Review Article

Personalized metformin treatment in PCOS: Integrating Artificial intelligence and Biomarkers

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ABSTRACT

Polycystic ovary syndrome (PCOS) is a heterogeneous endocrine disorder associated with reproductive dysfunction, insulin resistance, metabolic syndrome, and increased long-term cardiovascular risk. Metformin remains a cornerstone therapy in PCOS management because of its beneficial effects on insulin sensitivity, ovulation, menstrual regularity, and metabolic parameters. However, substantial inter-individual variability in therapeutic response limits its effectiveness, highlighting the need for precision medicine approaches. This narrative review synthesizes current evidence regarding biomarkers and artificial intelligence (AI)-based strategies for personalizing metformin therapy in PCOS. Key metabolic biomarkers such as HOMA-IR, fasting insulin, and HbA1c, alongside hormonal markers including anti-Müllerian hormone (AMH), testosterone, luteinizing hormone/follicle-stimulating hormone ratio, and sex hormone-binding globulin, demonstrate potential in predicting treatment response. Inflammatory biomarkers and emerging molecular markers, particularly microRNAs and pharmacogenomic variants, may further refine patient stratification. The review also evaluates the growing role of AI and machine learning in PCOS diagnosis, risk stratification, and treatment prediction. Machine learning models integrating clinical, biochemical, genomic, and lifestyle data could identify likely responders to metformin before treatment initiation, thereby reducing empirical prescribing and adverse effects. A conceptual AI-assisted clinical decision support framework is proposed to guide future translational research and clinical implementation. Despite promising advances, challenges related to dataset quality, model interpretability, algorithm bias, and external validation remain significant barriers. Future progress will require multi-center collaborations, standardized phenotyping, explainable AI models, and integration of multi-omics and digital health technologies to enable truly personalized metformin therapy in PCOS.

Key words: PCOS; Metformin; Artificial Intelligence; Biomarkers; Precision Medicine; Personalized Therapy; Insulin Resistance.

Polycystic ovary syndrome (PCOS) is a complex, multisystem endocrine disorder characterized by hyperandrogenism, ovulatory dysfunction, and polycystic ovarian morphology on ultrasound [1]. Diagnosed using the Rotterdam consensus criteria, PCOS affects approximately 6–21% of women of reproductive age, depending on the diagnostic criteria applied and the population studied [2]. Beyond its reproductive sequelae, PCOS imposes a substantial metabolic burden, with 50–80% of affected women demonstrating insulin resistance and up to 10% progressing to type 2 diabetes mellitus within a decade of diagnosis [3]. The clinical manifestations of PCOS are extraordinarily diverse, encompassing menstrual irregularity, anovulatory infertility, hirsutism, acne, alopecia, obesity, dyslipidemia, and psychological morbidity, including anxiety and depression [4].

This phenotypic heterogeneity reflects underlying differences in pathophysiology, genetic architecture, and environmental exposures, posing a significant challenge to both diagnosis and management [5]. The global economic burden of PCOS is considerable, with direct healthcare costs related to fertility treatments, metabolic monitoring, and long-term cardiovascular risk management [6]. Metformin, a biguanide originally licensed for type 2 diabetes, has been used off-label in PCOS management for over three decades. Its primary mechanism involves activation of AMP-activated protein kinase (AMPK), which in turn reduces hepatic gluconeogenesis and enhances peripheral insulin sensitivity [7].

These effects translate into clinically meaningful improvements in menstrual regularity, ovulation rates, androgen levels, and cardiometabolic parameters [8]. International guidelines from the Endocrine Society and the European Society of Human Reproduction and Embryology (ESHRE) currently recommend metformin as an adjunct in PCOS management, particularly for metabolic risk reduction

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and ovulation induction in clomiphene-resistant patients [9]. Despite its widespread use, metformin therapy in PCOS is hampered by significant inter-individual variability in treatment response. A proportion of patients achieve robust glycemic and reproductive improvements, whilst others derive minimal benefit or experience dose-limiting gastrointestinal adverse effects [10].

