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NARRATIVE REVIEW

Type 2 diabetes and gynecologic cancers: Immunometabolic convergence and translational implications

Mauricio A. Cuello[1,2,3] | Carolina Ibañez[3,4]

[1]Department of Gynecology, School of Medicine, Pontificia Universidad Católica de Chile (PUC), Santiago, Chile

[2]Gynecologic Oncology Unit, Hospital Clínico Universidad Católica, UC-Christus Health Network, Santiago, Chile

[3]Center for Cancer Prevention and Control (CECAN), Santiago, Chile

[4]Department of Hematology and Oncology, School of Medicine, Pontificia Universidad Católica de Chile (PUC), Santiago, Chile

Correspondence
Mauricio A. Cuello, Department of Gynecology, School of Medicine, Pontificia Universidad Católica de Chile, Diagonal Paraguay 362, Santiago, 8330077, Chile.
Email: mcuello@uc.cl

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Abstract

Type 2 diabetes mellitus (T2DM) is a highly prevalent chronic condition and an increasingly relevant host factor in cancer prevention, treatment, and survivorship. In gynecologic oncology, clinical observational data link diabetes and broader metabolic dysfunction phenotypes to adverse outcomes in selected malignancies, including HPV-related disease and cervical cancer outcomes, and more consistently reported observational associations in endometrial cancer cohorts. Mechanistically, convergent signaling hubs—insulin/IGF biology, PI3K/AKT/mTOR, and inflammatory circuits such as IL-6/JAK/STAT3 and NF-κB—provide biological plausibility for diabetes-related effects on tumor growth, immune regulation, and treatment response. Persistent hyperglycemia can induce durable immune and epigenetic remodeling consistent with metabolic memory and trained immunity frameworks. Translational evidence is most developed for metformin, including randomized presurgical evaluation in uterine malignancy settings, while other antidiabetic drug classes (e.g., SGLT2 inhibitors and incretin-based biology) have emerging mechanistic and observational oncology-relevant signals that warrant biomarker-driven evaluation. We integrate a targeted narrative synthesis with exploratory transcriptomic and spatial analyses to generate testable hypotheses and propose pragmatic clinical implications and research priorities to support metabolic assessment within gynecologic cancer care pathways.

KEYWORDS
gynecologic cancer, HPV, hyperglycemia, immunometabolism, metformin, PI3K/AKT/mTOR, trained immunity, type 2 diabetes mellitus

1 | INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a major global health challenge and a driver of chronic morbidity worldwide.[1] Increasing evidence links metabolic dysfunction—including diabetes and metabolic syndrome—to patterns of gynecologic cancer risk and adverse outcomes in some cohorts.[2,3] While causality cannot be inferred from observational associations, the consistency of these signals suggests that metabolic dysfunction may influence cancer biology, treatment tolerance, and survivorship trajectories.[3,4]

At the molecular level, diabetes-related hyperglycemia, hyperinsulinemia, and chronic low-grade inflammation intersect with canonical oncogenic programs. Insulin/IGF signaling and PI3K/AKT/mTOR activation promote proliferative and survival pathways, while inflammatory networks (IL-6/JAK/STAT3, NF-κB) shape tumor–host interactions and immune modulation.[3–8] These interconnected hubs are conceptually summarized in Figure 1, which maps shared signaling nodes linking metabolic dysregulation and tumor-promoting programs. These mechanisms can be interpreted as interconnected components of a broader immunometabolic convergence model, in

