

**ESTROGEN, PROGESTERONE, AND MOLECULAR SIGNALING PATHWAYS
IN THE DEVELOPMENT OF UTERINE LEIOMYOMAS: AN INTEGRATIVE
REVIEW OF MECHANISMS, CLINICAL EVIDENCE, REAL-WORLD DATA,
AND TRANSLATIONAL PERSPECTIVES**

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Abstract

Background: Uterine leiomyomas are benign monoclonal tumors whose development depends on the integration of ovarian steroid signaling, acquired molecular lesions, fibrotic extracellular-matrix remodeling, and interactions between differentiated tumor cells and tumor-associated stem or progenitor populations. Estrogen is not merely a direct mitogen: it supports progesterone receptor expression and alters the microenvironment in which progesterone-dependent growth signals operate. **Objective:** To critically integrate the mechanistic literature on estrogen, progesterone, MED12, HMGA2, WNT/ β -catenin, TGF- β /SMAD, PI3K/AKT/mTOR, MAPK, and mechanotransduction with evidence from clinical therapeutics and emerging real-world analytics. **Methods:** A structured, non-systematic evidence synthesis was organized around landmark experimental research, contemporary clinical reviews, regulator guidance, trial evidence, and digital health policy. **Methods for future observational analyses,** including propensity score matching, weighting, target-trial emulation, time-to-event models and machine learning, are specified without claiming that any new patient-level analysis was undertaken. **Results:** The evidence supports a model of genetic initiation and hormone-sensitive tumor maintenance in which progesterone acts through paracrine networks and matrix feedback. Molecular subtype, lesion location, reproductive plans, and symptom profile limit the usefulness of a single therapeutic algorithm. Clinical trials support hormonal suppression as an option for fibroid-associated heavy menstrual bleeding, whereas causal claims about long-term effectiveness require carefully designed comparative real-world studies. Artificial intelligence may support imaging, phenotyping, and treatment monitoring, but calibration, transportability, dataset shift and algorithmic fairness must be addressed before deployment. **Conclusions:** The clinical translation of leiomyoma molecular biology requires phenotype-specific

outcome definitions, transparent observational methods, prospective validation, safety surveillance, and equitable access. Evidence gaps are particularly important in low-resource health systems implementing electronic medical records and electronic prescribing.

Keywords: uterine leiomyoma; uterine fibroids; estrogen receptor; progesterone receptor; MED12; HMGA2; WNT/ β -catenin; TGF- β ; extracellular matrix; PI3K/AKT/mTOR; real-world evidence; causal inference; artificial intelligence; pharmacovigilance.

1. Introduction

Disease framing

Uterine leiomyomas are heterogeneous, typically benign smooth-muscle neoplasms of the myometrium. Their clinical importance cannot be captured by tumor diameter alone: heavy menstrual bleeding, pelvic pressure, pain, anemia, reproductive concerns, and repeated procedures generate different burdens depending on anatomy and patient priorities. Consequently, a mechanistic synthesis must distinguish tumor initiation, subsequent growth, symptomatic expression, and the consequences of treatment. The contemporary clinical overview by Stewart and Laughlin-Tommaso provides an evidence-based clinical context [1].

Hormones as permissive and instructive signals

Estrogen and progesterone should not be represented as interchangeable growth stimuli. Estradiol can increase progesterone-receptor abundance and condition stromal signaling, whereas progesterone-dependent transcription and paracrine mediators influence fibroid cell survival and expansion. The ovarian cycle supplies repeated exposures, yet identical endocrine environments produce different tumor phenotypes because somatic mutations, receptor context, inflammation, and extracellular matrix differ between lesions. This interaction explains why local tumors can behave differently in the same patient [2,3].

Genetic and tissue context

Recurrent MED12 variants, HMGA2 rearrangements or overexpression, fumarate hydratase-associated lesions, and other molecular alterations make a purely endocrine explanation incomplete. Molecular subtype is an important biological descriptor, but current clinical practice does not generally sequence every leiomyoma to allocate routine medication. It is methodologically hazardous to assume that a genotype discovered in excised tissue is available at the initial treatment decision or that it is a validated predictive marker of drug response [2–4].



RWD and RWE

Real-world data (RWD) are routinely collected information on health status and health-care delivery, including electronic health records, prescriptions, claims, registries and patient-generated digital data. Real-world evidence (RWE) refers to clinical evidence regarding use, benefits or risks derived from the analysis of RWD. The distinction is crucial: possessing a database does not itself establish comparative effectiveness. The intended estimand, eligibility criteria, treatment strategy, outcome ascertainment, and bias-control design determine whether information becomes interpretable evidence [5,6].

RCTs versus routine care

Randomized controlled trials (RCTs) usually provide stronger protection against baseline confounding, with prespecified interventions and standardized follow-up. However, eligibility restrictions, treatment adherence, protocol-defined visit frequency and limited observation periods may reduce correspondence with routine gynecologic care. RWE can address long-term persistence, switching, discontinuation, rare safety events and health-service inequities. It cannot automatically reproduce randomization: confounding by indication, outcome misclassification, and differential surveillance may dominate an otherwise large sample [5,7].

Efficacy and effectiveness

Efficacy describes benefit under controlled study conditions; effectiveness concerns the benefit achieved in ordinary care. In fibroids, efficacy might be assessed by protocolized bleeding reduction under an oral gonadotropin-releasing hormone antagonist regimen, whereas effectiveness must account for affordability, refill persistence, concurrent iron replacement, comorbid conditions, access to ultrasound and preferences about fertility. A smaller treatment effect in a health-system database may reflect implementation failures rather than molecular treatment resistance [1,8].

Regulatory context

FDA guidance addresses fitness for purpose of electronic health records and claims, data provenance, relevance and reliability, and the transparent use of RWD in regulatory decisions. EMA has expanded regulator-led RWE studies through DARWIN EU, while maintaining an explicit distinction between observational evidence and randomized findings. WHO guidance on artificial intelligence concentrates on safety, human autonomy, inclusiveness, transparency and accountability rather than endorsing specific fibroid algorithms. These positions are compatible but not interchangeable regulatory standards [5–10].

Artificial intelligence and scope

Image-based deep learning, natural-language processing of clinical narratives and outcome-prediction models may eventually combine sonographic lesion topology with endocrine treatment history. Yet an accurate segmentation network is not proof of an accurate treatment-effect model, and neither is a regulatory authorization for clinical use. This review is deliberately an integrative synthesis: it evaluates biological and methodological evidence without presenting manufactured patient cohorts, pooled effect estimates, or new experiments [9–11].

2. Materials and Methods

Study design. This manuscript is a critical integrative narrative review and a methodological proposal for future RWE research, not a completed systematic review, meta-analysis, or primary observational analysis. Literature discovery was informed by openly verifiable PubMed-indexed publications, journal articles, FDA and EMA guidance, WHO material, and Uzbekistan government communications. PubMed, Scopus, Web of Science, Embase and Cochrane Library are recommended search platforms for a fully reproducible update; comprehensive database access, duplicate removal and independent screening across each of them were not performed for this manuscript and are not claimed.