The current approach to metformin prescribing in PCOS remains largely empirical, lacking validated tools to prospectively identify likely responders. This 'one-size-fits-all' paradigm is increasingly inadequate in the era of precision medicine, wherein molecular phenotyping and data-driven decision-making offer the means to tailor therapies to individual patient profiles [11]. This narrative review aims to synthesize the current evidence on biomarkers and artificial intelligence approaches relevant to personalizing metformin therapy in PCOS. The review further identifies critical research gaps and proposes a conceptual AI-assisted clinical decision framework to guide future research and clinical application.

2. METFORMIN IN PCOS: CURRENT EVIDENCE

2.1 Mechanism of Action

The molecular pharmacology of metformin in PCOS is principally mediated through AMPK activation in hepatic and peripheral tissues. By inhibiting mitochondrial complex I, metformin raises the intracellular AMP/ATP ratio, triggering AMPK phosphorylation and subsequent suppression of fatty acid synthesis and hepatic glucose output [7]. In the ovarian microenvironment, metformin attenuates androgen biosynthesis by inhibiting the cytochrome P450c17 enzyme and reduces insulin-stimulated luteinizing hormone (LH) receptor expression on theca cells [12]. Additional mechanisms include modulation of the gut microbiome composition, reduction of circulating insulin-like growth factor-1 (IGF-1), and attenuation of inflammatory signaling cascades [13].

2.2 Reproductive Benefits

Randomized controlled trials have consistently demonstrated that metformin improves menstrual cycle regularity in oligo/anovulatory women with PCOS, with reported rates of menstrual normalization ranging from 40% to 70% in various cohort studies [14]. When used as an ovulation induction agent, metformin achieves ovulation rates of approximately 40%, a figure lower than clomiphene citrate but potentially superior in specific metabolic phenotypes [15]. Meta-analyses confirm that metformin combined with clomiphene yields higher live birth rates than either agent alone in clomiphene-resistant patients [16]. Continuing metformin throughout the first trimester may additionally reduce miscarriage risk and gestational diabetes incidence in PCOS pregnancies [17].

2.3 Metabolic Benefits

The metabolic efficacy of metformin in PCOS is well-established. Systematic reviews document significant reductions in fasting insulin, HOMA-IR, total testosterone, and LH/FSH ratio, as well as modest reductions in body mass index (BMI) and waist circumference [18]. Favorable effects on lipid profiles, notably reductions in total cholesterol and low-density lipoprotein (LDL), have also been reported, though the magnitude varies across studies [19]. Long-term metformin use is associated with a 40–50% reduction in the risk of progression from impaired glucose tolerance to overt type 2 diabetes in women with PCOS [20].

2.4 Limitations of Metformin Therapy

Notwithstanding its benefits, metformin therapy in PCOS is characterized by several important limitations. Gastrointestinal side effects, including nausea, diarrhea, and abdominal discomfort, affect up to 25% of patients and are a primary reason for discontinuation [21]. More critically, response rates are highly variable, with a subset of patients exhibiting no meaningful improvement in metabolic or reproductive parameters despite adequate dosing and adherence [22]. This variability is partly attributable to polymorphisms in the organic cation transporter 1 (OCT1) and OCT2 genes, which govern metformin intestinal absorption and renal elimination, respectively [23]. The absence of validated stratification tools means clinicians cannot reliably predict which patients will benefit before initiating therapy.

3. CLINICAL HETEROGENEITY OF PCOS

3.1 PCOS Phenotypes

The Rotterdam criteria identify four principal PCOS phenotypes based on the combination of hyperandrogenism (H), oligo-anovulation (O), and polycystic ovarian morphology (P): Phenotype A (H+O+P), the 'classic' or most severe form; Phenotype B (H+O), characterized by hyperandrogenism and anovulation without PCO morphology; Phenotype C (H+P), the 'ovulatory' phenotype with preserved menstrual cyclicity; and Phenotype D (O+P), the mildest variant lacking frank hyperandrogenism [1,2].