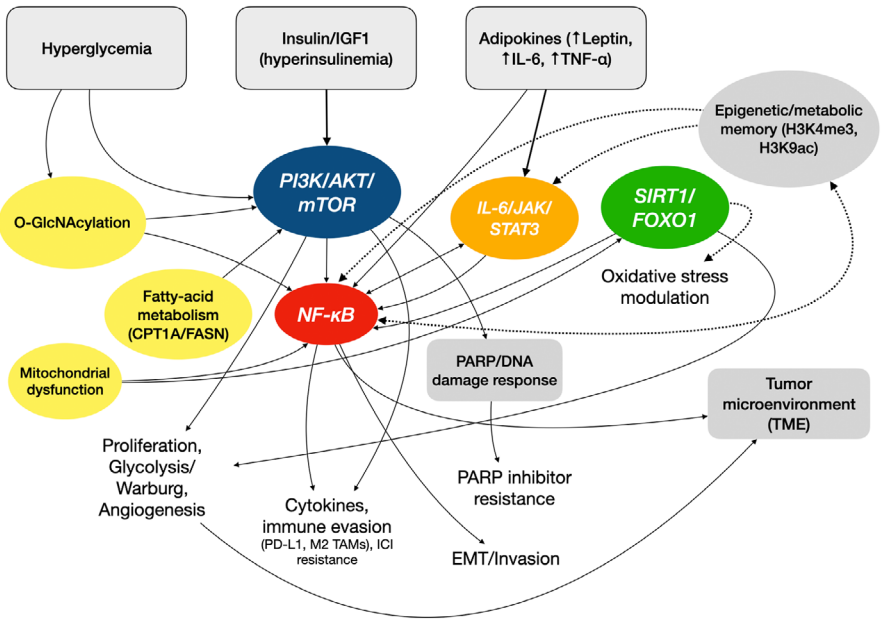

FIGURE 1 Shared immunometabolic signaling pathways linking diabetes and gynecologic cancers. Hyperglycemia, hyperinsulinemia (insulin/IGF1), and adipokine signaling (↑leptin, ↑IL-6, ↑TNF-α) converge on key hubs—PI3K/AKT/mTOR, NF-κB, IL-6/JAK/STAT3, and SIRT1/FOXO1. These pathways integrate metabolic alterations (O-GlcNAcylation, fatty-acid metabolism, mitochondrial dysfunction) with oncogenic signaling programs. Solid arrows denote direct activation, dashed arrows modulatory regulation, and bidirectional arrows reciprocal feedback. Downstream consequences include proliferation, angiogenesis, oxidative stress, immune evasion, epithelial–mesenchymal transition (EMT), and therapeutic resistance involving DNA damage response and PARP-related mechanisms within the tumor microenvironment (conceptual model). The diagram summarizes convergent mechanisms supported by experimental, translational, and epidemiologic literature; pathway interactions are simplified for clarity and do not represent quantitative signaling strength or context-specific directionality. The model integrates evidence across tumor types and metabolic states and should be interpreted as a hypothesis-generating framework rather than as a depiction of direct causal effects.

which systemic metabolic alterations are translated into coordinated oncogenic and immune responses.

In HPV-related disease, population-based studies support an association between diabetes and increased incidence of HPV-related anogenital precancer and cancer.[9] HPV oncogene-driven carcinogenesis and host immune regulation mechanisms[10,11] provide a framework in which metabolic and immune alterations may influence viral persistence and malignant progression. Durable immune reprogramming induced by hyperglycemia—captured by trained immunity and metabolic memory concepts[12,13]—offers a mechanistic bridge between systemic metabolic dysfunction and tumor immune escape, as illustrated in Figure 2.

Beyond synthesizing clinical and mechanistic evidence, this review proposes a translational framework linking metabolic host factors to therapy resistance and immune remodeling and integrates exploratory multiomic analyses to prioritize clinically testable hypotheses relevant to gynecologic oncology.

1.1 | Methodological approach and scope

1.1.1 | Literature identification and narrative synthesis

This manuscript is a targeted narrative review integrating exploratory transcriptomic and spatial analyses and does not follow formal systematic review methodology. A focused PubMed (MEDLINE) search conducted between August and December 2025 using combinations of terms including "type 2 diabetes," "hyperglycemia," "metabolic syndrome," "endometrial," "cervical," "ovarian," "HPV," "metformin," "SGLT2 inhibitors," "GLP-1," "PARP inhibitors," and "immune checkpoint inhibitors" retrieved 198 records; a subset of 42 references was cited in the main text due to journal space constraints. No start-date restriction was applied; the last search was performed in December 2025.

