AI-Driven Integrated Molecular Risk Stratification for Endometrial Cancer

A Clinical Decision Support System Architecture for Precision Oncology

WHITEPAPER

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Disclaimer: This whitepaper presents a conceptual framework for a clinical decision support system. Implementation requires validation through clinical trials and regulatory approval. This document is intended for research and educational purposes.

Abstract

Endometrial cancer (EC) is the most common gynecological malignancy in the developed world, yet its clinical management remains hampered by an outdated reliance on anatomical staging systems. The FIGO 2009 staging framework, while useful for describing tumor extent, fundamentally fails to capture the molecular heterogeneity that drives tumor behavior—leading to systematic undertreatment of molecularly aggressive early-stage tumors and overtreatment of biologically indolent advanced-stage disease.

This whitepaper presents a comprehensive architectural blueprint for an AI-driven Clinical Decision Support System (CDSS) designed to resolve this critical diagnostic gap. By integrating the genomic insights from The Cancer Genome Atlas (TCGA) molecular classification with advanced machine learning techniques—specifically Extreme Gradient Boosting (XGBoost) and Explainable AI (SHAP)—the proposed system delivers personalized recurrence probability assessments that transcend traditional staging limitations.

The framework addresses three fundamental challenges: (1) the "Discordance Hypothesis," where anatomical stage fails to predict biological risk; (2) the "Interaction Problem," where non-linear relationships between clinical variables cannot be captured by traditional statistical methods; and (3) the "Trust Gap," where opaque AI predictions fail to gain clinical adoption. Through validated molecular biomarkers (POLE, p53, MMR status, L1CAM) and interpretable risk explanations, this CDSS aims to operationalize precision medicine in endometrial cancer, aligning with the ongoing RAINBO clinical trial consortium.

Keywords: Endometrial Cancer, Molecular Classification, Clinical Decision Support System, XGBoost, Explainable AI, SHAP, Precision Oncology, TCGA, FIGO Staging, Risk Stratification

Contents

1 Introduction

1.1 The Clinical Problem

Endometrial cancer represents a paradigm case study in the limitations of anatomical oncology. For decades, clinicians have stratified patient risk—and consequently prescribed adjuvant therapies such as radiotherapy and chemotherapy—based almost exclusively on how far the tumor has spread. The underlying assumption is elegantly simple: Stage I is better than Stage II, which is better than Stage III.

However, this linear model of cancer progression fails catastrophically when confronted with molecular reality. Historically, endometrial cancer was bifurcated into two types based on the Bokhman dualistic model: Type I (estrogen-dependent, low-grade endometrioid, favorable prognosis) and Type II (non-endometrioid, high-grade, poor prognosis).[1] This classification underpinned the FIGO staging systems of 1988 and 2009, but has increasingly proven insufficient.

A Stage IA tumor harboring a *TP53* mutation carries a recurrence risk of 16–19%, comparable to many Stage III tumors.[2] Conversely, a Stage IIIC tumor with positive lymph nodes but carrying a *POLE* mutation exhibits near-perfect survival outcomes, making aggressive chemoradiation unnecessary and potentially harmful.[3]

Critical Finding

In a retrospective analysis of 720 patients comparing the 2009 FIGO system against the updated 2023 FIGO system with molecular classification, integrating molecular data resulted in the reclassification of **27.4%** of patients. Most critically, 182 patients were upstaged from Stage I to Stage II due to p53 abnormalities invisible to anatomical staging.[a]

[a] "2023 FIGO Staging of Endometrial Cancer with Molecular Classification: Dawn and Challenges," *J Cancer*, 2025;16:4400-4415. Available: https://www.jcancer.org/v16p4400.htm

1.2 The Paradigm Shift: From Anatomy to Biology

The Cancer Genome Atlas (TCGA) Research Network performed a comprehensive genomic, transcriptomic, and proteomic analysis of endometrial carcinomas, fundamentally transforming our understanding of the disease.[4] This analysis identified four molecularly distinct prognostic subgroups that transcend traditional histology and stage:

1. **POLE Ultramutated (POLEmut):** Excellent prognosis regardless of grade or stage
2. **Microsatellite Instability-High (MSI-H/MMRd):** Intermediate prognosis, immunotherapy-responsive
3. **Copy-Number Low (CNL/NSMP):** Heterogeneous "grey zone" requiring secondary biomarkers

[1] College of American Pathologists, "Molecular Classification and Staging of Endometrial Carcinoma," 2025. Available: https://documents-cloud.cap.org/appdocs/learning/DestinationCME/2025_POTC/PDFs/WED_04_Staging_Endometrial_Carcinoma.pdf

[2] "Recurrence rates and patterns of recurrence in stage IA p53abn endometrial cancer with and without myometrial invasion," *Gynecologic Oncology*, 2024. Available: https://pubmed.ncbi.nlm.nih.gov/38388178/

[3] Leon-Castillo A, et al., "Molecular Classification of the PORTEC-3 Trial for High-Risk Endometrial Cancer: Impact on Prognosis and Benefit From Adjuvant Therapy," *J Clin Oncol*, 2020;38(29):3388-3397. Available: https://pubmed.ncbi.nlm.nih.gov/32749941/

[4] The Cancer Genome Atlas Research Network, "Integrated genomic characterization of endometrial carcinoma," *Nature*, 2013;497:67-73.

4. **Copy-Number High (CNH/p53abn):** Worst prognosis, chemotherapy-sensitive

To translate complex genomic sequencing into routine pathology, the **ProMisE (Proactive Molecular Risk Classifier for Endometrial Cancer)** criteria were developed, utilizing accessible immunohistochemistry (IHC) for MMR proteins and p53, alongside targeted sequencing for *POLE*.[5]

The clinical validation of this classification came from the landmark **PORTEC-3 Trial**, which demonstrated that p53-abnormal patients derive massive survival benefits from chemotherapy addition (10-year OS: 52.7% vs. 36.6%, HR 0.52, p=0.021), while POLE-mutant patients showed excellent outcomes regardless of treatment arm.[6]

1.3 Document Objectives

This whitepaper provides:

- A comprehensive scientific justification for molecular-integrated risk stratification
- A detailed data dictionary for multidimensional feature engineering
- An architectural specification for XGBoost-based risk modeling
- Integration of Explainable AI (SHAP) for clinical interpretability
- Mock clinical outputs demonstrating real-world decision support

2 The Medical Justification

2.1 The Discordance Hypothesis

The core scientific premise for this AI agent is that **Anatomical Stage $\neq$ Biological Risk**. Current diagnostic workflows lack an "intelligent assistant" capable of resolving the discordance between how far a tumor has spread (anatomy) and how aggressively it behaves (biology).

2.1.1 The Failure of Linear Staging

The FIGO staging system provides a necessary description of tumor extent—differentiating between tumor confined to the corpus (Stage I), cervical invasion (Stage II), and extrauterine spread (Stage III/IV). However, it serves as an imperfect proxy for biological aggression.

Recent retrospective analyses have exposed critical limitations. The system struggles with reproducibility in histological grading and the assessment of lymphovascular space invasion (LVSI), both of which are subjective parameters subject to significant inter-observer variability.[7] The omission of peritoneal cytology in newer staging iterations also remains contentious, as it may lead to undertreatment of non-endometrioid subtypes where microscopic peritoneal spread is a harbinger of widespread disease.

[5] Talhouk A, et al., "Final validation of the ProMisE molecular classifier for endometrial carcinoma in a large population-based case series," *Ann Oncol*, 2018. Available: https://pubmed.ncbi.nlm.nih.gov/29432521/

[6] "Adjuvant chemoradiotherapy versus radiotherapy alone in women with high-risk endometrial cancer (PORTEC-3): 10-year clinical outcomes and post-hoc analysis by molecular classification," *Lancet Oncol*, 2025. Available: https://pubmed.ncbi.nlm.nih.gov/40921169/

[7] "2023 FIGO Staging of Endometrial Cancer with Molecular Classification: Dawn and Challenges," *J Cancer*, 2025. Available: https://www.jcancer.org/v16p4400.htm