These phenotypes differ substantially in their metabolic risk profiles. Phenotype A carries the greatest risk of insulin resistance, dyslipidemia, and cardiovascular disease, whilst Phenotype D is associated with the most favorable metabolic profile [3,4]. Hormonal disturbances also vary markedly: AMH levels are highest in Phenotypes A and B, and LH hypersecretion is most pronounced in non-obese phenotypes [5]. These distinctions have direct implications for the anticipated efficacy of metformin.

3.2 Impact on Metformin Response

Despite the clinical significance of PCOS phenotypic classification, phenotype-stratified metformin trials are conspicuously absent from the literature. Current evidence

suggests that women with the metabolic phenotype (high HOMA-IR, hyperinsulinemia) are more likely to respond to metformin [24], whereas those with predominantly androgenic or normal insulinemic phenotypes may derive lesser benefit [25]. This research gap underscores the need for prospective, phenotype-specific treatment trials and reinforces the rationale for biomarker-guided patient stratification.

4. BIOMARKERS FOR PERSONALIZED METFORMIN THERAPY

The identification of reliable predictive biomarkers is fundamental to any precision medicine approach. A range of metabolic, hormonal, inflammatory, and molecular biomarkers has been evaluated in the context of PCOS and metformin therapy, with varying degrees of evidence supporting their predictive utility.

4.1 Metabolic Biomarkers

Fasting insulin and the homeostatic model assessment of insulin resistance (HOMA-IR) are the most widely studied metabolic biomarkers in PCOS. Elevated baseline HOMA-IR has been consistently associated with a greater magnitude of glycemic improvement following metformin therapy, supporting its role as a stratification criterion [24]. HbA1c, whilst reflecting longer-term glycemic control, provides additional predictive information, particularly in patients with borderline dysglycemia [15]. Lipid biomarkers, elevated triglycerides, and reduced HDL cholesterol have been associated with greater cardiovascular risk in PCOS and may partially predict differential metformin response [19,26].

4.2 Hormonal Biomarkers

Anti-Müllerian hormone (AMH) has emerged as a clinically valuable biomarker in PCOS, reflecting antral follicle count and ovarian reserve. AMH levels are 2–4 times higher in PCOS patients compared to age-matched controls, and metformin therapy results in AMH reduction, which correlates with ovarian response normalization [27]. Total and free testosterone, measured by liquid chromatography-tandem mass spectrometry, serve as markers of androgenic burden; their reduction following metformin therapy reflects improvements in ovarian theca cell insulin sensitivity [8]. An elevated LH/FSH ratio (>2) is a sensitive indicator of hypothalamic dysregulation in PCOS and may identify patients most likely to benefit from metformin's gonadotrophin-modulating effects [28]. Sex hormone-binding globulin (SHBG) inversely correlates with insulin resistance and is an independent predictor of metformin response in several observational studies [29].

4.3 Inflammatory Biomarkers

Chronic low-grade inflammation is a pathological hallmark of PCOS, with circulating concentrations of high-sensitivity C-reactive protein (hsCRP), tumor necrosis factor-alpha (TNF-α), and interleukin-6 (IL-6) consistently elevated relative to controls [30]. Metformin exerts pleiotropic anti-inflammatory effects via NF-κB pathway suppression, and baseline inflammatory biomarker profiles may predict the magnitude of this anti-inflammatory response [31]. Elevated hsCRP before treatment initiation has been associated with attenuated metformin efficacy in some metabolic studies, suggesting that inflammation severity may modulate treatment responsiveness [32].