Suggested reproducible query: ("uterine leiomyoma" OR "uterine fibroid") AND (estrogen OR progesterone OR MED12 OR HMGA2 OR "WNT" OR "TGF-beta" OR mTOR OR "real-world evidence" OR "artificial intelligence"). A separate RWD search should combine leiomyoma and each treatment class with observational, registry, insurance claims, and comparative effectiveness. Dates emphasized: January 2020 to October 2026; earlier seminal causal-methodology and molecular-biology contributions are eligible where needed. Include peer-reviewed original studies, systematic reviews, randomized trial reports, practice guidelines and regulator reports. Exclude uncontrolled promotional material, inaccessible abstracts that cannot sustain a claim, duplicate records, and papers with unresolvable methodological flaws. No numerical PRISMA flow or pooled estimates are reported because there was no documented exhaustive systematic selection.

Propensity score matching

Estimate the conditional probability of receiving each prespecified treatment given pre-index covariates such as age, baseline hemoglobin, bleeding severity, lesion anatomy, reproductive intentions and previous therapy. Match patients on treatment propensity, evaluate standardized mean differences and empirical overlap, and report whether target



inference pertains to the matched population. Avoid controlling for variables that occur after treatment initiation.

Inverse probability weighting

Use stabilized inverse probability of treatment weights to construct a pseudopopulation with measured covariates balanced across treatment strategies. Examine positivity violations and extreme weights. For longitudinal switching or informative censoring, treatment and censoring weights may need time-varying models; conventional baseline weighting is not a universal fix.

Cox regression and survival analysis

Define time zero at treatment eligibility or initiation, not at an arbitrary later follow-up visit. Cox models estimate hazard ratios subject to proportional-hazards assumptions and adequate adjustment; consider restricted mean survival time if hazards are nonproportional. Clinically interpretable endpoints include time to surgery, recurrent heavy bleeding, anemia recurrence and discontinuation, each with carefully specified competing events.

Kaplan–Meier estimators

Estimate crude cumulative event-free survival with number-at-risk tables and confidence intervals; the method alone does not address confounding. For a competing event, such as hysterectomy precluding later fibroid-related fertility outcome, competing-risk cumulative incidence may be preferable to naive one-minus-Kaplan–Meier reporting.

Target trial emulation

Specify eligibility, assignment strategies, treatment start, grace periods, follow-up, primary outcome, causal contrast and analytic protocol before extracting records. Align eligibility and treatment assignment to limit immortal-time bias. A pragmatic comparison might evaluate early hormonal suppression versus an alternative eligible care strategy for women with measured fibroid-associated bleeding.

Causal inference and missing data

Draw directed acyclic graphs to identify confounders; consider sequential exchangeability, consistency and positivity. Multiple imputation assumes an explicit missingness process and requires compatible analyses; missing-not-at-random sensitivity analyses are needed when, for instance, follow-up imaging depends on symptom persistence. Negative-control outcomes and quantitative bias analysis strengthen interpretation.

Machine learning

Penalized regression, random forests and boosted trees can forecast clinical outcomes from structured covariates, but prediction is not estimation of counterfactual treatment benefit. Separate training and external validation institutions or time periods, avoid patient-level leakage across visits, and quantify calibration alongside discrimination. Report confidence intervals and clinically meaningful net benefit.

Deep learning and imaging

Convolutional and transformer-based networks may segment lesions on ultrasound or MRI. Reference segmentation should be blinded, multi-reader and sourced across scanners and institutions. Performance degradation by fibroid location, body habitus or operator can produce downstream inequities. Radiomics representations may capture image correlations without proving molecular subtype.

Natural language processing and LLMs

NLP can extract symptoms, pregnancy wishes, prior surgery, adverse effects and treatment discontinuation from narratives. LLM-based extraction must use controlled vocabularies, evidence spans, manual adjudication and prospective error audits. Hallucination, privacy leakage, spurious confidence and dialect variation require safeguards; generated clinical content must not silently replace a verified primary record.

3. Results: Integrated Evidence Synthesis

Results below are synthesized findings and reasoned interpretations from the cited literature, not estimates produced by an original dataset. Established molecular mechanisms are separated from plausible but insufficiently validated clinical translation. The largest analytical component is devoted to the cross-talk between hormones, genetic subtypes, extracellular-matrix biology, drug response, and real-world data systems.

3.1 Estrogen receptor signaling and tissue priming

Estradiol influences the uterine environment through nuclear estrogen receptors, receptor-associated transcription, and interactions with growth-factor signaling. The clinically relevant question is not whether estradiol is present but how its signaling is interpreted by mutated smooth-muscle cells, fibroblasts and progenitor populations. Local receptor expression, metabolizing enzymes and cross-talk with inflammatory mediators plausibly contribute to lesion-specific behavior. Estrogen-induced progesterone receptor expression constitutes a major bridge between the two hormonal systems. Selective manipulation of one receptor class may therefore reshape responsiveness to the other without fully switching off downstream matrix production.

Critical interpretation for estrogen receptor signaling and tissue priming: The biological evidence should be read alongside the clinical decision pathway rather than as a direct prescription rule. Studies often differ in lesion selection, comparator myometrium, hormonal exposure at sampling, assay platforms, and whether outcomes represent pathway activity, growth, bleeding or quality of life. A robust translational design would prespecify tissue and patient phenotypes, measure baseline severity before treatment, account for time-dependent intervention choices, and validate the proposed association in an independent cohort. Mechanistic plausibility alone is insufficient to infer a patient-level treatment advantage. The distinction is particularly important when a statistically associated molecular feature has no established actionable threshold or when follow-up procedures select patients according to persistent symptoms.

3.2 Progesterone receptor networks

Progesterone signaling is central to tumor persistence and growth. Differentiated cells that express progesterone receptors can stimulate neighboring stem-like cells through locally secreted WNT ligands and other paracrine factors. This model resolves an apparent paradox: a subset of tumor-initiating cells may exhibit low classical steroid receptor expression yet still depend on the systemic hormonal milieu. Functional response depends on receptor isoforms, co-regulators and downstream chromatin state. The tumor may thus resist a simple one-receptor, one-pathway therapeutic narrative.

Critical interpretation for progesterone receptor networks: The biological evidence should be read alongside the clinical decision pathway rather than as a direct prescription rule. Studies often differ in lesion selection, comparator myometrium, hormonal exposure at sampling, assay platforms, and whether outcomes represent pathway activity, growth, bleeding or quality of life. A robust translational design would prespecify tissue and patient phenotypes, measure baseline severity before treatment, account for time-dependent intervention choices, and validate the proposed association in an independent cohort. Mechanistic plausibility alone is insufficient to infer a patient-level treatment advantage. The distinction is particularly important when a statistically associated molecular feature has no established actionable threshold or when follow-up procedures select patients according to persistent symptoms.