Table 1: Limitations of Anatomical Staging in Endometrial Cancer

Limitation	Clinical Consequence
Inter-observer variability	Histological grading and LVSI assessment are subjective, leading to inconsistent risk classification
Molecular blindness	Cannot detect p53 mutations in early-stage tumors that predict aggressive behavior
Binary thinking	Forces tumors into discrete stages rather than continuous risk spectra
Peritoneal cytology exclusion	May undertreat non-endometrioid subtypes with microscopic peritoneal spread

2.1.2 The "Silent Killer" Problem

The most dangerous gap in current practice exists in Stage I patients with molecular high-risk features. Under standard guidelines, a Stage IA patient often receives observation or vaginal brachytherapy alone. However, molecular data reveals a starkly different risk profile.

Key Insight

Stage IA p53-abnormal tumors carry a recurrence rate of **16%**, rising to **19%** with residual disease.[a] Without an AI agent to flag this "Latent High Risk," these patients are routinely undertreated, leading to distant metastatic relapse that could have been prevented with systemic therapy.[b]

[a] "Recurrence rates and patterns of recurrence in stage IA p53abn endometrial cancer with and without myometrial invasion," *ResearchGate*, 2024. Available: https://www.researchgate.net/publication/378419648

[b] "Clinical Behavior and Molecular Landscape of Stage I p53-Abnormal Low-Grade Endometrioid Endometrial Carcinomas," *Clin Cancer Res*, 2023;29(23):4949-4959. Available: https://aacrjournals.org/clincancerres/article/29/23/4949/730230/

2.2 TCGA Molecular Classification: The Four Pillars

2.2.1 POLE Ultramutated (POLEmut)

This subgroup is defined by pathogenic somatic mutations in the exonuclease domain of the *POLE* gene (DNA polymerase epsilon). These tumors exhibit extraordinarily high tumor mutational burden (ultramutation), which paradoxically renders them highly immunogenic, attracting robust infiltration of CD8+ cytotoxic T-lymphocytes that contain the tumor.[8]

- **Prognostic Impact:** Excellent progression-free and overall survival regardless of tumor grade or stage. Studies have shown that even in Grade 3 or high-stage tumors, the presence of a *POLE* mutation confers a survival advantage that effectively "vetoes" the poor anatomical prognosis.[9]
- **Clinical Consequence:** Prime candidates for therapy de-escalation, sparing unnecessary toxicity.

[8] "POLE-mutated endometrial cancer: new perspectives on the horizon?" *Frontiers in Oncology*, 2025. Available: https://www.frontiersin.org/journals/oncology/articles/10.3389/fonc.2025.1633260/full

[9] "The game-changing impact of POLE mutations in oncology—a review from a gynecologic oncology perspective," *Int J Gynecol Cancer*, 2024. Available: https://pmc.ncbi.nlm.nih.gov/articles/PMC11374733/

- **Evidence:** PORTEC-3 showed 100% 5-year RFS with CTRT vs. 97% with RT alone (p=0.637), suggesting even radiation may be unnecessary.[10]

2.2.2 Microsatellite Instability-High (MSI-H/MMRd)

This group arises from defects in the DNA mismatch repair system (proteins MLH1, MSH2, MSH6, PMS2), leading to the accumulation of errors in repetitive DNA sequences (microsatellites).

- **Prognostic Impact:** Intermediate prognosis, distinct from p53-abnormal group.
- **Therapeutic Relevance:** The high mutational load creates neoantigens, making these tumors exceptionally responsive to immune checkpoint inhibitors (pembrolizumab, dostarlimab, durvalumab).
- **Ongoing Research:** The RAINBO MMRd-GREEN trial is specifically investigating the addition of durvalumab to radiotherapy in this subgroup.[11]

2.2.3 Copy-Number Low (CNL/NSMP)

The "catch-all" category comprising tumors lacking POLE mutations, TP53 mutations, and MMR deficiency. They are largely low-grade endometrioid carcinomas.