4.4 Emerging Molecular Biomarkers

The identification of circulating microRNAs (miRNAs) as stable, tissue-specific biomarkers has opened novel avenues for predicting drug response in PCOS. miR-93, miR-21, and miR-122 have been implicated in insulin signaling pathways relevant to PCOS pathophysiology, and their expression profiles may stratify patients according to metformin sensitivity [33,34]. Metabolomics profiling using nuclear magnetic resonance spectroscopy and mass spectrometry has identified distinct metabolic signatures in PCOS subgroups that correlate with insulin resistance severity and inflammatory status [35]. Integration of these omics-level biomarkers with clinical phenotyping represents the frontier of precision PCOS management. However, no validated composite biomarker panel currently exists to prospectively predict metformin response, representing a critical gap in the field [36] (Table 1).

Table 1: Biomarkers Evaluated for Predicting Metformin Response in PCOS

Biomarker	Category	Role in Metformin Response
HOMA-IR [24]	Metabolic	High HOMA-IR predicts better glycemic response
HbA1c [15]	Metabolic	Baseline HbA1c correlates with treatment efficacy
Fasting Insulin [25]	Metabolic	Elevated levels associated with a positive response
AMH [27]	Hormonal	Reduced by metformin; predicts reproductive outcome
Testosterone (total) [8]	Hormonal	Decline indicates androgenic improvement
CRP [31]	Inflammatory	High baseline CRP may reduce efficacy
miR-93 [36]	Molecular	Modulates insulin signaling; emerging biomarker

5. ARTIFICIAL INTELLIGENCE IN PCOS MANAGEMENT

5.1 Introduction to AI in Healthcare

Artificial intelligence (AI) and machine learning (ML) have undergone rapid translational development in medicine over the past decade, with demonstrated utility in medical image analysis, genomic interpretation, risk prediction, and drug response modelling [37]. AI encompasses a spectrum of computational methodologies, including supervised machine

learning (logistic regression, support vector machines, random forests), deep learning (convolutional and recurrent neural networks), and natural language processing (NLP), each with distinct strengths and application domains [38]. In the context of complex endocrine disorders characterized by multifactorial pathophysiology and phenotypic heterogeneity, AI methods offer particular promise for uncovering predictive patterns that elude conventional statistical approaches [39].

5.2 Machine Learning Applications in PCOS

The application of machine learning to PCOS diagnosis has yielded consistently high discriminatory performance. Support vector machine classifiers trained on clinical, biochemical, and ultrasound features have achieved AUC values exceeding 0.90 for PCOS diagnosis, outperforming logistic regression in several comparative studies [40]. Random forest models incorporating hormonal and metabolic variables have demonstrated robust performance for identifying metabolic syndrome risk in PCOS cohorts [41]. Neural network architectures have been applied to predict ovarian response to gonadotropin stimulation in assisted reproduction contexts, with promising early results [42].

Risk stratification represents another burgeoning application. ML algorithms applied to electronic health record (EHR) data have enabled identification of PCOS patients at elevated risk of type 2 diabetes and cardiovascular disease, facilitating early preventive intervention [43]. Clustering algorithms (k-means, hierarchical clustering) applied to multi-dimensional PCOS datasets have identified novel biological subgroups that partially recapitulate the Rotterdam phenotypes whilst revealing additional metabolic heterogeneity [44].

5.3 AI Models for Treatment Response Prediction

Despite the burgeoning literature on AI in PCOS diagnosis and risk stratification, models specifically designed to predict metformin treatment response remain scarce. A small number of studies have applied logistic regression and decision tree algorithms to predict glycemic response to metformin in broader diabetic populations, demonstrating that baseline HbA1c, BMI, and insulin secretory capacity are key predictive features [45]. Transferring these methodological approaches to PCOS-specific cohorts, incorporating PCOS-relevant biomarkers, represents a logical and high-impact research direction. Natural language processing applied to clinical narratives from EHR systems has demonstrated potential for retrospective identification of metformin responders and non-responders based on documented treatment outcomes [46].