3.3 MED12 and chromatin-associated regulation

MED12 encodes a Mediator-complex component involved in transcriptional regulation. Somatic changes, often affecting exon 2, identify a major molecular subtype and alter the relationship between chromatin regulation and growth signaling. Reported subtype proportions depend on sampling, histologic categorization and assay definitions; one

contemporary physiological review describes MED12 alterations in approximately 77% and HMGA2/1 abnormalities around 10% of the studied lesions [3]. These figures should not be casually generalized to every population or all lesions within a uterus. Within-patient multiclonality also complicates molecular extrapolation from one excised sample.

Critical interpretation for med12 and chromatin-associated regulation: The biological evidence should be read alongside the clinical decision pathway rather than as a direct prescription rule. Studies often differ in lesion selection, comparator myometrium, hormonal exposure at sampling, assay platforms, and whether outcomes represent pathway activity, growth, bleeding or quality of life. A robust translational design would prespecify tissue and patient phenotypes, measure baseline severity before treatment, account for time-dependent intervention choices, and validate the proposed association in an independent cohort. Mechanistic plausibility alone is insufficient to infer a patient-level treatment advantage. The distinction is particularly important when a statistically associated molecular feature has no established actionable threshold or when follow-up procedures select patients according to persistent symptoms.

3.4 HMGA2, alternative subtypes and heterogeneity

HMGA2-associated alterations change transcriptional architecture and may affect growth-factor programs, matrix accumulation and proliferation. Fumarate hydratase–related lesions represent another biologically distinct group with implications beyond routine hormonal response, including appropriate consideration of hereditary syndromes when indicated. Molecular subsets differ in morphology, signaling and potentially microenvironment. The present evidence does not justify prescribing specific drug classes solely on the basis of HMGA2 or MED12 status without prospective treatment-response validation.

Critical interpretation for hmga2, alternative subtypes and heterogeneity: The biological evidence should be read alongside the clinical decision pathway rather than as a direct prescription rule. Studies often differ in lesion selection, comparator myometrium, hormonal exposure at sampling, assay platforms, and whether outcomes represent pathway activity, growth, bleeding or quality of life. A robust translational design would prespecify tissue and patient phenotypes, measure baseline severity before treatment, account for time-dependent intervention choices, and validate the proposed association in an independent cohort. Mechanistic plausibility alone is insufficient to infer a patient-level treatment advantage. The distinction is particularly important when a statistically associated molecular feature has no established actionable threshold or when follow-up procedures select patients according to persistent symptoms.

3.5 WNT/ β -catenin and paracrine stem-cell activation

WNT signaling illustrates why hormone dependence need not coincide with uniform hormone receptor expression. Differentiated fibroid cells can provide WNT-family ligands, activating β -catenin-associated programs in neighboring compartments. Experimental demonstrations vary by tissue model and assay, however, and differential expression does not always establish causal necessity. A useful translational study would pair spatial transcriptomics with perturbation of WNT ligand production and independent validation of clinically relevant growth trajectories, rather than treating pathway enrichment as proof of therapeutic efficacy.

Critical interpretation for wnt/ β -catenin and paracrine stem-cell activation: The biological evidence should be read alongside the clinical decision pathway rather than as a direct prescription rule. Studies often differ in lesion selection, comparator myometrium, hormonal exposure at sampling, assay platforms, and whether outcomes represent pathway activity, growth, bleeding or quality of life. A robust translational design would prespecify tissue and patient phenotypes, measure baseline severity before treatment, account for time-dependent intervention choices, and validate the proposed association in an independent cohort. Mechanistic plausibility alone is insufficient to infer a patient-level treatment advantage. The distinction is particularly important when a statistically associated molecular feature has no established actionable threshold or when follow-up procedures select patients according to persistent symptoms.

3.6 TGF- β /SMAD signaling and fibrosis

TGF- β signaling drives fibroblast activation, collagen accumulation and changes in extracellular-matrix turnover, producing a fibrotic lesion rather than merely excess myocyte division. SMAD-mediated transcription connects secreted cytokines to structural remodeling. Quantifying this biology requires attention to matrix composition, cross-linking, tissue stiffness and perfusion; a change in tumor volume is an imperfect surrogate for fibrotic burden. If new pathway inhibitors are considered, adverse effects on wound healing and physiological tissue maintenance must be anticipated.

Critical interpretation for tgf- β /smad signaling and fibrosis: The biological evidence should be read alongside the clinical decision pathway rather than as a direct prescription rule. Studies often differ in lesion selection, comparator myometrium, hormonal exposure at sampling, assay platforms, and whether outcomes represent pathway activity, growth, bleeding or quality of life. A robust translational design would prespecify tissue and patient phenotypes, measure baseline severity before treatment, account for time-dependent intervention choices, and validate the proposed association in an independent cohort.

Mechanistic plausibility alone is insufficient to infer a patient-level treatment advantage. The distinction is particularly important when a statistically associated molecular feature has no established actionable threshold or when follow-up procedures select patients according to persistent symptoms.

3.7 PI3K/AKT/mTOR and growth-factor integration

PI3K/AKT/mTOR integrates nutrient, survival and growth-factor cues. Findings in fibroid tissues suggest functional interaction with hormone-sensitive proliferation and altered autophagy, but molecular activation is not equivalent to a proven druggable vulnerability. Clinical development must distinguish target engagement, lesion-volume response, symptom relief and safety. Cross-talk with WNT and TGF- β creates potential compensatory signaling, so single-pathway inhibition may be bypassed in heterogeneous tissue.

Critical interpretation for pi3k/akt/mtor and growth-factor integration: The biological evidence should be read alongside the clinical decision pathway rather than as a direct prescription rule. Studies often differ in lesion selection, comparator myometrium, hormonal exposure at sampling, assay platforms, and whether outcomes represent pathway activity, growth, bleeding or quality of life. A robust translational design would prespecify tissue and patient phenotypes, measure baseline severity before treatment, account for time-dependent intervention choices, and validate the proposed association in an independent cohort. Mechanistic plausibility alone is insufficient to infer a patient-level treatment advantage. The distinction is particularly important when a statistically associated molecular feature has no established actionable threshold or when follow-up procedures select patients according to persistent symptoms.

3.8 MAPK, ERK and steroid-growth factor cross-talk

MAPK/ERK acts downstream of diverse receptor tyrosine kinases and may mediate proliferative responses in hormone-primed cells. Ex vivo pathway changes are context-sensitive, and concentration-dependent effects may not reflect achievable exposure in patients. Future experiments should stratify by molecular subtype, menstrual-cycle stage, and prior hormonal therapy to distinguish intrinsic signaling from medication-induced shifts.

