight	**20-30 %**
Metabolic	Obesity, insulin resistance, CV risk	Often less obvious hyperandrogenism	**65-80 %**
Type of androgen excess (AE): Gonadal-derived (GAE) Adrenal-derived (AAE) Mild(MAE)	 Gonadal androgen overproduction Elevated adrenal androgens (11-oxy) Slightly elevated androgens	 Molecular/omics research Early biomarkers, not yet clinical	 **22 %*** **22 %*** **57 %***
Genomic/Multi-omic	Omics-driven, molecular/genetic markers	Research phase, future clinical use	
HA-PMOS (Hyperandrogenic)	Highest levels of testosterone and DHEA-S, reflecting profound hyperandrogenism	Highest incidence of dyslipidemia and an increased risk of second-trimester pregnancy loss	**25 %****
OB-PMOS (Overweight-Obesity)	Highest BMI, fasting glucose, and fasting insulin levels, indicating severe metabolic dysfunction	Most severe metabolic complications (e.g., type 2 diabetes, hypertension, MASLD) but also the highest PMOS remission rate	**26 %****
SHBG-PMOS (High-SHBG)	Highest SHBG level and the lowest BMI among the four clusters	Mildest form, exhibiting the lowest incidence of type 2 diabetes, hypertension, and the best overall IVF outcomes	**26 %****
LH-PMOS (High-LH-AMH)	Highest levels of LH, FSH, and AMH	Greatest risk of moderate or severe Ovarian Hyperstimulation Syndrome (OHSS) during IVF	**23 %****

** DAISy-PMOS study interim analysis of 488 UK patients.*

*** Gao et al analysis of over 11900 women over a median of 6.5 years.*

Table 2: Classic and emerging PMOS subtypes

2.4 Current Treatment of PMOS

Current treatments for PMOS focus on symptom management rather than addressing the underlying pathology, and no curative approach exists. International guidelines highlight that in adolescents with PMOS, maintaining sufficient menstrual frequency – at least one menstruation every 21–45 days, or 6–7 cycles per year – is vital to prevent unopposed estrogen and its complications, such as endometrial hyperplasia and increased cancer risk. The American College of Obstetricians and Gynecologists (ACOG) recommends tracking menstrual cycles as a "vital sign" for adolescent health.

Lifestyle intervention is the recommended first-line approach, targeting weight, metabolic health, and well-being. For hirsutism, options include laser therapy (costly, and often not covered by payers), oral contraceptives, anti-androgens, or topical agents. Menstrual irregularities, like infrequent periods, are central to all PMOS subtypes. Metformin is a cost-effective approach to improve menstrual cyclicity and insulin sensitivity in overweight adolescents, particularly when com-

bined oral contraceptives (COCs) cannot be used. The best therapies for lean adolescents remain under investigation. Additional medications address metabolic complications, and surgical options are reserved for resistant cases. For patients desiring fertility, ovulation induction agents or assisted reproduction may be needed if initial therapies fail. Fertility treatments in PMOS are often complex due to unpredictable ovarian response, higher risks of ovarian hyperstimulation, and frequent resistance to first-line drugs.

The following table summarizes current treatment modalities for PMOS, their indications, and specific considerations: **It is important to note that, to date, there are no FDA-approved therapies specifically for the underlying pathophysiology of PMOS. The only FDA-approved drug for PMOS is clomiphene (Clomid), which targets ovulation induction in the context of PMOS-associated infertility.**

Category	Treatment/Agent	Indication/Use	Notes
Medications for Menstrual Irregularities and Hyperandrogenism			
Hormonal Contraceptives	COCs	Regulate menstrual cycles, reduce acne/hirsutism	First-line for most women with PMOS
	Progestin-only pills or intrauterine systems (IUS)	Protect endometrium from unopposed estrogen	Alternative for women who cannot use estrogen
	Diane-35 (cyproterone acetate/ethinyl estradiol)	Moderate-severe acne, hirsutism in androgen sensitivity (Europe/Canada)	Not approved in US; stronger antiandrogenic effect; increased VTE risk; used off-label in PMOS
Anti-androgens	Spironolactone, flutamide, finasteride	Reduce hirsutism, acne	Often combined with COCs, due to risk of teratogenicity Drospirenone containing combination COP (in US)
Topical Treatments	Eflornithine cream	Facial hirsutism	
Medications for Infertility			
Ovulation Induction	Clomiphene citrate (SERM)	First-line for ovulation induction	Traditionally preferred
	Letrozole (aromatase inhibitor)	Ovulation induction	Recommended first-line treatment; higher live birth rates, lower risk of multiples
	Metformin	Ovulation induction, especially with insulin resistance	May be used alone or combined with clomiphene/letrozole
Gonadotropins	FSH/LH injections	Ovulation induction if oral agents fail	Higher risk of hyperstimulation, multiple pregnancies
Assisted Reproductive Technologies (ART)	In vitro fertilization (IVF)	Infertility if other treatments fail	
Medications for Metabolic Complications			
Metformin	Metformin	Improve insulin sensitivity, menstrual regularity, weight management	
SGLT-2 Inhibitors / GLP-1 Receptor Agonists	SGLT-2 inhibitors, GLP-1 agonists	Weight loss, metabolic improvement (off-label)	Not approved for PMOS, current warnings in patients seeking pregnancy and those trying to conceive
Statins	Statins	Dyslipidemia	

Surgical and Device-Based Options			
Ovarian Drilling	Laparoscopic ovarian drilling	Infertility if unresponsive to medication	Less commonly used today, displaced by IVF treatments
Minimally Invasive Devices	May Health Rebalancing method (investigational)	Infertility; LOD literature points to broader impact on metabolic symptoms which will be collected as secondary outcomes in Rebalance trial	Office-based, ultrasound-guided procedure; ongoing trials (see details in section 2.7)

Table 3: Therapies prescribed for PMOS patients

Some treatments are off-label or investigational and may not be universally endorsed by guidelines or widely available.