5.4 Challenges and Limitations

Several substantive challenges limit the current deployment of AI in PCOS management. Training datasets frequently suffer from class imbalance, limited sample sizes, and insufficient clinical annotation, which compromise model generalizability [47]. The 'black box' nature of deep learning architectures creates interpretability barriers that impede clinical adoption, particularly in regulatory and ethical contexts requiring transparent decision rationale [48]. Algorithm bias arising from the underrepresentation of ethnic minorities, obese phenotypes, and low-income populations in training datasets poses a significant equity concern [49]. Prospective external validation studies are largely absent, and without rigorous validation in diverse, independent cohorts, the clinical utility of existing AI models for PCOS management cannot be confirmed [50].

6. INTEGRATING AI AND BIOMARKERS FOR PERSONALIZED METFORMIN THERAPY

6.1 Conceptual Framework

A precision medicine framework for metformin therapy in PCOS requires the systematic integration of multi-domain input variables into a clinically actionable prediction model. The proposed input architecture includes: (1) clinical characteristics are Age, BMI, phenotype classification, disease duration, family history of type 2 diabetes; (2) hormonal biomarkers are AMH, total testosterone, LH/FSH ratio, SHBG; (3) metabolic biomarkers are fasting insulin, HOMA-IR, HbA1c, lipid profile; (4) inflammatory markers are hsCRP, IL-6; and (5) lifestyle factors are physical activity level, dietary patterns, smoking status. This multi-domain feature matrix would serve as input to an ML prediction model trained on labelled cohorts of PCOS patients with documented metformin treatment outcomes [11,39].

6.2 AI-Based Prediction Models

The proposed model would stratify patients into three response categories: high responder, moderate responder, and poor responder, enabling pre-treatment individualization of therapeutic strategy. High responders characterized by elevated HOMA-IR, BMI ≥25 kg/m², Phenotype A classification, and elevated AMH would be prioritized for early metformin initiation at target doses. Moderate responders may benefit from adjunct lifestyle interventions or combination pharmacotherapy. Poor responders, potentially those with normal insulinemic phenotypes or significant inflammatory burden, could be redirected toward alternative agents (inositol, GLP-1 receptor agonists) without incurring the delay and side effect exposure of a failed metformin trial [10,22].

Ensemble ML methods, including gradient boosting (XGBoost, Light GBM) and stacked classifiers, have demonstrated superior performance in multi-class clinical prediction tasks compared to single algorithms [37,41]. Incorporating Shapley additive explanations (SHAP) or local interpretable model-agnostic explanations (LIME) into the model architecture would provide feature-level explanations for individual predictions, directly addressing the interpretability challenge and supporting clinician-facing deployment [48].

6.3 Clinical Decision Support Systems

The ultimate translational objective of this framework is a clinical decision support system (CDSS) integrated within the electronic health record workflow. Clinicians would receive a real-time, explainable recommendation at the point of prescribing, for example: 'Based on this patient's metabolic profile (HOMA-IR 4.2, fasting insulin 22 mU/L, Phenotype A), this patient is classified as a highly likely responder to metformin. Recommended initiation dose: 500 mg twice daily with gradual up-titration.' This paradigm represents a significant departure from current empirical practice and aligns PCOS management with the precision medicine approaches already established in oncology and pharmacogenomics [11,43]. Importantly, the CDSS must be designed with interpretability, user-interface usability, and workflow integration as primary design constraints, and must undergo prospective clinical validation before (Table 2).

Table 2: Current Clinical Uses of Metformin in PCOS

Clinical Indication	Dose Range	Evidence Level
Insulin resistance / T2DM prevention [8]	500–2000 mg/day	Level A
Menstrual cycle regulation [14]	1000–1500 mg/day	Level B
Ovulation induction [15]	1500–2000 mg/day	Level A
Weight management (adjunct) [16]	1000–2000 mg/day	Level B
Prevention of gestational DM [17]	500–2500 mg/day	Level B