Critical interpretation for mapk, erk and steroid-growth factor cross-talk: The biological evidence should be read alongside the clinical decision pathway rather than as a direct prescription rule. Studies often differ in lesion selection, comparator myometrium, hormonal exposure at sampling, assay platforms, and whether outcomes represent pathway activity, growth, bleeding or quality of life. A robust translational design would prespecify tissue and

patient phenotypes, measure baseline severity before treatment, account for time-dependent intervention choices, and validate the proposed association in an independent cohort. Mechanistic plausibility alone is insufficient to infer a patient-level treatment advantage. The distinction is particularly important when a statistically associated molecular feature has no established actionable threshold or when follow-up procedures select patients according to persistent symptoms.

3.9 YAP/TAZ, Rho/ROCK and mechanotransduction

Accumulated extracellular matrix changes the physical properties of the tumor. Mechanosensitive pathways such as YAP/TAZ and Rho/ROCK can transduce stiffness into transcriptional and cytoskeletal responses, maintaining a feedback loop among fibrosis, cell survival and local mechanical strain. The clinical relevance extends to imaging: stiffness-sensitive measures could provide complementary disease characterization, yet scanner standardization and evidence of incremental value over basic anatomical classification remain necessary.

Critical interpretation for yap/taz, rho/rock and mechanotransduction: The biological evidence should be read alongside the clinical decision pathway rather than as a direct prescription rule. Studies often differ in lesion selection, comparator myometrium, hormonal exposure at sampling, assay platforms, and whether outcomes represent pathway activity, growth, bleeding or quality of life. A robust translational design would prespecify tissue and patient phenotypes, measure baseline severity before treatment, account for time-dependent intervention choices, and validate the proposed association in an independent cohort. Mechanistic plausibility alone is insufficient to infer a patient-level treatment advantage. The distinction is particularly important when a statistically associated molecular feature has no established actionable threshold or when follow-up procedures select patients according to persistent symptoms.

3.10 Hypoxia, angiogenesis and inflammation

As fibroids increase in size, vascular organization, localized oxygen tension, inflammation and extracellular-matrix deposition interact. Hypoxia-related responses might contribute to metabolic adaptation and growth factors, but a mechanistic observation is not evidence that every fibroid has pathological hypoxia. Lesion perfusion affects drug delivery and imaging contrast. Tissue oxygenation and angiogenesis must therefore be interpreted jointly with tissue architecture and clinical outcomes.

Critical interpretation for hypoxia, angiogenesis and inflammation: The biological evidence should be read alongside the clinical decision pathway rather than as a direct prescription

rule. Studies often differ in lesion selection, comparator myometrium, hormonal exposure at sampling, assay platforms, and whether outcomes represent pathway activity, growth, bleeding or quality of life. A robust translational design would prespecify tissue and patient phenotypes, measure baseline severity before treatment, account for time-dependent intervention choices, and validate the proposed association in an independent cohort. Mechanistic plausibility alone is insufficient to infer a patient-level treatment advantage. The distinction is particularly important when a statistically associated molecular feature has no established actionable threshold or when follow-up procedures select patients according to persistent symptoms.

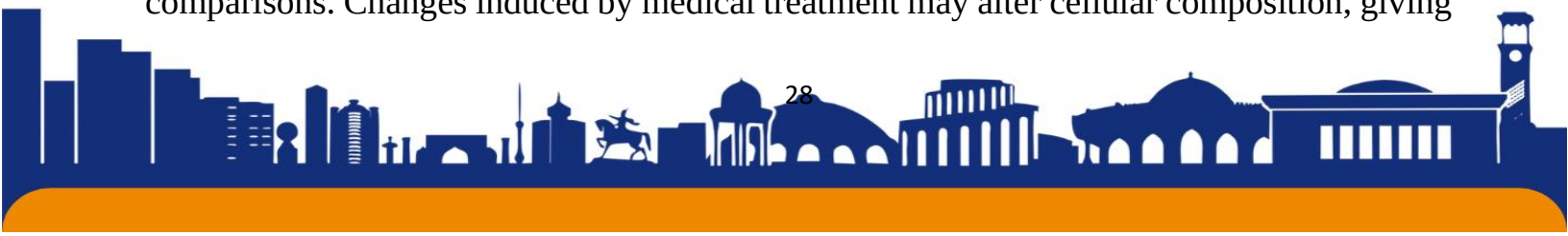
3.11 Extracellular matrix as a dynamic disease compartment

The extracellular matrix is both the product and amplifier of signaling abnormalities. Collagens, proteoglycans, matrix metalloproteinases and mechanical cues influence diffusion, cell-cell communication and tissue tension. A phenotype characterized by abundant matrix can behave differently from one with relatively high cellularity. Fibroid pharmacology should consequently measure bleeding, volume, symptom severity, anemia and quality of life rather than assuming that volume reduction alone is a sufficient endpoint.

Critical interpretation for extracellular matrix as a dynamic disease compartment: The biological evidence should be read alongside the clinical decision pathway rather than as a direct prescription rule. Studies often differ in lesion selection, comparator myometrium, hormonal exposure at sampling, assay platforms, and whether outcomes represent pathway activity, growth, bleeding or quality of life. A robust translational design would prespecify tissue and patient phenotypes, measure baseline severity before treatment, account for time-dependent intervention choices, and validate the proposed association in an independent cohort. Mechanistic plausibility alone is insufficient to infer a patient-level treatment advantage. The distinction is particularly important when a statistically associated molecular feature has no established actionable threshold or when follow-up procedures select patients according to persistent symptoms.

3.12 Epigenetic and transcriptomic regulation

Hormonal transcription factors bind within an epigenetic landscape shaped by somatic alterations, DNA methylation and chromatin accessibility. Spatial and single-cell studies have the potential to distinguish tumor smooth-muscle populations from fibroblasts, immune cells and vascular cells; however, sampling and batch effects complicate comparisons. Changes induced by medical treatment may alter cellular composition, giving



the false impression of pathway downregulation when the underlying effect is loss of one cell type.

Critical interpretation for epigenetic and transcriptomic regulation: The biological evidence should be read alongside the clinical decision pathway rather than as a direct prescription rule. Studies often differ in lesion selection, comparator myometrium, hormonal exposure at sampling, assay platforms, and whether outcomes represent pathway activity, growth, bleeding or quality of life. A robust translational design would prespecify tissue and patient phenotypes, measure baseline severity before treatment, account for time-dependent intervention choices, and validate the proposed association in an independent cohort. Mechanistic plausibility alone is insufficient to infer a patient-level treatment advantage. The distinction is particularly important when a statistically associated molecular feature has no established actionable threshold or when follow-up procedures select patients according to persistent symptoms.