2.5 Clinical Course, Unmet Needs, and Patient Perspectives

Symptoms typically develop in adolescence or early adulthood – initially as irregular cycles, acne, or hirsutism – and evolve over time toward reproductive and metabolic complications. The trajectory often differs by phenotype:

- Lean, hyperandrogenic patients may first present with dermatologic symptoms
- Metabolic phenotypes experience early insulin resistance or weight gain

Despite these variations, all individuals with PMOS face an elevated risk of infertility, metabolic syndrome, type 2 diabetes, fatty liver/MASH, cardiovascular disease, and endometrial cancer over their lifespan. Until today, the management of PMOS remains predominantly symptomatic – addressing fertility, metabolic, or cosmetic concerns – rather than true disease modification or prevention.

Patient Voice

A patient shared her long, frustrating journey to a PMOS diagnosis – years marked by persistent acne, unwanted hair growth, fatigue, and irregular periods. Multiple providers dismissed her concerns, leaving her feeling invisible. Beyond the physical symptoms, the emotional toll was profound: anxiety about body image, and fear of infertility disrupted her daily life. Even when not trying to conceive, the looming threat of infertility remained a constant source of distress.

Her story is not unique. Many women with PMOS describe unpredictable, interconnected symptoms and a sense of isolation. Pain, hormonal swings, and fatigue interfere with work, relationships, and mental health. Struggles with weight, skin, and hair contribute to low self-esteem, while the lack of clear treatment pathways often leads to self-blame and chronic stress.

"I spent years bouncing between clinics for my skin and cycles, feeling dismissed and helpless. No one explained the long-term health risks. Even now, I struggle to access care that looks beyond trying to get me pregnant." – PMOS Patient

Systemic Gaps:

- Delayed or fragmented diagnosis – especially for adolescents or those with atypical profiles
- Narrow focus on fertility or cosmetic endpoints
- Insufficient education and long-term monitoring of metabolic/CVD risks
- High treatment costs (e.g., for IVF or laser therapies)
- Psychological burden and lack of coordinated mental health support

2.6 Learning from the Past and Looking Forward: Segmentation and Precision in PMOS Care

PMOS research may lead to a fundamental shift in care – from managing symptoms to understanding and targeting the underlying biology. New research is helping define biologically distinct subtypes of PMOS, offering the potential for more personalized, effective care tailored to each woman's disease profile, risk factors, and life stage.

Biology-based subtyping could transform the PMOS journey – enabling earlier prevention, more targeted treatments, and truly personalized care.

Improved diagnostics are a critical first step, but the real turning point will come when we connect specific disease mechanisms to therapies that can modify the course of PMOS. This kind of segmentation lays the groundwork for smarter, more focused drug development – targeting the root causes rather than just managing symptoms.

In past trials, drug candidates for PMOS have shown underwhelming results (see Table 4). Their mechanism of action (MoA) might have targeted only a limited number of patients since so far patients have not been stratified according to their underlying differences. Without biomarker-guided subtyping, potential benefits for certain groups may have been lost in the noise. As our knowledge deepens, future clinical trials that use biological stratification and precision biomarkers will be better positioned to show real clinical benefit, and to succeed in gaining regulatory approval.

Early patient segmentation could fundamentally change the PMOS journey – enabling timely prevention, more effective and targeted early interventions, and individualized care that evolves through each phase of life.

Program (Company)	Target/Mechanism	Failure Reasons/Status	Key Lessons for future PMOS Studies
AR Blocker (Bayer)	Androgen receptor inhibition	– Teratogenicity concerns – Payer resistance (hirsutism seen as "cosmetic" endpoint)	Cosmetic endpoints are insufficient for reimbursement
AKR1C3 Inhibitor (Bayer)	AKR1C3 inhibition	– Hepatotoxicity in endometriosis phase 2 study – Lack of payer interest in hirsutism endpoints	– Need for robust biomarkers (androsterone validated) – Safety profiling is critical for chronic therapies – Target engagement does not guarantee clinical efficacy – Combine hirsutism + metabolic endpoints
Two preclinical programs (Celmatix/Bayer)	Undisclosed	Both preclinical programs were shelved following strategic reprioritization away from preclinical women's health research at Bayer	Early stage pharma partnerships can be risky, as promising programs may be discontinued due to shifting priorities at larger companies

Program (Company)	Target/Mechanism	Failure Reasons/Status	Key Lessons for future PMOS Studies
Melatonin Agonist Program (Celmatix)	Peripheral melatonin receptor agonist	Deprioritized due to funding constraints and the lack of validated translational models	Greater investment in validated translational disease models would enable small companies to focus resources on drug discovery for novel and validated targets
Tildacerfont (Spruce Biosciences)	CRF1 receptor (adrenal androgen modulation)	– Small effect size (on DHEAS biomarker) – Suboptimal study design (sequential dosing) – Limited patient stratification – Failed to demonstrate meaningful clinical benefit	**Key needs:** targeted subgroups (e.g., adrenal androgen excess), optimized trial design parallel vs. sequential, better androgen biomarkers, patient-centric endpoints
Pavinetant (Millendo/AstraZeneca)	NK3 (neurokinin-3) antagonist	Trial stopped due to hepatotoxicity in phase 2. Study focused on hormone profiles rather than clinical ovulation endpoints.	Early studies show hormonal benefits, but duration too short to confirm ovulation effects. Pavinetant demonstrated significant reduction in LH levels and LH pulse frequency—about a 40% drop after 7 days of treatment, and FSH concentrations were reduced by about 20%. Trials need 6–12 months follow-up to assess menstrual regularity, ovulation, and fertility outcomes. RWD or investigator-led trials may support label extension to PMOS. Long-term safety registries recommended.
Fazolinetant (Ogeda/Astellas)	NK3 receptor antagonist	Did not demonstrate significant efficacy on primary endpoint of restored menstrual cycling in phase 2a, despite a decrease in LH and testosterone.	
GLP-1 Agonist Repurposing (various)	GLP-1 receptor (metabolic/ovarian)	Teratogenicity risk in reproductive-age women. Adjacent indications (obesity, diabetes) seen as lower risk/higher return.	RWD can support label expansion; long-term safety registries are needed

Table 4: Lessons learned from preclinical and clinical drug programs

Key Considerations for the Design of Clinical Trials in PMOS

The study design for new PMOS therapies should integrate:

- Adequate trial duration – long enough to capture meaningful endpoints such as menstrual cyclicity, ovulation, and fertility, as well as long-term safety.
- Robust safety monitoring – for early detection and mitigation of adverse events.
- Patient-centered outcomes – improvements that matter to patients, beyond lab values.
- Patient segmentation – based on subgroups most likely to respond to the drug or its mechanism of action.