- **Prognostic Impact:** Heterogeneous—many do well, but a subset drives recurrence.
- **Risk Refinement:** Because this group is a "diagnosis of exclusion," the AI agent must rely on secondary biomarkers:
  - *L1CAM* overexpression: L1CAM-positive NSMP tumors behave aggressively, similar to p53abn tumors.[12]
  - *CTNNB1* (β-catenin) mutations: Associated with lower recurrence-free survival within the NSMP group.[13]
  - ER/PR hormone receptor status

2.2.4 Copy-Number High (CNH/p53abn)

Characterized by *TP53* mutations and extensive somatic copy-number alterations (aneuploidy). It includes most serous carcinomas and a subset of high-grade endometrioid tumors.

- **Prognostic Impact:** Highest-risk group with worst PFS and OS outcomes. Recurrences are frequent and often distant (metastatic) rather than locoregional.
- **Clinical Evidence:** In the molecular analysis of PORTEC-3, patients with p53abn tumors derived a massive, statistically significant survival benefit from the addition of chemotherapy.

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[10] Leon-Castillo A, et al., "Molecular Classification of the PORTEC-3 Trial," *J Clin Oncol*, 2020. Available: https://pubmed.ncbi.nlm.nih.gov/32749941/

[11] "The RAINBO MMRd-GREEN trial: A phase III trial on the addition of adjuvant durvalumab to radiotherapy in patients with high-risk MMRd endometrial cancer," *J Clin Oncol*, 2023;41(suppl):TPS5633. Available: https://ascopubs.org/doi/10.1200/JCO.2023.41.16_suppl.TPS5633

[12] "L1CAM further stratifies endometrial carcinoma patients with no specific molecular risk profile," *Br J Cancer*, 2018;119:480-486. Available: https://pmc.ncbi.nlm.nih.gov/articles/PMC6134076/

[13] "ARID1A and CTNNB1/β-Catenin Molecular Status Affects the Clinicopathologic Features and Prognosis of Endometrial Carcinoma," *Cancers*, 2021;13(5):950. Available: https://www.mdpi.com/2072-6694/13/5/950

The 10-year overall survival was 52.7% with CTRT versus 36.6% with RT alone (HR 0.52, p=0.021).[14]

Clinical Implication

The hypothesis that molecular subtypes alter prognosis independent of stage is validated by Level 1 evidence (PORTEC-3). The CDSS is not merely "optimizing" care; it is correcting fundamental classification errors inherent in the anatomical system. The shift from "How far has it spread?" to "What is driving it?" must be the core logic of the AI agent.

3 Data Architecture: Feature Engineering

To bridge the gap between anatomy and biology, the AI must ingest a multidimensional feature space capturing the interplay between tumor biology, patient host factors, and anatomical extent.

3.1 Clinical Variables (Host Factors)

Endometrial cancer, particularly the endometrioid subtype, is strongly linked to metabolic dysregulation. "Host factors" are critical not only for tumorigenesis but for predicting overall survival and competing risks of mortality.[15]

Table 2: Clinical Feature Dictionary

Variable	Type	Criticality	Rationale
Age	Continuous	High	Age >60 is independent predictor of poor PFS; correlates with p53abn biology[16]
BMI	Continuous	Medium	Obesity drives Type I EC via peripheral aromatization; BMI >40 complicates treatment delivery
Diabetes	Binary	Medium	Part of "metabolic triad"; associated with higher all-cause mortality
ECOG Status	Categorical	High	Determines eligibility for adjuvant chemotherapy

3.2 Pathological Variables (Tumor Morphology)

Despite the molecular shift, traditional pathology remains the scaffold upon which molecular data is overlaid. The AI must integrate these features to refine risk, particularly within the NSMP molecular group.