7. FUTURE DIRECTIONS

7.1 Multi-Omics Integration

The next frontier in PCOS biomarker science involves the systematic integration of genomics, transcriptomics, proteomics, and metabolomics data within unified analytical frameworks. Genome-wide association studies (GWAS) have identified over 30 loci associated with PCOS susceptibility, including variants in the LHCGR, THADA, DENND1A, and YAP1 genes, several of which influence insulin sensitivity and androgen biosynthesis [33]. Pharmacogenomic variants, particularly in OCT1 (SLC22A1) and MATE1 (SLC47A1), exert documented effects on metformin bioavailability and tubular secretion and represent candidate predictors of treatment response [23]. Metabolomics studies using untargeted mass spectrometry have identified branched-chain amino acid accumulation, altered sphingolipid metabolism, and disrupted one-carbon metabolism as PCOS-specific signatures that may differentially predict metformin efficacy [35].

7.2 Explainable AI Models

As AI models transition from research tools to clinical instruments, explainability becomes non-negotiable. Explainable AI (XAI) methods such as SHAP values, attention mechanisms in transformer architectures, and counterfactual explanations enable clinicians to understand the basis of algorithmic recommendations and maintain clinical oversight [48]. Regulatory frameworks in the European Union (EU AI Act) and the United States (FDA Software as a Medical Device guidance) increasingly mandate transparency and explainability for AI-based clinical tools, making XAI integration a practical prerequisite for market authorization. Future PCOS AI models should be developed with XAI as an architectural requirement rather than a post-hoc addition [49].

7.3 Digital Health and Wearable Technologies

Continuous physiological monitoring via wearable technologies offers the potential to dramatically enrich the input data available to PCOS precision medicine models. Continuous glucose monitors (CGM) provide longitudinal glycemic variability metrics, time-in-range, and glycemic excursion frequency that are not captured by spot HbA1c measurements and may be more sensitive predictors of metformin response [43]. Accelerometers and heart rate variability monitors provide objective physical activity and autonomic function data; smart scales capture serial weight and body composition trajectories. Integration of wearable-derived data streams into ML prediction pipelines represents a technically feasible and clinically impactful innovation, subject to data standardization and interoperability challenges.

7.4 Precision Medicine Approaches

The broader precision medicine agenda in endocrinology is gaining momentum, with pharmacogenomics-guided prescribing already informing practice in diabetes (CYP2C9-guided sulphonyl urea dosing) and thyroid disease (TPMT-guided ethionamide therapy) [11]. Applying analogous pharmacogenomic reasoning to metformin therapy in PCOS—integrating OCT1 genotype, inflammatory biomarker profile, and PCOS phenotype could reduce the duration of ineffective treatment and mitigate adverse effects. International research consortia are needed to generate the large, well-annotated datasets required to train and validate such models across diverse ethnic populations [50].

7.5 Development of Personalized Treatment Algorithms

Realizing the vision of personalized metformin therapy in PCOS will require coordinated effort across clinical endocrinology, reproductive medicine, medical informatics, bioinformatics, and ethics. A proposed research roadmap encompasses: (1) establishment of a multi-center PCOS biobank with standardized phenotyping, biobanking protocols, and treatment outcome documentation; (2) development of a composite biomarker scoring tool validated in prospective cohorts; (3) training and external validation of an ensemble ML model for metformin response prediction; (4) co-design of a clinician-facing CDSS with human-computer interaction specialists; and (5) regulatory submission and real-world effectiveness evaluation through pragmatic trials.

8. PROPOSED RESEARCH FRAMEWORK TO FILL EXISTING GAPS

The current literature is characterized by a critical absence of validated tools for pre-treatment identification of metformin responders in PCOS. This gap perpetuates a cycle of empirical prescribing, adverse effect exposure, and therapeutic delay that impairs patient outcomes and healthcare efficiency.

We propose the development of an AI-driven Metformin Response Prediction Model (MRPM-PCOS) incorporating the following multi-domain input variables: PCOS phenotype (Rotterdam classification); baseline HOMA-IR and fasting insulin; HbA1c; total testosterone and AMH; hsCRP; BMI and waist-to-hip ratio; relevant pharmacogenomic variants (OCT1, OCT2); and lifestyle parameters (physical activity score, dietary quality index). The primary outcome variable for model training would be 'significant metformin response,' defined as a ≥30% reduction in HOMA-IR and/or restoration of ovulatory menstrual cycles at 6 months.