Developing such programs is resource-intensive, typically requiring pharma/biotech sponsorship, potentially supported by public–private partnerships, NIH/European Horizon grants, or disease-focused foundations. Large, multi-center trials designed to meet regulatory standards – whether focused on reproductive, metabolic, or other clinically important outcomes – are difficult for academic groups to sustain without substantial external funding and know-how.

2.7 New Targets in Development & Mechanisms of Action

The clinical pipeline in PMOS is empty and there are only a few products in preclinical development. Advances in drug design, genetics, neuroendocrinology, and metabolomics are unveiling novel modalities/targets aimed at addressing the syndrome's heterogeneity and root causes.

Targets in Androgen Excess: AKR1C3 Inhibition

Rationale:
Androgen excess is a central feature of PMOS in many patients. Research has identified the enzyme AKR1C3 (aldo-keto reductase 1C3) as a key mediator in the conversion of adrenal precursors to potent 11-oxygenated androgens. AKR1C3 is highly expressed not only in ovarian theca cells, but also in adipose (fat) tissue, suggesting that adipocyte-derived androgens may fuel both reproductive and metabolic features of PMOS.

Selective AKR1C3 inhibitors, such as BAY1128688, have demonstrated suppression of androgen biosynthesis in early trials, though development was halted due to off-target safety concerns. Meanwhile, 11β-HSD1 inhibition has shown improvements in insulin sensitivity and androgen burden in preclinical models. Continued investigation into these enzymatic pathways may offer new precision therapies for reducing the metabolic and reproductive burden of PMOS.

Clinical Development:
PostEra is developing an AKR1C3 inhibitor aimed at reducing systemic androgen levels and breaking the vicious cycle of hyperandrogenism and insulin resistance. AKR1C3 is upregulated in the adipose and ovarian tissue of PMOS patients and is directly linked to pathogenic androgen excess and an impaired metabolic phenotype. Pharmacologic inhibition has shown metabolic benefits in vitro by lowering both intra adipose androgens and lipid synthesis. However, definitive evidence of improvement in reproductive outcomes or normalization of ovarian structure in PMOS is still pending. Clinical studies are crucial to establish whether AKR1C3 inhibition can deliver safe disease modification in PMOS.

Device Innovation: Minimally Invasive Ovarian Rebalancing

May Health has pioneered a minimally invasive device and procedure to induce ovulation in women with PMOS-related infertility. This outpatient method uses a device attached to a transvaginal ultrasound probe, enabling the clinician to both visualize the ovary and deliver electrothermal energy for precision ovarian ablation. The technique specifically targets excess androgen-producing theca cells, removing a small proportion of ovarian tissue, while preserving ovarian reserve.

Clinical Pathway:
This approach is designed for women who have failed, are contraindicated or declined first-line fertility treatment. Early results from the "ULTRA" trials showed that 45% achieved spontaneous ovulation at 3 months, 66% achieved ovulation at 6 months with the addition of first-line ovulation induction agents that previously failed . The larger, ongoing REBALANCE trial is enrolling up to 195 women in the US, with ovulation rate as the primary endpoint, alongside pregnancy rates, metabolic improvements, and durability of effects. IVF is available to patients who are not achieving ovulation within six months, ensuring continuity of care. The procedure remains investigational, pending further safety and efficacy data.

Metabolic Pathways: GLP-1 Receptor Agonists and Real-World Data Opportunities

While GLP-1 receptor agonists and dual incretin agonists (e.g., semaglutide and tirzepatide) are approved for diabetes and obesity, they are not specifically indicated for PMOS, though real-world evidence suggests they may improve weight, insulin sensitivity, and ovulation rates in PMOS. However, large randomized trials in women pursuing fertility remain absent, due to safety concerns around potential teratogenicity, the long timelines required, and diminishing commercial incentives as patent exclusivity expires.

Real-World Data Initiatives

Analysis of claims data, such as from the Wegovy Pregnancy Registry, may help clarify the safety, efficacy, and pregnancy outcomes of GLP-1 agonists used off-label in PMOS patients – paving the way for potential label expansions in the future.

Neuroendocrine Pathways: Beyond Targeting GnRH

Therapies targeting neuroendocrine dysfunction in PMOS are in active development. NK3R modulators (such as fezolinetant), already approved for menopausal vasomotor symptoms, have shown short-term improvements in PMOS-related hormone levels in a 12-week phase 2a study. However, these agents have not yet demonstrated significant reproductive or symptomatic benefits in clinical trials, and industry focus appears to have shifted away from PMOS. A key challenge is our limited understanding of how long it takes for the underlying neuroendocrine vicious cycle to reset. In PMOS, this cycle is driven by increased GnRH pulse frequency → excess LH secretion → ovarian androgen overproduction → impaired follicular development and insulin resistance → further disruption of GnRH signaling. This self-reinforcing loop sustains both reproductive and metabolic dysfunction, making short-term interventions unlikely to achieve lasting benefit. Without longer-duration studies or validated surrogate markers, it remains unclear whether therapies that transiently normalize hormones can break this cycle, or whether more prolonged treatment is required to restore durable reproductive and metabolic health.

Emerging neuroendocrine targets include:

- Kisspeptin receptor agonists: MVT-602, a kisspeptin receptor agonist showed to increase levels of LH in a phase 2a trial. It aims to treat anovulatory disorders by triggering oocyte maturation and ovulation in the context of IVF/ treatment.
- Selective progesterone receptor modulators (SPRMs): Intended to normalize hypothalamic-pituitary feedback and reproductive hormone dynamics.

Prenatal and Developmental Interventions: Translational Frontiers

Although preclinical animal studies suggest that intervening in androgen signalling during early life – including the neonatal phase or so-called "mini-puberty" – may provide lifelong prevention of PMOS traits, such as adult hyperandrogenism and metabolic dysfunction, these findings are not directly translatable to humans. For example, while administration of AMHR2 antibodies during neonatal "mini-puberty" in mice can block the later development of PMOS-like features, and adrenal steroidogenesis inhibitors show some preventative effects, these strategies remain experimental and highly speculative. No human studies have tested such early-life interventions, and it is highly unlikely that preventive treatments targeting neonates will ever be feasible in clinical practice due to significant ethical, practical, and safety concerns.