We prioritized human evidence in gynecologic cancers (population-based cohorts, meta-analyses, and randomized trials when available). Preclinical studies were included to support biological plausibility rather than to establish clinical causality. Given the narrative scope, formal PRISMA screening and quantitative meta-analysis were not undertaken. Nevertheless, explicit transparency regarding search domains, reference inventory retention, and analytic assumptions was prioritized to enhance reproducibility and interpretive clarity. Study selection was guided by methodological robustness, clinical relevance to gynecologic oncology, and contribution to mechanistic or translational insight.

To further support transparency and reproducibility, the narrative synthesis was developed following established principles for high-quality narrative reviews, including structured identification of relevant literature, explicit justification of inclusion based on clinical and mechanistic relevance, and critical interpretation of evidence.

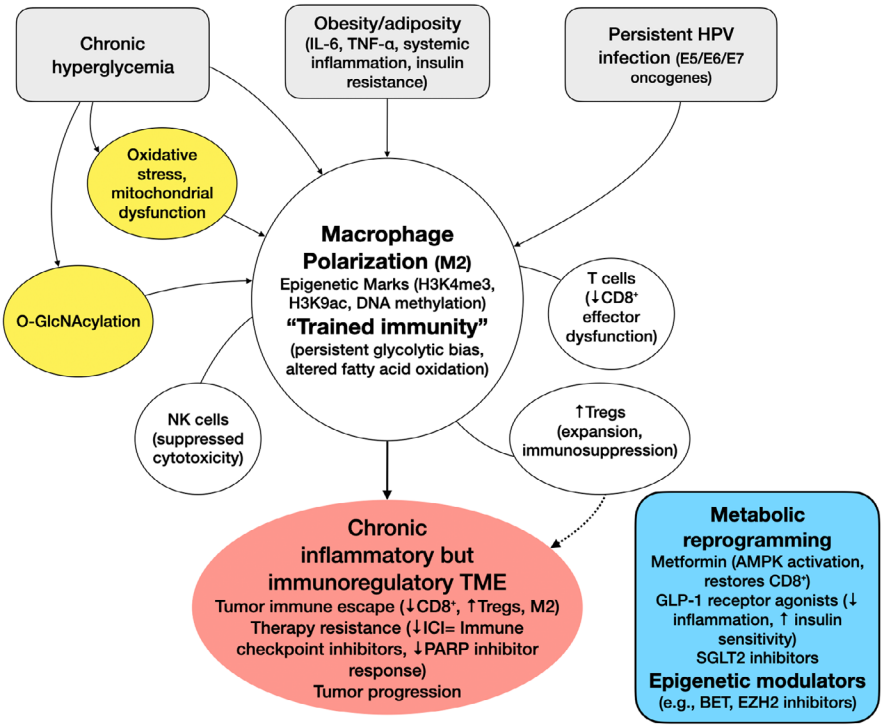

FIGURE 2 Immunometabolic memory linking diabetes, obesity, and HPV infection to immune escape. Chronic hyperglycemia, adiposity-driven inflammation, and persistent HPV oncogene expression (E5/E6/E7) induce O-GlcNAcylation, mitochondrial dysfunction, and oxidative stress, promoting macrophage M2 polarization and epigenetic reprogramming (e.g., H3K4me3, H3K9ac, DNA methylation). This establishes a form of trained immunity characterized by glycolytic bias and altered fatty acid oxidation, contributing to $CD8^+$ T-cell dysfunction, NK-cell suppression, and Treg expansion. The resulting tumor microenvironment is chronically inflammatory but immunoregulatory, facilitating immune evasion and potentially contributing to reduced responsiveness to immune checkpoint inhibitors (ICIs) and PARP inhibitors (PARPi). Potential metabolic and epigenetic reprogramming strategies include metformin, GLP-1 receptor agonists, SGLT2 inhibitors, and chromatin-modifying agents (Conceptual model). The depicted immune alterations represent biologically plausible mechanisms derived from experimental and translational studies. Direct causality between systemic diabetes and tumor-level immune remodeling in individual patients cannot be inferred from this schematic representation.