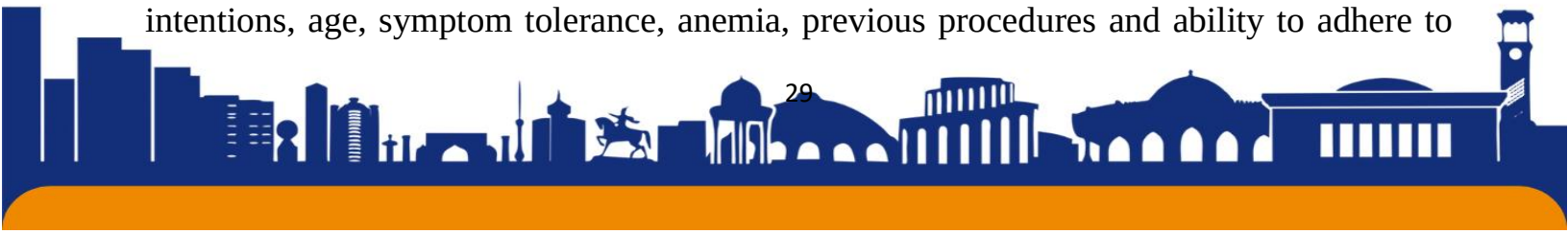
3.13 Anatomic phenotype and imaging

Submucosal, intramural and subserosal lesions differ in symptom generation and reproductive implications. Detailed ultrasound or MRI assessment provides an anatomical phenotype that molecular testing currently cannot replace. In an effectiveness model, location and total burden are candidate effect modifiers as well as confounders. These variables should be recorded consistently at baseline and across follow-up, particularly where the decision to intervene is strongly dependent on bleeding severity.

Critical interpretation for anatomic phenotype and imaging: The biological evidence should be read alongside the clinical decision pathway rather than as a direct prescription rule. Studies often differ in lesion selection, comparator myometrium, hormonal exposure at sampling, assay platforms, and whether outcomes represent pathway activity, growth, bleeding or quality of life. A robust translational design would prespecify tissue and patient phenotypes, measure baseline severity before treatment, account for time-dependent intervention choices, and validate the proposed association in an independent cohort. Mechanistic plausibility alone is insufficient to infer a patient-level treatment advantage. The distinction is particularly important when a statistically associated molecular feature has no established actionable threshold or when follow-up procedures select patients according to persistent symptoms.

3.14 Fertility and patient-centered goals

The same biological tumor may justify different decisions depending on pregnancy intentions, age, symptom tolerance, anemia, previous procedures and ability to adhere to



medical therapy. Conflating control of heavy menstrual bleeding with improvement in live-birth probability can mislead patients. Trials focused on symptom response cannot automatically establish reproductive benefit. Research protocols must prespecify pregnancy outcomes, treatment exposure windows, and a defensible approach to competing interventions.

Critical interpretation for fertility and patient-centered goals: The biological evidence should be read alongside the clinical decision pathway rather than as a direct prescription rule. Studies often differ in lesion selection, comparator myometrium, hormonal exposure at sampling, assay platforms, and whether outcomes represent pathway activity, growth, bleeding or quality of life. A robust translational design would prespecify tissue and patient phenotypes, measure baseline severity before treatment, account for time-dependent intervention choices, and validate the proposed association in an independent cohort. Mechanistic plausibility alone is insufficient to infer a patient-level treatment advantage. The distinction is particularly important when a statistically associated molecular feature has no established actionable threshold or when follow-up procedures select patients according to persistent symptoms.

3.15 RCT evidence and its limits

Randomized investigations of gonadotropin-releasing hormone antagonists and combination regimens support meaningful control of fibroid-associated heavy menstrual bleeding in selected participants. Trial endpoints, duration, add-back therapy and adverse-effect ascertainment differ, making indirect comparisons unreliable. Short-term bleeding improvement should not be equated with permanent disappearance of genetically initiated tumors. Post-treatment recurrence, bone-health considerations and subsequent surgery require longitudinal clinical follow-up.

Critical interpretation for rct evidence and its limits: The biological evidence should be read alongside the clinical decision pathway rather than as a direct prescription rule. Studies often differ in lesion selection, comparator myometrium, hormonal exposure at sampling, assay platforms, and whether outcomes represent pathway activity, growth, bleeding or quality of life. A robust translational design would prespecify tissue and patient phenotypes, measure baseline severity before treatment, account for time-dependent intervention choices, and validate the proposed association in an independent cohort. Mechanistic plausibility alone is insufficient to infer a patient-level treatment advantage. The distinction is particularly important when a statistically associated molecular feature has no established actionable threshold or when follow-up procedures select patients according to persistent symptoms.

3.16 Therapeutic translation and endocrine tradeoffs

Systemic ovarian suppression can decrease bleeding and tumor-related symptoms but may create hypoestrogenic harms without adequate risk mitigation. Add-back regimens are designed to balance bleeding control against estrogen-deprivation effects; they do not eliminate the need for individual contraindication screening. Local progestin-containing approaches can reduce bleeding in appropriate circumstances but are not universally effective at reducing leiomyoma volume. Decisions require lesion location, uterine cavity distortion, comorbidity and reproductive priorities.

Critical interpretation for therapeutic translation and endocrine tradeoffs: The biological evidence should be read alongside the clinical decision pathway rather than as a direct prescription rule. Studies often differ in lesion selection, comparator myometrium, hormonal exposure at sampling, assay platforms, and whether outcomes represent pathway activity, growth, bleeding or quality of life. A robust translational design would prespecify tissue and patient phenotypes, measure baseline severity before treatment, account for time-dependent intervention choices, and validate the proposed association in an independent cohort. Mechanistic plausibility alone is insufficient to infer a patient-level treatment advantage. The distinction is particularly important when a statistically associated molecular feature has no established actionable threshold or when follow-up procedures select patients according to persistent symptoms.

3.17 Biomarker development and precision medicine

Potential biomarkers include circulating molecules, imaging signatures, tissue genotype, steroid receptor expression and patient-level clinical trajectories. A diagnostic marker that distinguishes fibroids from normal myometrium is not necessarily predictive of differential treatment response. Precision medicine requires interaction tests demonstrating that a marker changes the relative effect of one treatment versus another. Clinical utility additionally demands that marker-informed management improves outcomes compared with care without the marker.

Critical interpretation for biomarker development and precision medicine: The biological evidence should be read alongside the clinical decision pathway rather than as a direct prescription rule. Studies often differ in lesion selection, comparator myometrium, hormonal exposure at sampling, assay platforms, and whether outcomes represent pathway activity, growth, bleeding or quality of life. A robust translational design would prespecify tissue and patient phenotypes, measure baseline severity before treatment, account for time-dependent intervention choices, and validate the proposed association in an independent cohort. Mechanistic plausibility alone is insufficient to infer a patient-level treatment advantage.

The distinction is particularly important when a statistically associated molecular feature has no established actionable threshold or when follow-up procedures select patients according to persistent symptoms.

3.18 Real-world sources: EHR, e-prescription and laboratory

Electronic medical records provide symptom descriptions, imaging results, hemoglobin, diagnoses and clinician decisions. Electronic prescriptions may establish intended drug initiation, but not ingestion. Laboratory systems can document anemia and treatment-related monitoring. Linking these data permits meaningful longitudinal trajectories only when patient identity, timestamp integrity and medication coding are reliable. Bleeding is frequently reported narratively, making validated abstraction rules and missingness auditing essential.