A new generation of treatments aims to tackle PMOS's root causes. Advances in basic science provide many promising avenues, but regulatory, commercial, and translational barriers remain significant obstacles. Overcoming these will require sustained research investment, policy innovation, and new approaches to clinical endpoint definition – offering hope that future therapies will achieve remission (or even a cure), not just symptom control, for women living with PMOS.

Target/Therapy	Mechanism	Clinical Status	Notes
AKR1C3 inhibitors	Blocks androgen production in fat/ovary	Early-phase human trials	No definitive PMOS efficacy data yet; promise for disease modification
Ovarian device ablation	Reduces androgenic theca cells	Ongoing pivotal trial (REBALANCE)	Non-IVF alternative; investigational
GLP-1 agonists	Improves insulin sensitivity, ↓VAT	Off-label, RWD accruing	No pivotal PMOS trials; real-world data in progress
NK3R modulators	Modulates neuroendocrine feedback	Not advancing in PMOS	Biochemical effects, but failed clinical endpoints
Kisspeptin agonists	Restores GnRH pulsatility	Preclinical/early clinical	Exploratory
AMHR2/11β-OHase blockade	Prevents developmental androgen excess	Animal data only	No human studies

Table 5: Emerging PMOS Treatment Targets and Status

3 ASPECTS OF DRUG DEVELOPMENT

- PMOS is a spectrum disorder; accurate, biologically informed segmentation is necessary for effective therapy, trial success, and resource allocation.
- The value of any stratification tool is dependent on having therapies to match one or more segments; diagnostic innovation and therapeutic development must progress together.
- Genotyping, though not yet exploited clinically, will likely contribute to future segmentation and therapy selection.
- Academia and industry are advancing the discovery and development of new markers and risk scores to enhance the understanding of PMOS and facilitate.

Translational and Commercial Hurdles: The Celmatix Experience

- Celmatix, in collaboration with major pharmaceutical partners, spent several years investigating PMOS subtypes and endpoints but ultimately discontinued PMOS as a lead indication, highlighting how early partnerships can pose risks, as promising women's health programs may be discontinued due to shifting priorities at larger companies.
- Major hurdles included the difficulty of demonstrating clinical or economic superiority over widely available, inexpensive symptomatic therapies (e.g., metformin, contraceptives), and the lack of regulatory frameworks valuing true disease modification.
- The absence of robust translational models also forces small biotechs like Celmatix to allocate scarce capital toward model development rather than drug discovery. Increased investment in shared, validated translational models would enable innovators to focus on discovering and advancing novel therapeutics.
- The company argues that economic and regulatory incentives – even for drug repurposing – are inadequate, and that innovation in PMOS (and certain other women's health indications) will require policy reform and/or philanthropic involvement to prioritize disease-modifying interventions.

3.1 Inclusion Criteria: Choosing the Right Patient Population

The Need for Patient Segmentation in PMOS

Current guidelines emphasize diagnosis without distinguishing patients by levels of need, disease severity or pathophysiologic subtypes, leaving us without established measures linked to long-term outcomes. Patient segmentation is increasingly recognized as a vital strategy for addressing the unique medical requirements of different cohorts. By segmenting patients, drug developers can better demonstrate the clinical efficacy of treatments targeted to each group's underlying causes, satisfy regulatory and payer expectations, and ultimately deliver more personalized care.

Segmentation is not just an abstract goal – it is essential for progress in several key areas of PMOS research and clinical management, including:

- **Mechanistic Targeting:** Because PMOS mechanisms vary widely, stratification by underlying biology enables mechanism-specific treatments to be tested in matched patient populations, increasing both clinical relevance and regulatory success.
- **Optimizing Segment-Specific Therapy:** Segmentation is critical for targeted approaches, such as tailored infertility treatments. For example, studies like the BAMBINI trial (see box) reveal that weight loss is not sufficient for all patients to achieve ovulation; targeted approaches must address specific hormonal and metabolic pathways.

Time-to-Ovulation as a Clinical Endpoint in PMOS Therapeutics: Lessons from BAMBINI

In the BAMBINI (bariatric surgery vs medical care for obesity and polycystic ovarian syndrome related infertility) multicentre randomized controlled trial, bariatric surgery led to a significant increase in spontaneous ovulation rates – 2.5 times higher than medical therapy in women with PMOS, obesity, and oligomenorrhoea/amenorrhoea. Notably, biochemically confirmed ovulatory events began to rise by 8 weeks post-intervention, suggesting that clinical trials targeting ovulation induction in PMOS should include follow-up assessments starting as early as two months and extend for at least one year to robustly capture treatment effects on ovulation. However, not all individuals achieved ovulation despite substantial weight loss, highlighting the need for further research into patient-specific factors influencing treatment response targeting weight loss.

- **Enabling Innovation:** Traditional diagnostic criteria identify PMOS but do not distinguish between subtypes, severity, or actionable biology. The integration of novel biomarkers unlocks opportunities for precise classification and drives development of new therapies. Genetic variation across populations, though not yet harnessed for treatments, points to future personalization
- **Regulatory and Payer Demands:** Regulators and payers now explicitly require evidence for specific subgroups and risk profiles benefiting from therapy, shaping both trial design and reimbursement decisions – especially for chronic therapies. Focusing on specific high-need subgroups may also help to navigate trade-offs between the cost of new treatments and the size of the targeted patient populations.
- **Defining and Measuring Outcomes:** Clear patient subgroups improve not only industry-sponsored trials supporting new drug approvals, but also improve real-world monitoring and academic studies, supporting progress in both clinical research and care delivery.