[14] "Adjuvant Chemoradiotherapy vs Radiotherapy for High-Risk Endometrial Cancer: 10-Year PORTEC-3 Outcomes," *The ASCO Post*, September 2025. Available: https://ascopost.com/news/september-2025/adjuvant-chemoradiotherapy-vs-radiotherapy-for-high-risk-endometrial-cancer-10-year-portec-3-outcomes/

[15] "Correlation of Metabolic Factors with Endometrial Atypical Hyperplasia and Endometrial Cancer: Development and Assessment of a New Predictive Nomogram," *Cancer Manag Res*, 2021. Available: https://pmc.ncbi.nlm.nih.gov/articles/PMC8536844/

[16] "Clinical characteristics and prognostic characterization of endometrial cancer," NIH PMC, 2023. Available: https://pmc.ncbi.nlm.nih.gov/articles/PMC10015692/

Table 3: Pathological Feature Dictionary

Variable	Format	Criticality	Rationale
Histological Subtype	Categorical	High	Non-endometrioid types historically high-risk; p53-mutant endometrioid equally aggressive
FIGO Grade	G1/G2/G3	High	G3 implies poor differentiation (nullified by POLE mutation)
Myometrial Invasion	<50%/≥50%	High	Deep invasion increases LVSI and nodal spread probability
LVSI Status	None/Focal/Substantial	Very High	Substantial LVSI confers risk equivalent to nodal metastasis[17]
Lymph Node Status	Neg/Pelvic+/Para-aortic+	High	Nodal involvement mandates systemic therapy

3.3 Molecular Variables (The Biological Engine)

These features are the primary differentiators of the new FIGO 2023m staging system and carry the highest predictive weight.

Table 4: Molecular Feature Dictionary

Variable	Format	Criticality	Rationale
POLE Status	Mutated/Wildtype	**Critical**	Dominant favorable factor; overrides poor histology and high grade[18]
p53 IHC	Wildtype/Abnormal	**Critical**	Defines CNH group; associated with dismal outcomes and chemosensitivity
MMR Status	pMMR/dMMR	High	Identifies MSI-H; flags immunotherapy eligibility
L1CAM	Positive/Negative	High	Vital differentiator in NSMP; L1CAM+ mimics p53abn behavior
CTNNB1	Mutated/Wildtype	Medium	Identifies worse prognosis within NSMP group
ER/PR	Percentage (%)	Medium	Loss correlates with higher grade and worse outcomes

3.4 Emerging Data Streams: Radiomics

To ensure the CDSS remains cutting-edge, the architecture must support ingestion of radiomic features derived from pre-surgical CT or MRI scans.

[17] "Molecular Classification in Patients With Endometrial Cancer After Fertility-Preserving Treatment," *Front Oncol*, 2022. Available: https://pmc.ncbi.nlm.nih.gov/articles/PMC9160735/

[18] "The TCGA Molecular Classification of Endometrial Cancer and Its Possible Impact on Adjuvant Treatment Decisions," *Cancers*, 2021;13(6):1478. Available: https://www.mdpi.com/2072-6694/13/6/1478

Key Insight

Machine learning models trained on CT radiomic features (texture, shape, intensity) have demonstrated AUCs of **0.86–0.90** in predicting recurrence, often capturing sub-visual tumor heterogeneity that correlates with molecular subtypes.[a]

[a] "A Radiomic-Based Machine Learning Model Predicts Endometrial Cancer Recurrence Using Pre-operative CT Radiomic Features: A Pilot Study," *Cancers*, 2023;15(18):4534. Available: https://www.mdpi.com/2072-6694/15/18/4534

4 AI Architecture: XGBoost and Explainability

The selection of machine learning architecture is dictated by the nature of medical data: tabular, high-dimensional, heterogeneous (categorical and continuous variables), and governed by complex non-linear biological interactions.

4.1 Algorithm Selection: The Superiority of Gradient Boosting

4.1.1 The Interaction Problem

In endometrial cancer, the impact of one variable is often entirely dependent on the state of another:

> *Grade 3 histology increases risk—UNLESS a POLE mutation is present, in which case risk remains low.*

Logistic Regression Failure:

- Requires explicit creation of interaction terms ($x_{\text{Grade}} \times x_{\text{POLE}}$)
- With 50+ variables, the number of potential interactions is combinatorial ($n(n-1)/2$), leading to model bloat and overfitting
- Assumes linearity between features and log-odds—biologically false in this context[19]

XGBoost Advantage:

- Tree-based ensemble naturally learns non-linear decision boundaries
- Sequential tree building where each new tree corrects previous errors
- Automatically discovers that "POLE = Mutated" branch leads to low risk regardless of Grade value, without requiring manual feature engineering[20]

4.1.2 Empirical Performance

Empirical comparisons in oncology consistently favor gradient boosting:

[19] "XGBoost vs Logistic Regression," *Medium*, 2023. Available: https://medium.com/@heyamit10/xgboost-vs-logistic-regression-a3dc03b0e6f8

[20] "Tabular Data Classification and Regression: XGBoost or Deep Learning with Retrieval-Augmented Generation," *ResearchGate*, 2024. Available: https://www.researchgate.net/publication/387099599

Table 5: XGBoost vs. Logistic Regression in Medical Applications

Application	XGBoost AUC	LR AUC	Source
COVID-19 ICU Risk	0.86	0.69	PMC8531027[21]
Glioma Prognosis	0.803	Lower	PubMed 36110992[22]
Thyroid Malignancy	0.928	0.764 (TIRADS)	PMC12339320[23]

4.1.3 Handling Missing Data

Clinical datasets rarely have complete molecular profiles for all patients. Specific biomarkers like *CTNNB1* or *L1CAM* may be missing.

- **LR Limitation:** Requires imputation (filling blanks with averages), introducing noise and bias
- **XGBoost Advantage:** Utilizes "Sparsity Aware Split Finding"—during training, it learns a default direction for missing values for each split in the tree, allowing the model to handle incomplete molecular profiles gracefully without hallucinating data

4.2 The Explainability Imperative: SHAP

A "Black Box" AI outputting a risk score of "85%" without justification will never achieve clinical adoption. The molecular tumor board requires the *etiology* of risk.

4.2.1 Theoretical Foundation

SHAP (Shapley Additive Explanations) derives from cooperative game theory, assigning a "marginal contribution" value to each feature for every individual prediction.[25]

$$f(x) = E[f(x)] + \sum_{i=1}^{n} \phi_i \tag{1}$$

Where:

- $f(x)$ = Final predicted risk score
- $E[f(x)]$ = Average population baseline risk
- ϕ_i = SHAP value (contribution) of feature i

Interpretation: Risk Score = Population Average + Sum of Feature Contributions

[22]"Machine learning using XGBoost predicts 5-day delta of SOFA score at ICU admission in COVID-19 patients," *J Crit Care*, 2022. Available: https://pmc.ncbi.nlm.nih.gov/articles/PMC8531027/

[23]"XGBoost algorithm and logistic regression to predict the postoperative 5-year outcome in patients with glioma," *Ann Transl Med*, 2022. Available: https://pubmed.ncbi.nlm.nih.gov/36110992/

[24]"XGBoost-based machine learning model combining clinical and ultrasound data for personalized prediction of thyroid nodule malignancy," *Front Endocrinol*, 2024. Available: https://pmc.ncbi.nlm.nih.gov/articles/PMC12339320/

[25]"Interpretable AI for bio-medical applications," *Complex & Intelligent Systems*, 2023. Available: https://pmc.ncbi.nlm.nih.gov/articles/PMC10074303/

4.2.2 Clinical Implementation: Waterfall Visualization

The SHAP Waterfall plot provides intuitive risk explanation:[26]

- **Base Value:** Starts at average recurrence rate (e.g., 15%)
- **Risk Drivers (Red):** Features pushing risk upward (+40% for p53abn)
- **Protective Factors (Blue):** Features pushing risk downward (-10% for Stage IA)
- **Final Output:** Personalized risk probability

Clinical Implication

This transforms a "Black Box" into a "Glass Box." If the AI predicts high risk for an early-stage patient, the SHAP plot explicitly shows the p53 mutation bar dominating the Stage I bar, validating biological logic to the clinician.[a]

[a] "Using SHAP to Explain Predictions in Healthcare ML Models," *Medium*, 2024. Available: https://medium.com/@yiannismastoras/using-shap-to-explain-predictions-in-healthcare-ml-models-with-code-and-visuals-175b9e3e3f41

4.3 Technical Stack Specification

Table 6: Proposed Technology Stack

Component	Specification
Language	Python 3.9+
Core ML Library	`xgboost` (v1.6+)
Interpretability	`shap`
Preprocessing	`pandas`, `scikit-learn`
Hyperparameter Optimization	`optuna` (Bayesian tuning)
Validation	Stratified K-Fold Cross-Validation (k=10)

5 Clinical Output Specification

The ultimate objective is resolving the dichotomy of undertreatment and overtreatment. Outputs must be actionable, directly informing adjuvant therapy choices.