This approach is consistent with the domains described in the Scale for the Assessment of Narrative Review Articles (SANRA) framework, and a structured assessment is provided in Table S1.

Full search terms and a summary of the selection approach are provided in Supplementary Methods (Appendix S1).

1.1.2 | In silico analyses (hypothesis-generating)

Publicly available datasets from large-scale cancer consortia and single-cell/spatial atlases were interrogated using a predefined diabetes-associated gene panel (Table S2) derived from genetic fine-mapping and curated cancer driver catalogs.[14,15]

The diabetes-associated transcriptional score (DATS) was constructed using standardized expression values of the selected gene panel. Tumors were stratified into high-score and low-score groups using a median split approach.

The predefined diabetes-associated gene panel included 65 genes selected a priori based on replicated fine-mapping evidence in type 2 diabetes and cross-referenced with curated cancer driver catalogs. Gene inclusion was restricted to loci with functional annotation plausibly linking metabolic regulation and oncogenic signaling. No data-driven feature selection was applied at the stage of score construction in order to minimize overfitting. This panel was used as the initial feature space for downstream analyses without a priori weighting. Subsequent analytical steps enabled the identification of a reduced subset of genes with consistent and biologically relevant transcriptional patterns across datasets, reflecting dominant signals within the broader transcriptional program rather than predefined weighting within the score.

The DATS is intended to prioritize shared biology and generate testable hypotheses rather than to function as a validated clinical prognostic model. Any potential clinical utility would require external validation in independent cohorts with metabolic annotation and multivariable adjustment.

Survival associations (overall survival and progression-free interval) were explored without adjustment for tumor stage, systemic therapy exposure, or metabolic clinical variables and therefore should be interpreted as hypothesis-generating rather than causal.

Optimal cutpoints were explored using maximally selected rank statistics, but the primary stratification presented uses a predefined median split to minimize overfitting. Results based on maximally selected statistics are not presented in the main figures to avoid inflation of type I error. Hazard ratios were estimated using univariable Cox proportional hazards models. No multivariable adjustment for tumor stage, grade, treatment exposure, or metabolic clinical variables was performed. *p* Values were not adjusted for multiple testing given the exploratory nature of the analyses.

All analyses are intended to inform future clinical investigation rather than establish definitive associations. Accordingly, the DATS should be interpreted as a composite signal reflecting pathway-level convergence, while highlighted genes represent dominant transcriptional signals emerging from downstream analyses rather than individual predictive determinants. Cohort identifiers, sample sizes, normalization procedures, and statistical methods are detailed in the Supplementary Analytic notes (Appendix S1).

2 | CLINICAL IMPACT AND EPIDEMIOLOGY

Diabetes is clinically relevant in gynecologic oncology because it co-occurs with metabolic features that influence cancer risk, treatment tolerance, and long-term outcomes.[1,3] In cervical cancer, clinical studies report associations between diabetes-related parameters and survival outcomes, although effect sizes and confounding structures vary across datasets.[16,17] Broader gynecologic cancer associations have also been described in the context of metabolic syndrome.[2]

In HPV-related malignancies, nationwide registry-based evidence shows increased incidence of HPV-related anogenital precancer and cancer in women with diabetes.[9] These epidemiologic signals intersect with biological mechanisms depicted in Figure 2, which integrates HPV oncogene biology with immunometabolic memory frameworks.

Importantly, health-system factors also contribute to outcome differences. Diabetes has been associated with reduced cervical cancer screening adherence in some populations,[18] underscoring that both biological and structural determinants likely contribute to observed disparities.