Method/Domain	Example	Strengths & Limitations
Androgen profiling	11-oxygenated androgens, testosterone, DHT, DHEAS, androstenedione	May reflect true biological subtypes; only actionable if matched therapies exist
Neuroendocrine markers	LH, LH/FSH ratio, GnRH test	Suggests hypothalamic/adrenal circuits; still investigational
Metabolic markers	HOMA-IR, glucose tolerance, lipid profile	Useful for risk stratification; not yet therapy-defining
Genetic/multi-omic clusters/ epigenetics	Genomics, metabolomics, multi-omic signatures	Future potential for precision subgroups; clinical value depends on targeted therapies
Symptom patterns	Fertility status, hirsutism, menstrual patterns, BMI	Guide endpoint selection and characterize cohorts; may not indicate underlying mechanism
AMH (Anti-Müllerian hormone)	Ovarian reserve marker	Aids diagnosis; limited value for stratification or therapy choice at this time

Note: While population genetic differences are known, robust matching to mechanisms of action and clinical application is not yet established but is expected to shape future segmentation.

Table 6: Current and Emerging Stratification Markers

Conclusion

No single stratification method is validated for everyday clinical care or for directing therapy in PMOS yet. The promising markers and molecular clusters under investigation will only translate into clinical value if their use is paired with the development and testing of **mechanism-based therapies** for identified patient groups. Future precision medicine in PMOS must prioritize the co-development of meaningful stratification tools and effective, personalized interventions.

Academia and industry are advancing the discovery and development of new markers and risk scores to enhance the understanding of PMOS and finding personalized PMOS care.

3.2 Regulatory Aspects and Patient Expectations: Rethinking Clinical Trial Endpoints

Current Endpoints and Their Limitations

Most PMOS trials still focus on short-term outcomes such as ovulation, menstrual regularity, and immediate hormonal shifts, typically measured within weeks or a few months. While these endpoints are feasible, they fail to capture what patients and clinicians increasingly value: durable improvements in metabolic and cardiometabolic health. Long-term outcomes – such as diabetes prevention, sustained ovulatory function, and cardiovascular risk reduction – are rarely incorporated. This disconnect underscores the ongoing challenge of bringing trial designs into closer alignment with real-world priorities and long-term health outcomes.

The Mismatch Between Clinical Needs and Trial Feasibility

There is a fundamental mismatch between the clinical need for durable improvements and the practical constraints of trial design. Achieving and demonstrating restoration of regular ovulation or clinically meaningful increases in pregnancy rates may require interventions and follow-up lasting 6-12 months, yet many early-stage studies are limited to 3-6 months due to cost and feasibility constraints. Evidence from trials such as BAMBINI and pharmacologic ovulation induction studies indicates that some patients achieve ovulation and pregnancy within the first months, but sustained or population-level effects, as well as live birth outcomes, typically require longer assessment periods. Industry sponsors, wary of the expense and complexity of extended trials, often hesitate to invest in PMOS drug development, slowing innovation. Addressing this mismatch requires regulatory flexibility and greater integration of surrogate endpoints, real-world evidence (RWE), and patient registries to balance robust outcome measurement with realistic study designs.

Learning from Oncology: Surrogate Endpoints and Patient Segmentation

In oncology, progress accelerated once surrogate endpoints (e.g., tumor response rates) were validated and paired with real-world registry data. Companion diagnostics allowed risk-based patient segmentation, enabling targeted therapies and regulatory approval pathways that were both faster and more precise. PMOS drug development could benefit from a similar approach – using validated biomarkers, registries, and adaptive trial designs to bridge the gap between short-term feasibility and long-term relevance.

The Role of Emerging Technologies

New technologies are now making this shift more achievable. Advances in metabolomics and hormonal profiling can stratify PMOS patients into biologically distinct subgroups with different risks. For example, 11-oxygenated androgens and other metabolomic signatures may soon identify women at higher risk for insulin resistance and cardiometabolic complications. Stratification by such biomarkers allows more targeted trial designs, improves the likelihood of detecting meaningful benefit in relevant subgroups, and supports the development of companion diagnostics. These approaches not only improve scientific rigor but also align endpoints with regulatory expectations for risk-based assessment.

Solution: Integrating RWE, Registries, and Companion Diagnostics

To modernize PMOS trials, endpoints should be expanded beyond short-term reproductive markers to include long-term metabolic outcomes and patient-centered measures of quality of life. RWE (real-world evidence) from electronic health records and disease registries (e.g., diabetes, obesity, or fertility registries) can provide critical longitudinal insights that traditional trials alone cannot. Pairing these data sources with emerging diagnostic tools – such as metabolomic risk profiles – enables adaptive trial designs, more precise inclusion criteria, and a stronger case for regulatory acceptance.

Addressing the Ovulation–Duration Gap

The persistent challenge remains how to demonstrate meaningful improvements in ovulation within feasible trial durations. Here, surrogate endpoints informed by biomarker profiles, combined with longitudinal follow-up through registries, may help. For example, metabolomic signatures linked to improved insulin sensitivity could serve as early predictors of eventual ovulatory recovery, reducing the need for prohibitively long trials while still demonstrating patient-relevant benefit. For now, this remains highly speculative and the signatures would need to be validated, as illustrated by metformin, which improves insulin resistance but does not reliably restore ovulation in PMOS.

Evidence from Ongoing and Recent Trials in PMOS

Recent and ongoing clinical trials illustrate how endpoints remain focused on short-term reproductive outcomes or metabolic surrogates, with relatively limited integration of long-term measures. The following table summarizes representative examples, highlighting inclusion criteria, primary endpoints, and secondary outcomes.