5.1 Mock Clinical Report

The following demonstrates the proposed EHR-integrated output format for a patient presenting a classic "clinical dilemma":

[26] "SHAP Waterfall Plot Documentation," SHAP Library. Available: https://shap.readthedocs.io/en/latest/example_notebooks/api_examples/plots/waterfall.html

PRECISION ONCOLOGY RISK REPORT

System: XGBoost Ensemble v4.2 | Explainability: SHAP
Patient ID: 554-90-21 | **Age:** 64 | **BMI:** 32.5
Anatomical Stage: FIGO IA | **Histology:** Endometrioid

1. INTEGRATED RECURRENCE RISK

78% (HIGH RISK)

Baseline risk for Anatomical Stage IA: ∼5–15%

2. MOLECULAR CLASSIFICATION

Assigned Group: **p53 Abnormal (Copy-Number High)**

POLE:	Wildtype
MMR:	Proficient (pMMR)
p53:	**Abnormal (Null type)**
L1CAM:	**Positive (>10%)**

3. EXPLAINABLE RATIONALE (SHAP Analysis)

Why is a Stage IA patient classified as High Risk?

Risk Drivers:

- p53 Abnormality: **+45%** risk contribution
- L1CAM Positivity: **+15%** risk contribution
- Grade 3: **+10%** risk contribution
- Age >60: **+5%** risk contribution

Protective Factors:

- Stage IA: **-10%** risk contribution

4. CLINICAL DECISION SUPPORT

Alert: Anatomical stage INSUFFICIENT for risk assessment.
Recommendation: Adjuvant Chemoradiotherapy (EBRT + Cisplatin/Paclitaxel)
Evidence: PORTEC-3 demonstrates OS benefit HR 0.52 for p53abn patients
Trial Eligibility: RAINBO p53abn-RED (Chemoradiation + Olaparib)

5.2 Impact Analysis

5.2.1 Solving Undertreatment

The mock report above illustrates the solution for the "Silent Killer" scenario. A clinician relying solely on the pathology report ("Stage IA, Endometrioid") might prescribe only observation. The AI agent:

1. Flags the discordance between stage and molecular profile
2. Cites specific recurrence rates (16–19%)
3. References PORTEC-3 survival benefits (HR 0.52)
4. Empowers the oncologist to justify chemotherapy toxicity

5.2.2 Solving Overtreatment

Consider a patient with **Stage IIIC1 (Node Positive), Grade 3, POLE-mutated** cancer:

- **Standard Care:** Aggressive chemoradiotherapy
- **AI Output:** Low Risk (<5%)

- **SHAP Rationale:** POLE mutation provides massive negative contribution (-60%), neutralizing nodal positivity and high grade
- **Recommendation:** De-escalation; eligibility for RAINBO POLEmut-BLUE trial
- **Outcome:** Patient spared from radiation cystitis, neuropathy, bone marrow suppression

6 Future Directions: The RAINBO Horizon

This CDSS is designed to be future-proof. It aligns with the ongoing **RAINBO** (Refining Adjuvant treatment IN endometrial cancer Based On molecular features) clinical trial program, which assigns adjuvant therapy based strictly on molecular subtype:[27]

Table 7: RAINBO Trial Arms by Molecular Subtype

Trial	Molecular Group	Intervention
p53abn-RED	p53 Abnormal	Chemoradiation + PARP Inhibitor (Olaparib)
MMRd-GREEN	MSI-H/MMRd	Radiation + Immunotherapy (Durvalumab)
NSMP-ORANGE	No Specific Profile	Progestogens vs. Chemoradiation
POLEmut-BLUE	POLE Mutated	De-escalation (Observation)

By structuring data and risk logic around these molecular pillars today, the AI agent prepares healthcare systems for tomorrow's precision therapies. As soon as RAINBO reports results, the logic can be updated to recommend specific targeted agents (PARP inhibitors, immunotherapy) rather than generic chemotherapy.