Critical interpretation for real-world sources: ehr, e-prescription and laboratory: The biological evidence should be read alongside the clinical decision pathway rather than as a direct prescription rule. Studies often differ in lesion selection, comparator myometrium, hormonal exposure at sampling, assay platforms, and whether outcomes represent pathway activity, growth, bleeding or quality of life. A robust translational design would prespecify tissue and patient phenotypes, measure baseline severity before treatment, account for time-dependent intervention choices, and validate the proposed association in an independent cohort. Mechanistic plausibility alone is insufficient to infer a patient-level treatment advantage. The distinction is particularly important when a statistically associated molecular feature has no established actionable threshold or when follow-up procedures select patients according to persistent symptoms.

3.19 Registries, claims and pharmacovigilance

Disease and procedure registries can support treatment persistence, procedural outcomes and repeated-intervention analyses. Claims datasets are useful for reimbursed utilization but may misclassify indication and leave uncovered care invisible. Spontaneous adverse-event reporting supports safety signal generation rather than incidence estimation: denominator uncertainty, stimulated reporting and duplicate reports prevent straightforward risk comparisons. Combining complementary sources should use a declared data-linkage governance framework.

Critical interpretation for registries, claims and pharmacovigilance: The biological evidence should be read alongside the clinical decision pathway rather than as a direct prescription rule. Studies often differ in lesion selection, comparator myometrium, hormonal exposure

at sampling, assay platforms, and whether outcomes represent pathway activity, growth, bleeding or quality of life. A robust translational design would prespecify tissue and patient phenotypes, measure baseline severity before treatment, account for time-dependent intervention choices, and validate the proposed association in an independent cohort. Mechanistic plausibility alone is insufficient to infer a patient-level treatment advantage. The distinction is particularly important when a statistically associated molecular feature has no established actionable threshold or when follow-up procedures select patients according to persistent symptoms.

3.20 Wearables, mobile applications and PROs

Wearables and menstrual tracking applications can capture symptoms, fatigue, activity and longitudinal patient-reported outcomes, but their measurement validity for menstrual blood loss is not guaranteed. Digital inclusion matters because device ownership and engagement correlate with socioeconomic status and health literacy. Patient-generated records may improve shared decision-making when measurements are interpretable, voluntarily shared and linked to clinical context rather than promoted as stand-alone diagnostic instruments.

Critical interpretation for wearables, mobile applications and pros: The biological evidence should be read alongside the clinical decision pathway rather than as a direct prescription rule. Studies often differ in lesion selection, comparator myometrium, hormonal exposure at sampling, assay platforms, and whether outcomes represent pathway activity, growth, bleeding or quality of life. A robust translational design would prespecify tissue and patient phenotypes, measure baseline severity before treatment, account for time-dependent intervention choices, and validate the proposed association in an independent cohort. Mechanistic plausibility alone is insufficient to infer a patient-level treatment advantage. The distinction is particularly important when a statistically associated molecular feature has no established actionable threshold or when follow-up procedures select patients according to persistent symptoms.

3.21 ML, deep learning and reinforcement learning

Gradient-boosted methods can identify nonlinear associations between baseline imaging, anemia and treatment trajectories; deep learning can support automated lesion characterization. Reinforcement learning is sometimes proposed for longitudinal treatment policies, but retrospective policy evaluation is fragile when action probabilities are unknown and important clinical states are unmeasured. No model should be described as prescribing an optimal fibroid regimen without prospective demonstration of patient benefit and safety.



Critical interpretation for ml, deep learning and reinforcement learning: The biological evidence should be read alongside the clinical decision pathway rather than as a direct prescription rule. Studies often differ in lesion selection, comparator myometrium, hormonal exposure at sampling, assay platforms, and whether outcomes represent pathway activity, growth, bleeding or quality of life. A robust translational design would prespecify tissue and patient phenotypes, measure baseline severity before treatment, account for time-dependent intervention choices, and validate the proposed association in an independent cohort. Mechanistic plausibility alone is insufficient to infer a patient-level treatment advantage. The distinction is particularly important when a statistically associated molecular feature has no established actionable threshold or when follow-up procedures select patients according to persistent symptoms.

3.22 NLP and large language models in evidence generation

NLP may standardize narrative phrases such as flooding, menstrual disruption, pelvic pressure or desire for pregnancy. Large language models may assist literature triage and structured data extraction but can invent references, overinterpret diagnostic wording and propagate age or language bias. For research use, each extracted endpoint should be traceable to a source sentence and evaluated against a blinded clinical reference standard. LLM output cannot replace an independently adjudicated adverse event.

Critical interpretation for nlp and large language models in evidence generation: The biological evidence should be read alongside the clinical decision pathway rather than as a direct prescription rule. Studies often differ in lesion selection, comparator myometrium, hormonal exposure at sampling, assay platforms, and whether outcomes represent pathway activity, growth, bleeding or quality of life. A robust translational design would prespecify tissue and patient phenotypes, measure baseline severity before treatment, account for time-dependent intervention choices, and validate the proposed association in an independent cohort. Mechanistic plausibility alone is insufficient to infer a patient-level treatment advantage. The distinction is particularly important when a statistically associated molecular feature has no established actionable threshold or when follow-up procedures select patients according to persistent symptoms.

3.23 Forecasting treatment response in comorbid populations

Diabetes, cardiovascular conditions, oncology, infection and neurological disease inform fibroid treatment selection mainly through comorbid risk, contraindications and health-system complexity. Disease-specific drug-response models from these specialties do not

automatically transfer to a fibroid cohort. Transfer learning must test transportability, medication interactions and different competing risks. An ethical precision strategy begins with validated gynecologic outcomes and only then considers cross-specialty predictors.

Critical interpretation for forecasting treatment response in comorbid populations: The biological evidence should be read alongside the clinical decision pathway rather than as a direct prescription rule. Studies often differ in lesion selection, comparator myometrium, hormonal exposure at sampling, assay platforms, and whether outcomes represent pathway activity, growth, bleeding or quality of life. A robust translational design would prespecify tissue and patient phenotypes, measure baseline severity before treatment, account for time-dependent intervention choices, and validate the proposed association in an independent cohort. Mechanistic plausibility alone is insufficient to infer a patient-level treatment advantage. The distinction is particularly important when a statistically associated molecular feature has no established actionable threshold or when follow-up procedures select patients according to persistent symptoms.

3.24 Drug safety and signal detection

Adverse drug reactions can arise from endocrine suppression, altered bleeding, procedure-related medication use or coexisting treatment. Safety analytics should distinguish unexpected events from manifestations of baseline anemia or the underlying disease. Signal detection can screen spontaneous reports or structured records, but any signal requires medical review, exposure denominator assessment where possible, duplicate handling and comparison with established background rates.