Trial/Identifier	Inclusion Criteria (age, BMI, hyperandrogenism, PMOS status)	Primary Endpoint	Secondary Endpoints
Tildacerfont NCT05370521	Women aged 18–40; PMOS by NIH criteria; elevated adrenal androgens (DHEAS); BMI not specified	Change in adrenal androgens (DHEAS) over 25 weeks	Other androgen levels, ovulation rate, metabolic profile, safety
Elagolix NCT03951077	Women aged 18–35; BMI 18.5–38; PMOS diagnosis; FSH ≤10 IU/L; elevated total or free testosterone	Menstrual cycle normalization (2 cycles in 4 months)	Change in LH AUC, hormone levels, ovulation rate, safety
Fezolinetant EudraCT 2014-004409-34	Women with PMOS, age range not specified in public registry; biochemical or clinical hyperandrogenism required	Change in total testosterone, LH-to-FSH ratio (3 months)	Menstrual normalization, other hormones, PMOSQ, safety
May Health NCT06206746	Women with infertility due to PMOS, who have not responded to first-line ovulation induction or are contraindicated; age, BMI, androgen status not specified in summary	Restore ovulation post intervention (at least 1 ovulation in 3 months)	Cumulative ovulation rate, pregnancy, various hormone levels, pain after procedure, activities of daily living, safety
Semaglutide vs. Metformin NCT05646199	Women aged ≥18 (typically 18–40); obese (BMI ≥30); diagnosed PMOS	Amount of weight lost over 28 weeks	Quality of life, metabolic & hormonal parameters, cardiovascular risk, safety

Table 7: Examples of endpoints used in past and ongoing clinical trials

3.3 The Payer Perspective: Health-Economic Burden and Barriers to Innovation in PMOS

From a payer perspective, the consequences of PMOS are substantial: recent health-economic analyses estimate the direct U.S. healthcare burden of PMOS to exceed $15 billion annually, a magnitude comparable to the direct costs of ovarian, prostate, or breast cancer.

Yet unlike cancer, **no PMOS-specific therapies exist.** Treatment consists largely of generic symptom-management strategies or costly procedural interventions such as IVF. This mismatch between burden and innovation reflects not a lack of scientific opportunity, but a structural stalemate between payers, industry, regulators, and funders. **Breaking this deadlock will require payers to recognize PMOS as a high-cost, chronic condition and to support pathways that make innovation both feasible and sustainable.**

Category	Estimated Annual Cost
Initial evaluation	$166 million
Menstrual dysfunction	$2.4 billion
Infertility care	$951 million
Hirsutism	$1.1 billion
Type 2 diabetes	$1.5 billion
Stroke	$2.4 billion
Pregnancy complications	>$2 billion
Mental health disorders (anxiety, depression, eating disorders)	$4.26 billion

Table 8: PMOS patients induced direct costs

Beyond these direct costs, PMOS drives substantial indirect losses in productivity, absenteeism, and work-related impairment – costs rarely captured in payer decision-making.

In short: PMOS imposes a societal and healthcare burden rivaling that of major cancers, yet continues to be treated as a minor reproductive or cosmetic concern.

Payer Barriers and the Innovation Gap

Despite its scale, no PMOS-specific therapies exist. Care relies almost entirely on inexpensive off-label generics or procedural interventions such as IVF. This gap reflects not therapeutic irrelevance but a self-reinforcing cycle:

- No approved drugs → no reimbursement frameworks.
- Cheap generics anchor pricing benchmarks.
- Fragmented coding obscures systemic costs.
- Long-term benefits misalign with short payer budget cycles.
- Symptoms like infertility or hirsutism are framed as elective, limiting coverage.

As a result, **payers lack tailored value models, industry avoids investment, regulators provide no trial guidance, and patients remain with symptomatic rather than disease-modifying options.**

Breaking the Cycle: Pathways to Solutions

Unlocking innovation requires payers and stakeholders to recognize PMOS as a reimbursable, systemic disorder. Key levers include:

- **PMOS-specific value models** linking burden to measurable outcomes (e.g., ovulation, HbA1c, live births, CV risk).
- **Unified diagnostic coding** (ICD-11 5A80.1) to present PMOS as a chronic systemic disease.
- **Outcome-based reimbursement** contracts tied to near-term clinical outcomes.
- **Reframing complications as medical needs**, drawing on models from dermatology and mental health.
- **Cross-disease benchmarking** against IVF or diabetes prevention programs, not generics.

The PMOS Funding Environment

Research and innovation remain underfunded, mirroring endometriosis. Cheap generics create an illusion of adequacy, industry avoids the field, funders underestimate the burden, and regulators provide no PMOS-specific trial standards. This four-way misalignment perpetuates underinvestment.

Breaking the Catch-22 requires alignment:

- Payers: recognize PMOS as a systemic chronic condition with cancer-scale costs.
- Industry: design trials and RWE aligned with payer value models.
- Funders: prioritize PMOS as a major unmet need.
- Regulators: establish clear clinical guidance and endpoints.

Without coordinated action, the absence of therapies will persist – not because of biology, but because of **broken incentives across the healthcare system.**

3.4 The Industry Perspective

PMOS represents one of the largest unmet needs in women's health today. Yet therapeutic progress remains slow. No FDA- or EMA-approved therapies specifically target PMOS, reflecting both regulatory uncertainty and scientific hurdles such as the absence of new, clinically validated molecular targets and biomarkers. Disease heterogeneity further complicates trial design and drug development.

Market and Economic Barriers

Innovation is also stalled by economic dynamics. The current market is dominated by low-cost generics (e.g., combined oral contraceptives, metformin, antiandrogens), which effectively address some symptoms but do not modify disease progression. IVF remains the main intervention for infertility, but it is expensive, has a high failure rate, and is highly profitable for clinics. Because IVF is often funded out-of-pocket by patients, payers and regulators have little incentive to support investment in broader, disease-modifying therapies. Moreover, contraceptives and antiandrogens are unsuitable for women actively seeking pregnancy, leaving a critical therapeutic gap.

Untapped Market Opportunity

Despite these barriers, PMOS represents a substantial and largely untapped market. Innovative therapies that simultaneously improve metabolic and reproductive dysfunctions could transform care, improve long-term outcomes, and reduce reliance on IVF. For developers, this is an opportunity to address a high-prevalence, lifelong condition where demand for effective, patient-centered solutions far outstrips supply.

Path Forward

For PMOS to become a more active field of innovation, industry stakeholders must work with academia, regulators, patients and payers to:

- Validate surrogate endpoints and biomarkers (e.g., metabolomic signatures, ovulation recovery predictors).
- Demonstrate long-term value through RWE and outcomes-based reimbursement.
- Position therapies not as cosmetic or niche fertility interventions but as lifelong, disease-modifying treatments that reduce cost and improve quality of life.
- Overcoming these barriers could benefit both patients and industry stakeholders, positioning PMOS as a frontier for innovation in women's health.