The expected clinical impact of this model includes: improved treatment outcomes through early identification of high responders; reduced trial-and-error prescribing and associated adverse effects; better patient stratification enabling targeted recruitment for future clinical trials; and healthcare cost savings through avoidance of ineffective treatment courses. Implementation would require prospective data collection from multi-ethnic cohorts, rigorous cross-validation, and transparent reporting according to the TRIPOD-ML guidelines for clinical prediction model development.

9. CHALLENGES AND ETHICAL CONSIDERATIONS

The development and deployment of AI-assisted precision medicine tools in PCOS requires careful navigation of several intersecting ethical and practical domains. Data privacy is paramount: the collection of genomic, hormonal, and lifestyle data from vulnerable patient populations necessitates robust informed consent frameworks, de-identification protocols, and compliance with GDPR (General Data Protection Regulation) and HIPAA (Health Insurance Portability and Accountability Act) standards [49]. Federated learning architectures, which allow model training across distributed datasets without centralizing raw patient data, offer a promising technical solution to privacy preservation in multi-center PCOS research.

Algorithm bias represents a substantial equity concern. Most existing PCOS ML models have been developed on datasets overrepresenting White, Western, and normal-weight populations, limiting generalizability to South Asian, East Asian, and African populations, in whom PCOS phenotypes and insulin resistance patterns differ markedly [50]. Ensuring demographic diversity in training datasets and implementing fairness-aware machine learning techniques are ethical imperatives for equitable AI deployment. Clinical validation challenges include the absence of standardized outcome definitions across PCOS trials, variable metformin adherence measurement, and the heterogeneity of co-interventions (dietary modification, physical activity programs, concomitant medications) that confound treatment response attribution [22].

Accessibility in low-resource settings is a further consideration. AI-driven CDSS tools requiring advanced laboratory biomarker panels and genomic testing may be inaccessible in primary care settings in low- and middle-income countries (LMICs), where the burden of PCOS is high. Future model development should incorporate LMIC-feasible biomarker subsets and explore mobile health (mHealth) delivery platforms to maximize global applicability. Clinician education regarding AI tool limitations, appropriate use, and shared decision-making with patients is essential to safe and effective implementation.

CONCLUSION

PCOS represents one of the most clinically challenging and under-resourced endocrine disorders, combining reproductive, metabolic, and psychological morbidity in a heterogeneous patient population. Metformin remains a cornerstone of management, yet its therapeutic utility is constrained by significant inter-individual variability in response that current clinical tools cannot predict. This review has synthesized the evidence supporting the use of metabolic, hormonal, inflammatory, and molecular biomarkers as predictors of metformin response and has evaluated the expanding landscape of AI applications in PCOS diagnosis, risk stratification, and treatment optimization.

The convergence of validated biomarker panels with advanced machine learning architectures offers a transformative precision medicine opportunity: an AI-assisted clinical decision support framework capable of stratifying PCOS patients by predicted metformin response before treatment initiation. Such a framework would reduce empirical prescribing, minimize adverse effect exposure, and align PCOS management with the personalized medicine paradigm, transforming oncology and other medical disciplines. Realizing this vision requires coordinated investment in multi-centre biobanking, phenotype-specific clinical trials, explainable AI model development, and rigorous prospective validation across ethnically diverse populations.

The integration of digital health technologies, continuous glucose monitoring, wearable biosensors, mHealth platforms with multi-omics data, and AI analytics will further enrich the precision medicine ecosystem for PCOS. The field stands at an inflection point: the scientific and technological tools required to personalize metformin therapy are within reach, awaiting the clinical will, research infrastructure, and interdisciplinary collaboration to translate them into practice.

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