Type 2 diabetes frequently coexists with obesity and metabolic syndrome, and many epidemiologic datasets cannot fully disentangle the independent contributions of hyperglycemia, adiposity, insulin resistance, and systemic inflammation. For clarity, this review uses "metabolic dysfunction" as an umbrella construct encompassing T2DM, insulin resistance, obesity-related adipose inflammation, and related cardiometabolic comorbidity. Where evidence is specific to diagnosed T2DM, we state this explicitly; when exposures overlap or are not separable, we refer to metabolic dysfunction as a composite host phenotype. When obesity and diabetes-related effects cannot be disentangled, findings are interpreted conservatively as reflecting overlapping metabolic phenotypes rather than isolated glycemic effects.

3 | CONVERGENT MECHANISMS: SHARED SIGNALING NODES

3.1 | Insulin/IGF and PI3K/AKT/mTOR convergence

Insulin/IGF biology is a well-established axis connecting metabolic state to growth signaling in cancer.[6,19] Downstream activation of PI3K/AKT/mTOR represents a central oncogenic pathway relevant to tumor proliferation and targeted therapy resistance.[5] In diabetes, hyperinsulinemia and altered nutrient signaling can amplify these programs.[3,4] These interconnections are summarized in Figure 1, which highlights potential therapeutic entry points.

3.2 | Inflammatory signaling and tumor microenvironment effects

Chronic inflammation in metabolic disease intersects with tumor-promoting cytokine programs. IL-6/JAK/STAT3 signaling is a key inflammatory axis in the tumor microenvironment,[8] while NF-κB contributes to immune modulation and tumor survival.[7] These inflammatory circuits integrate with metabolic signaling in a manner consistent with immunometabolic principles,[4,20] reinforcing the systemic-host perspective emphasized in Figure 1. In this context, metabolic and inflammatory signaling should not be viewed as parallel processes but as interdependent pathways that jointly shape tumor behavior and immune regulation.

3.3 | Adipokine signaling as a mechanistic bridge

In endometrial cancer models, leptin activates JAK/STAT3 and PI3K/AKT-related pathways,[21] illustrating how adiposity-associated signaling can reinforce proliferative and inflammatory loops. These findings provide mechanistic plausibility rather than direct clinical causality.

3.4 | Hyperglycemia, oxidative stress, and metabolic remodeling

Chronic hyperglycemia contributes to oxidative stress and inflammatory activation in diabetes.[22,23] These systemic perturbations can interact with tumor metabolism and immune signaling, consistent with systemic disease models of cancer complexity.[24] This metabolic–inflammatory interface informs the conceptual framework illustrated in Figure 2. Taken together, these observations suggest