4 DEVELOPING TARGET PRODUCT PROFILES

Developing a commercially viable therapy for PMOS is uniquely challenging. Scientific uncertainty, regulatory ambiguity, and operational hurdles have historically stalled innovation. Unlike other chronic conditions, PMOS lacks standardized comparators, and clear regulatory guidance – making it difficult for drug developers to define what success should look like in a Target Product Profile (TPP).

4.1 Core Hurdles in Defining a TPP

A PMOS TPP must address three categories of challenges:

1. Endpoints: While the "birth of a healthy baby" is the ultimate clinical goal for patients seeking fertility, this is often impractical for early-phase development. Fertility restoration (e.g., menstrual cycle regularity), quality-of-life metrics, and metabolic biomarkers may offer more feasible and patient-centered alternatives.

2. Comparators: Placebo controls remain common, but background therapies such as combined oral contraceptives or metformin complicate trial design. Defining the right comparator is essential for both regulatory approval and payer acceptance.

3. Operational Constraints: Heterogeneous patient populations, long disease timelines, and high trial costs limit the feasibility of large-scale outcome studies. Companion diagnostics, surrogate markers, and registry-based follow-up may help to bridge this gap.

4.2 Integrating Patient Advocacy

Patient advocacy groups highlight that fertility is not the sole priority. Women want holistic therapies that also address hyperandrogenism, metabolic health, and mental well-being.

Core Focus	What Was Shared or Highlighted
Patient Experience & Impact	Real-life stories of symptoms, emotional burden, diagnostic challenges, and quality-of-life issues.
Unmet Treatment Needs	Frustration with symptom management strategies and the absence of therapies targeting PMOS at its root.
Clinical Priorities	Patient-preferred endpoints, biomarkers, and meaningful outcomes for future trials.
Informing Policy and Development	Using patient insights to influence drug approval strategies, trial designs, and regulatory priorities.
Collaborative Input	Inclusive dialogue among patients, the FDA, industry, and researchers to align on goals and expectations.

Table 9: The 2023 FDA externally-led patient-focused drug development meeting emphasized on these core topics to be addressed when developing new treatments for PMOS.

In essence, the PMOS EL-PFDD meeting held on November 3, 2023 and organized by the patient advocacy group PMOS Challenge focused on bringing the lived experiences, unmet clinical needs, and treatment priorities of PMOS patients directly into the FDA and research ecosystem – with a clear goal of catalyzing the development of effective, patient-centered therapies for this chronic and impactful condition.

Incorporating these insights into TPP design not only aligns with patient needs but will also strengthen regulatory and payer negotiations.

4.3 Learning from Other Indications

Other chronic conditions offer important lessons:

- Eosinophilic asthma: Initial broad trials of mepolizumab failed until developers refined the target population using blood eosinophils and shifted endpoints from lung function to exacerbations.
- Rheumatoid arthritis: Progress came when trials measured both symptom relief and disease modification, supported by novel imaging biomarkers.

4.4 Toward a Framework for a PMOS TPP

A forward-looking TPP for PMOS might include:

- **Population:** Stratified by phenotype (hyperandrogenic profile, metabolic, inflammatory, or reproductive goal).
- **Comparators:** Placebo and/or background standard-of-care (COC, metformin).
- **Biomarkers/Companion Diagnostics:** Androgen panels (including 11-oxygenated androgens), AMH, LH:FSH ratio.
- **Evidence Generation:** Real-world registries, pregnancy outcomes, long-term follow-up.
- **Endpoints**: Endpoints in PMOS research can be assessed over different time horizons, ranging from short-term biochemical markers to long-term clinical outcomes. To illustrate this, the table below summarizes **potential clinical endpoints by domain and time frame** that may be relevant for clinical trial design.

Domain	Short-term (8–12 weeks)	Medium-term (3–6 months)	Long-term (≥6–12 months)
Reproductive	Ovulation induction, cycle regularity, endometrial changes	Sustained ovulation, conception, early pregnancy	Live birth rates, pregnancy out-comes, endometrial protection
Endocrinology	LH/FSH ratio, androgens (T, DHEAS), AMH, SHBG, 11-oxy	Stable androgen profile, improved gonadotropins, ↓ ovarian volume	Hormonal normalization, prevention of sequelae
Metabolism	Fasting insulin/glucose, HOMA-IR, lipid shifts	HbA1c, weight/BMI, waist circumference, OGTT	Diabetes prevention, sustained metabolic health
Cardiovascular	BP, endothelial function	Lipid normalization, CRP, arterial stiffness	↓ Hypertension, CVD events, subclinical atherosclerosis, stroke
Hirsutism	Minimal visible change, slight cosmetic relief	↓ modified Ferriman–Gallwey score (mFG), less cosmetic hair removal	Clear/sustained reduction
Acne	Lesion count/severity improves	Sustained clearance	Long-term remission
Mental health / QoL	QoL/mood scores, ↓ body image distress	Sustained mood/QoL gains, adherence	↓ Depression/anxiety, stigma
Other systemic	Liver enzymes, CRP	↓ Hepatic fat, improved sleep (OSA)	Prevention of MASLD/NASH, ↓ cardiometabolic risk

Table 10: Potential Endpoints in PMOS by Time Horizon

This framework highlights how endpoints evolve from immediate biochemical or symptomatic changes (e.g., insulin resistance, acne improvement) to medium-term measures (e.g., HbA1c, conception rates, early hirsutism reduction), and finally to long-term outcomes that matter most to patients and regulators (e.g., live births, cardiovascular risk reduction, sustained quality-of-life improvements).

Such a structured approach ensures that trials capture both early treatment signals and long-term patient-relevant outcomes.

4.5 Future Patient Journey (Aspirational Vision)

In an ideal scenario, PMOS care would move from delayed, fragmented, and symptom-based management to personalized, proactive, and preventive care:

- Early diagnosis with non-invasive biomarkers.
- Patient stratification enabling precision therapies.
- Integrated management of reproductive, metabolic, and mental health needs.
- Long-term disease modification, reducing infertility, cardiovascular, and oncologic risks.

The business case for PMOS innovation may begin with infertility, but its full potential lies in addressing the broader, lifelong burden of the condition. A clear, patient-centered TPP framework – supported by biomarkers, advocacy insights, and lessons from other chronic diseases – can help unlock investment and accelerate development toward disease-modifying therapies.