7 Conclusion

The "one-size-fits-all" approach to endometrial cancer staging is obsolete. The reliance on anatomical extent as the sole arbiter of prognosis has resulted in systematic failure to treat the biology of disease, leading to preventable recurrences and unnecessary toxicities.

This whitepaper presents a comprehensive framework for an AI-driven Integrated Molecular Risk Stratification Agent that bridges this gap. By ingesting high-dimensional data—from BMI and metabolic comorbidities to POLE status and L1CAM expression—and processing it through an Explainable Gradient Boosting architecture, this CDSS offers nuanced, individualized risk assessment.

The system respects disease complexity, acknowledging that:

- A Stage I tumor can be deadly (p53abn)
- A Stage III tumor can be indolent (POLEmut)

Through SHAP interpretability, it maintains transparency, treating oncologists as partners rather than passive data recipients. Implementation represents a critical step toward a future where every endometrial cancer patient receives the right treatment, for the right biological reason, at the right time.

[27] Wortman BG, et al., "Refining adjuvant treatment in endometrial cancer based on molecular features: the RAINBO clinical trial program," *Int J Gynecol Cancer*, 2023;33:109-117. Available: https://pmc.ncbi.nlm.nih.gov/articles/PMC9811074/

A Appendix: Algorithm Pseudocode

Algorithm 1 Integrated Molecular Risk Stratification Agent

Require: Patient data vector $\mathbf{x} = [x_{\text{clinical}}, x_{\text{pathological}}, x_{\text{molecular}}]$
Ensure: Risk score $R \in [0, 1]$ with SHAP explanation $\mathbf{\Phi}$

// **Step 1: Molecular Classification**
if $x_{\text{POLE}} = \text{Mutated}$ **then**
    MolecularGroup $\leftarrow$ POLEmut
else if $x_{\text{MMR}} = \text{Deficient}$ **then**
    MolecularGroup $\leftarrow$ MSI-H
else if $x_{\text{p53}} = \text{Abnormal}$ **then**
    MolecularGroup $\leftarrow$ p53abn
else
    MolecularGroup $\leftarrow$ NSMP
end if
// **Step 2: XGBoost Risk Prediction**
$R \leftarrow \text{XGBoost.predict\_proba}(\mathbf{x})$
// **Step 3: SHAP Explanation**
$\mathbf{\Phi} \leftarrow \text{SHAP.TreeExplainer}(\text{model}, \mathbf{x})$
$E[f(x)] \leftarrow \text{baseline\_risk}$
Explanation $\leftarrow \text{WaterfallPlot}(E[f(x)], \mathbf{\Phi})$
// **Step 4: Clinical Decision Mapping**
if MolecularGroup = p53abn **and** $x_{\text{Stage}} \leq \text{IB}$ **then**
    Alert $\leftarrow$ "Latent High Risk - Consider CTRT"
else if MolecularGroup = POLEmut **and** $x_{\text{Stage}} \geq \text{III}$ **then**
    Alert $\leftarrow$ "Consider De-escalation - RAINBO BLUE"
end if
return $(R, \mathbf{\Phi}, \text{MolecularGroup}, \text{Alert})$

B Appendix: Feature Importance Hierarchy

Based on literature review and SHAP analysis from comparable models, the expected feature importance hierarchy is:

1. **POLE Status** (Protective veto effect)
2. **p53 IHC Status** (Dominant risk driver)
3. **LVSI Status** (Substantial > Focal > None)
4. **L1CAM Expression** (NSMP differentiator)
5. **Myometrial Invasion Depth**
6. **FIGO Stage**
7. **Histological Grade**
8. **Age at Diagnosis**
9. **MMR Status**
10. **CTNNB1 Mutation**

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