Critical interpretation for drug safety and signal detection: The biological evidence should be read alongside the clinical decision pathway rather than as a direct prescription rule. Studies often differ in lesion selection, comparator myometrium, hormonal exposure at sampling, assay platforms, and whether outcomes represent pathway activity, growth, bleeding or quality of life. A robust translational design would prespecify tissue and patient phenotypes, measure baseline severity before treatment, account for time-dependent intervention choices, and validate the proposed association in an independent cohort. Mechanistic plausibility alone is insufficient to infer a patient-level treatment advantage. The distinction is particularly important when a statistically associated molecular feature has no established actionable threshold or when follow-up procedures select patients according to persistent symptoms.

3.25 Pharmacogenomics and molecularly stratified care

Somatic MED12 or HMGA2 findings concern tumor biology and must not be conflated with inherited pharmacogenetic variants affecting systemic drug metabolism. Germline pharmacogenomics might inform exposure to specific medications if validated treatment-specific associations arise, but it currently does not substitute for standard eligibility assessment. A future precision trial might stratify by tumor subtype and receptor biology, then explicitly test treatment-by-marker interactions.

Critical interpretation for pharmacogenomics and molecularly stratified care: The biological evidence should be read alongside the clinical decision pathway rather than as a direct prescription rule. Studies often differ in lesion selection, comparator myometrium, hormonal exposure at sampling, assay platforms, and whether outcomes represent pathway activity, growth, bleeding or quality of life. A robust translational design would prespecify tissue and patient phenotypes, measure baseline severity before treatment, account for time-dependent intervention choices, and validate the proposed association in an independent cohort. Mechanistic plausibility alone is insufficient to infer a patient-level treatment advantage. The distinction is particularly important when a statistically associated molecular feature has no established actionable threshold or when follow-up procedures select patients according to persistent symptoms.

3.26 Uzbekistan: infrastructure and opportunity

Uzbekistan is developing digital prescribing and other electronic health initiatives. A December 2025 official communication describes phased e-prescription implementation, including systemic hormonal medicines among the initial categories [12]. This is evidence of a policy framework, not proof that nationwide fibroid-specific longitudinal records are complete or interoperable. A practical uterine-fibroid registry would define standardized ultrasound findings, bleeding scales, hemoglobin, interventions, adverse effects and patient-reported outcomes.

Critical interpretation for uzbekistan: infrastructure and opportunity: The biological evidence should be read alongside the clinical decision pathway rather than as a direct prescription rule. Studies often differ in lesion selection, comparator myometrium, hormonal exposure at sampling, assay platforms, and whether outcomes represent pathway activity, growth, bleeding or quality of life. A robust translational design would prespecify tissue and patient phenotypes, measure baseline severity before treatment, account for time-dependent intervention choices, and validate the proposed association in an independent cohort. Mechanistic plausibility alone is insufficient to infer a patient-level treatment advantage. The distinction is particularly important when a statistically associated molecular feature

has no established actionable threshold or when follow-up procedures select patients according to persistent symptoms.

3.27 Uzbekistan: clinical pharmacology and governance

Implementation should connect gynecologic services, clinical pharmacology and medical informatics through structured medication reconciliation and safety monitoring. Data dictionaries need Uzbek and Russian clinical terminology, a consistent coding approach, secure record linkage and a consent/legal-basis framework. Audit indicators should include completeness of FIGO location classification, anemia follow-up, prescriptions actually dispensed and documented treatment changes. Independent ethics and clinical oversight are prerequisites for deploying decision-support algorithms.

Critical interpretation for uzbekistan: clinical pharmacology and governance: The biological evidence should be read alongside the clinical decision pathway rather than as a direct prescription rule. Studies often differ in lesion selection, comparator myometrium, hormonal exposure at sampling, assay platforms, and whether outcomes represent pathway activity, growth, bleeding or quality of life. A robust translational design would prespecify tissue and patient phenotypes, measure baseline severity before treatment, account for time-dependent intervention choices, and validate the proposed association in an independent cohort. Mechanistic plausibility alone is insufficient to infer a patient-level treatment advantage. The distinction is particularly important when a statistically associated molecular feature has no established actionable threshold or when follow-up procedures select patients according to persistent symptoms.

3.29 Trial endpoint interpretation

The phase 3 LIBERTY studies supply a concrete example of why endpoints must be reproduced accurately. A PubMed-indexed trial report describes response rates of 73% and 71% with relugolix combination therapy in two replicate trials versus 19% and 15% on placebo under a prespecified definition combining menstrual-loss volume below 80 mL and a reduction of at least 50% from baseline [20]. These are trial-specific responses, not percentages of fibroids cured, and should not be extrapolated to patients outside eligibility criteria. Secondary symptom, anemia and quality-of-life outcomes contribute separate clinical information, while long-term withdrawal studies examine sustained benefit and safety in selected prior responders. A regulator, clinician or guideline developer should not compare these response rates naively with surgical success percentages based on different follow-up definitions.

Critical interpretation for trial endpoint interpretation: The biological evidence should be read alongside the clinical decision pathway rather than as a direct prescription rule. Studies often differ in lesion selection, comparator myometrium, hormonal exposure at sampling, assay platforms, and whether outcomes represent pathway activity, growth, bleeding or quality of life. A robust translational design would prespecify tissue and patient phenotypes, measure baseline severity before treatment, account for time-dependent intervention choices, and validate the proposed association in an independent cohort. Mechanistic plausibility alone is insufficient to infer a patient-level treatment advantage. The distinction is particularly important when a statistically associated molecular feature has no established actionable threshold or when follow-up procedures select patients according to persistent symptoms.

3.30 Cross-population validation and uncertainty

A treatment model trained in a multinational randomized trial is not intrinsically transportable to a community clinic. Differences in hemoglobin measurement, access to specialist imaging, patterns of hormonal prescribing, co-prescribed iron, follow-up completeness and surgical referral thresholds can change both baseline event rates and apparent response. Equitable validation therefore requires reporting whether model calibration remains adequate within clinical sites and relevant groups. Where confidence intervals are wide, clinical decision support should display that uncertainty rather than transform unstable estimates into categorical treatment preferences. A clinically meaningful prospective validation should measure net benefit, potential harms from decision errors and the workload of verifying automated recommendations.

Critical interpretation for cross-population validation and uncertainty: The biological evidence should be read alongside the clinical decision pathway rather than as a direct prescription rule. Studies often differ in lesion selection, comparator myometrium, hormonal exposure at sampling, assay platforms, and whether outcomes represent pathway activity, growth, bleeding or quality of life. A robust translational design would prespecify tissue and patient phenotypes, measure baseline severity before treatment, account for time-dependent intervention choices, and validate the proposed association in an independent cohort. Mechanistic plausibility alone is insufficient to infer a patient-level treatment advantage. The distinction is particularly important when a statistically associated molecular feature has no established actionable threshold or when follow-up procedures select patients according to persistent symptoms.



3.31 Molecular research to clinically measurable outcomes

A robust translation pipeline begins with a mechanistic hypothesis, then independently tests whether a laboratory measure is reproducible, correlated with a prospectively defined outcome and incremental to inexpensive clinical features. Randomization remains preferable for determining whether treatment benefit varies by marker group, because retrospective molecular profiling can be affected by post-treatment sampling and selective availability of surgical tissue. Prespecification of molecular thresholds, reliable inter-laboratory assays and transparent reporting of failed hypotheses are necessary to prevent optimism bias. The decisive endpoint should be improved patient outcomes rather than increased complexity of the biomarker panel.