5 CONCLUSIONS AND NEXT STEPS

Throughout this document, we outline the scientific, regulatory, and economic barriers that have slowed therapeutic innovation relative to patient needs. Today, however, a combination of scientific progress, growing advocacy, and rising industry engagement creates a rare opportunity to reset the trajectory of PMOS drug and device development.

5.1 Key Catalysts for Change

Several emerging developments could serve as inflection points:

- **GLP-1 receptor agonists and related therapies:** As a class, these drugs have helped to focus the industry on the medical need and commercial opportunity that lies in common, chronic conditions which have been neglected for decades. They also demonstrate how a targeted intervention can create health benefits across various organ systems (weight loss, metabolic health, cardiovascular risk etc).
- **Biomarkers to stratify patients** early are critical for linking short-term efficacy with long-term risk mitigation and enabling targeted therapies. Among emerging candidates, 11-oxygenated androgens show promise: if validated, they could provide a stratification tool to direct patients to effective treatments.
- **Ovarian ablation/Laparoscopic ovarian drilling as a therapeutic:** Traditionally an underutilized surgical option in PMOS, recent device-based innovations aim to reimagine this approach as a minimally invasive, standardized therapy that could expand treatment options for women unresponsive to medication.
- **Awareness among patients, physicians, industry, payers, and scientists**
- **Novel targets** more early-stage/speculative target classes
- **Other activities:** e.g., engagement of pharma with academic innovators to catalyze translational research, use of novel technologies, including AI, along the whole value chain, from target ID/validation to medicinal chemistry, preclinical models, better trials, and improved regulatory guidance)

Over the past 10 years, clinical trials and translational research have greatly expanded our understanding of PMOS, identifying pathophysiological differences and patient-specific pathways. This progress means innovation is no longer constrained by a lack of hypotheses, but rather by the challenge of aligning endpoints, incorporating patient voices, and meeting regulatory expectations. To translate these advances into therapies, patients, regulators, investors, scientists, and industry must work together to adapt requirements and enable new treatments.

5.2 What Is Needed – And From Whom?

To translate this momentum into approved therapies, coordinated action is required across the ecosystem:

- **Research Community:** Expand mechanistic studies and clinical trials that validate disease pathways, biomarkers, and surrogate endpoints (as highlighted in recent Nature reviews). Well-designed GLP-1 trials in PMOS patients a near-term priority.
- **Industry:** Invest in targeted product profiles that integrate patient-reported outcomes, use real-world evidence and registries to accelerate insights, and explore novel drug targets such as AKR1C3 or neurokinin pathways.
- **Clinicians:** Build multidisciplinary expertise (endocrinology, cardiology, gynecology, psychiatry) and develop integrated care models that treat PMOS holistically, not as isolated symptoms.
- **Patients and Advocacy Groups:** Continue to drive awareness, co-create endpoints, and push for inclusion of mental health, quality of life, and long-term risk reduction in trial design.
- **Regulators and Payers:** Provide clearer guidance on acceptable endpoints, comparators, and trial duration, while recognizing PMOS as a serious, lifelong condition deserving of disease-modifying therapies.

5.3 Looking Forward

The next decade offers an opportunity to reshape the PMOS treatment landscape. By validating new biomarkers, running mechanism-driven trials, and embedding patient perspectives into every stage of development, stakeholders can create therapies that meaningfully improve fertility, metabolic health, and quality of life.

The reward is two-fold: improved outcomes for millions of women worldwide and the establishment of PMOS as a high-potential field for innovation in women's health.

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8 ABBREVIATIONS

Abbrevation	Full Term	Definition/Context
AMH	Anti-Müllerian Hormone	Hormone typically elevated in PMOS due to the increased number of small antral follicles, making it a useful marker for assessing ovarian reserve and supporting the diagnosis of PMOS.
COCs	Combined Oral Contraceptives	Birth control pills containing estrogen and progestin, often used in PMOS management.
DHEAS	Dehydroepiandrosterone sulfate	DHEAS is a sulfated form of the adrenal androgen pre-cursor dehydroepiandrosterone (DHEA); it is commonly used as a marker of adrenal androgen production in clinical testing.
DHT	Dihydrotestosterone	DHT is a potent androgen derived from testosterone and involved in the development of male characteristics and some features of androgen excess.
KOLs	Key Opinion Leaders	Experts who influence medical practice, research, and policy.
GnRH	Gonadotropin-Releasing Hormone	Hormone controlling the release of LH and FSH from the pituitary.

Abbrevation	Full Term	Definition/Context
LH	Luteinizing Hormone	Pituitary hormone regulating ovulation and androgen production.
FSH	Follicle-Stimulating Hormone	Pituitary hormone regulating ovarian follicle growth and estrogen release.
MASLD	Metabolic dysfunction–associated steatotic liver disease	Liver fat due to metabolic dysfunction.
MASH	Metabolic dysfunction-associated steatohepatitis	MASLD with inflammation and liver damage.
mFG	modified Ferriman–Gallwey score	It's a clinical tool used to assess the severity of hirsutism (excess male-pattern hair growth in women).
MoA	Mechanism of Action	How a drug or intervention produces its effects in the body.
PMOS	Polyendocrine metabolic ovarian syndrome	A common endocrine disorder in women causing infertility, irregular menses, and hyperandrogenism.
PRO	Patient reported outcomes	Direct reports from patients about their health status, symptoms, or quality of life, without interpretation by clinicians.
RWD	Real World Data	Data on health care and outcomes collected outside clinical trials, from sources like electronic health records, registries, insurance claims, or patient-generated data.
SHBG	Sex Hormone-Binding Globulin	Protein that binds sex hormones and regulates their bioavailability.
TPP	Target Product Profile	The TPP defines the desired characteristics, intended use, and key development goals of a new medical product to guide research, regulatory, and commercial decision-making throughout the development process.
VAT	Visceral Adipose Tissue	Fat stored within the abdominal cavity, surrounding internal organs such as the liver, pancreas, and intestines. VAT is metabolically active and strongly associated with increased risks of insulin resistance, cardiovascular disease, metabolic syndrome, and inflammation, distinguishing it from subcutaneous fat which is located beneath the skin.

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