Critical interpretation for molecular research to clinically measurable outcomes: The biological evidence should be read alongside the clinical decision pathway rather than as a direct prescription rule. Studies often differ in lesion selection, comparator myometrium, hormonal exposure at sampling, assay platforms, and whether outcomes represent pathway activity, growth, bleeding or quality of life. A robust translational design would prespecify tissue and patient phenotypes, measure baseline severity before treatment, account for time-dependent intervention choices, and validate the proposed association in an independent cohort. Mechanistic plausibility alone is insufficient to infer a patient-level treatment advantage. The distinction is particularly important when a statistically associated molecular feature has no established actionable threshold or when follow-up procedures select patients according to persistent symptoms.

3.28 Future international comparative studies

A prospective multi-institutional cohort could record standardized imaging, bleeding, laboratory markers, medications and procedure outcomes while defining an eligible comparison at treatment initiation. External validation in different health systems would test whether prediction performance and treatment-effect heterogeneity are robust. Molecular analyses could be nested within surgical biobanks, but the biopsy-restricted nature of those subgroups must be acknowledged when applying results to all patients.

Critical interpretation for future international comparative studies: The biological evidence should be read alongside the clinical decision pathway rather than as a direct prescription rule. Studies often differ in lesion selection, comparator myometrium, hormonal exposure at sampling, assay platforms, and whether outcomes represent pathway activity, growth, bleeding or quality of life. A robust translational design would prespecify tissue and patient phenotypes, measure baseline severity before treatment, account for time-dependent intervention choices, and validate the proposed association in an independent cohort.

Mechanistic plausibility alone is insufficient to infer a patient-level treatment advantage. The distinction is particularly important when a statistically associated molecular feature has no established actionable threshold or when follow-up procedures select patients according to persistent symptoms.

Evidence domain	Established contribution	Key limitation
Steroid signaling	Estrogen primes progesterone response; progesterone supports paracrine growth [2,3]	Tumor-specific response varies
Molecular subtypes	MED12/HMGA2 provide mechanistic stratification [3,4]	No routine genotype-directed drug allocation
ECM pathways	TGF- β , WNT, YAP/TAZ connect fibrosis to proliferation [2]	Experimental activity does not establish clinical benefit
Oral hormonal therapy	Selected RCTs demonstrate bleeding benefit [1]	Long-term persistence and generalizability require RWE
Digital cohorts	EHR, claims and e-prescriptions can support longitudinal research [5,6]	Confounding and missing outcomes
AI and prediction	Potential for segmentation and risk stratification [9,10]	External validation and governance

4. Discussion

Triangulating molecular and clinical evidence

A coherent causal account of fibroid development must allow hormonal maintenance to coexist with genetic initiation and structural feedback. A molecular assay suggesting greater pathway activation cannot, by itself, predict the effect of a given drug because treatment also acts systemically, modifies other pathways and alters clinical behavior. Convergent support from controlled experiments, longitudinal human observations and randomized

interventions is more convincing than repeated associations from the same source of tissue samples.

Bias and data-quality threats

Confounding by indication is severe in fibroid studies: larger, more symptomatic lesions are more likely to receive aggressive treatment. Hospital-only datasets may miss patients managed conservatively; repeated imaging can be more common after persistent symptoms. Administrative procedure codes may be accurate while symptom severity is not. Attrition and outcome-dependent follow-up can produce misleading apparent success even with a large registry. Substantive clinical input into the analysis plan is indispensable.

Missingness, time and causality

Missing baseline hemoglobin, lesion location or fertility intentions does not become harmless because machine learning can impute it. Missingness may reflect site-level capabilities and clinician judgement. Improper assignment of treatment status after an initial untreated period creates immortal time. Conditioning on future imaging or surgery can introduce collider selection. Sensitivity analyses should quantify plausible departures from exchangeability and present absolute risks as well as relative comparisons.

Explainable and ethical AI

Saliency maps cannot guarantee causal explanations for a neural network prediction. Explainability must address the question clinicians actually ask: which information supports a decision, what uncertainty remains, and what would happen if data are unavailable? The WHO ethics framework favors human accountability, transparency and equity. Subgroup audit by age, language, access to specialist imaging and care setting should precede deployment of any decision-support model.

Regulatory science

Regulatory suitability depends on the intended use and deployment environment. The FDA provides guidance on fitness for purpose of EHR and medical claims as well as good machine-learning practice. EMA's RWE work, including DARWIN EU, demonstrates infrastructure for regulator-led studies but does not equate every database association with a validated treatment claim. A gynecologic AI tool intended to guide medication decisions warrants different evidence from one used only to annotate research images.

Clinical decision support

An appropriate clinical decision support system would display lesion phenotype, anemia, prior treatments, risks, patient preferences, evidence strength and uncertainty. It should not autonomously convert molecular pathway expression into a drug order. Safety procedures

include review of contraindications, override recording, validation after software updates and processes to detect performance drift. Patient-centered decisions may legitimately favor surgery or expectant management even where pharmacologic response is predicted.

Global RWE and health equity

International trends emphasize data networks, transparent protocols, common data models and lifecycle evidence rather than simply collecting more records. Low- and middle-income health systems face distinctive challenges in reliable identifiers, imaging documentation and affordability. Replicating an algorithm developed in a tertiary specialist center without local validation risks worsening inequities. Registry development can be incremental, starting with a small mandatory dataset and audited completeness.

Limits of this review

This integrative analysis does not establish an exhaustive study count, formal risk-of-bias distribution, quantitative synthesis or pooled meta-analytic effect. Literature coverage is selective and favors accessible verifiable sources; claims about particular drug classes must therefore be interpreted with the underlying trials and labels. No individual-level RWD were received, so regression coefficients, Kaplan–Meier curves, hazard ratios and subgroup estimates are intentionally absent. This limitation protects against presenting a research proposal as completed empirical evidence.

5. Conclusion

Uterine fibroid growth is best interpreted as an interaction between acquired molecular abnormalities and estrogen–progesterone-dependent signaling within a mechanically and biochemically active extracellular matrix. MED12 and HMGA2 subtypes, WNT/ β -catenin, TGF- β , mTOR and mechanotransduction pathways offer biologically credible targets, but the transition from tissue association to clinically useful precision treatment remains incomplete. Randomized trials inform short-term efficacy for selected regimens; careful target-trial emulation and pharmacovigilance are required to understand practical effectiveness and safety. AI may facilitate phenotyping and data extraction only when externally validated, transparent, secure, and anchored to clinician review. For Uzbekistan, standardized fibroid registries linked to electronic prescribing, imaging and laboratory follow-up are actionable foundations for future research rather than evidence of already achieved national interoperability.

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