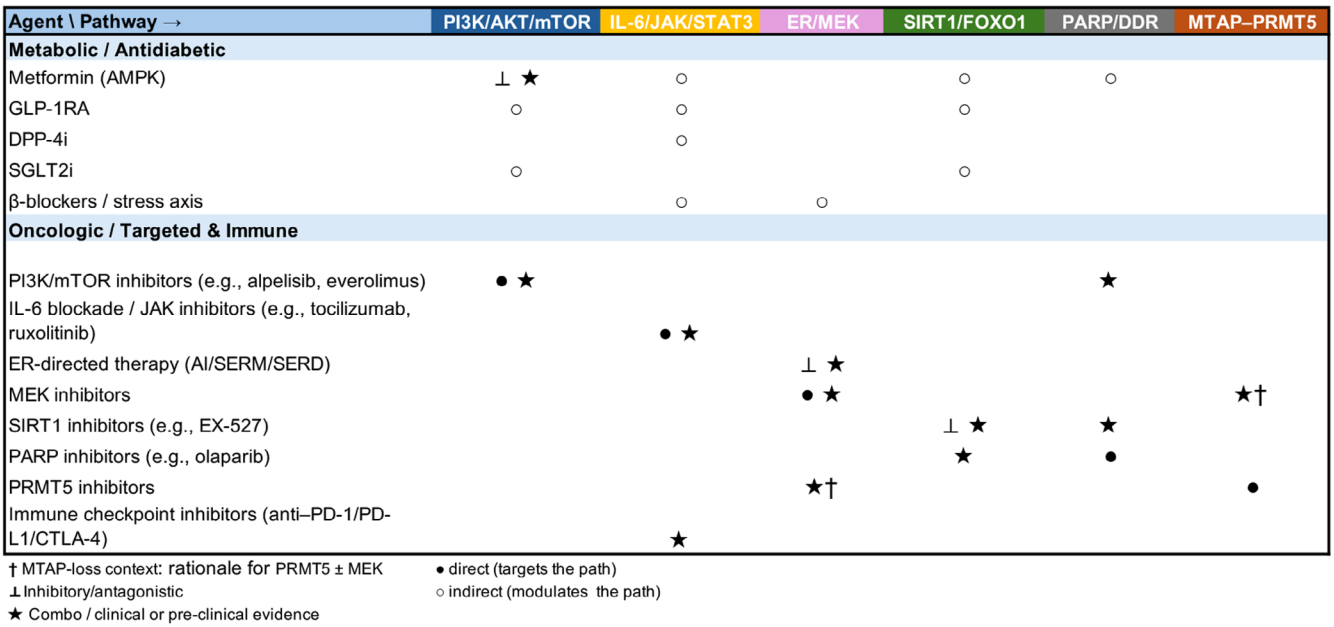

FIGURE 3 Therapeutic cross-talk between antidiabetic and oncologic agents. Matrix mapping drugs across major signaling axes (PI3K/AKT/mTOR, IL-6/JAK/STAT3, ER/MEK, SIRT1/FOXO1, MTAP–PRMT5, PARP/DDR) illustrates rational combinatorial strategies based on pathway convergence. Agents include both clinically evaluated therapies (e.g., metformin) and mechanistically inferred pathway modulators supported by preclinical evidence. The matrix is intended to generate testable hypotheses rather than to imply established clinical efficacy. Pathway assignments are based on predominant reported mechanisms and may not capture context-dependent pleiotropic effects. Clinical benefit in gynecologic cancers remains investigational unless supported by completed phase 3 data.

that metabolic dysfunction operates through a coordinated network of biological processes rather than isolated pathways, supporting the need for an integrative conceptual framework.

4 | DNA DAMAGE RESPONSE AS AN INTERSECTION

PARP-related biology represents another convergence point. In experimental diabetes models, PARP inhibition ameliorates inflammatory and oxidative pathways.[25] In gynecologic cancers, PARP inhibitors are established therapeutics, and resistance mechanisms are actively studied.[26–29] The interplay between metabolic stress, inflammatory activation, and DNA repair dependencies is integrated into the signaling landscape depicted in Figure 1, while therapeutic implications are positioned within the cross-talk matrix in Figure 3.

5 | GENE-LEVEL CONVERGENCE AND PROGNOSTIC FRAMEWORK

Cross-referencing curated cancer gene resources and diabetes fine-mapping efforts identifies overlapping pathways and candidate nodes relevant to both diseases.[14,15] The methodological integration of these datasets underpins the prognostic framework summarized in Table 1, which presents diabetes-linked genes with gynecologic cancer survival associations.

A broader catalog of mechanistic intersections and gene prioritization resources is detailed in Tables S3–S5, which respectively summarize functional gene roles across cancer and β-cell biology, cancer driver genes with diabetes-related roles, and shared genes with therapeutic targets.[14,15]

6 | TRANSLATIONAL THERAPEUTIC CROSS-TALK

6.1 | Metformin: most developed clinical translational evidence base

Metformin has the most developed oncology translational pipeline. Randomized presurgical evaluation in uterine malignancy settings has been performed,[30] and mechanistic reviews summarize plausible anticancer effects.[31,32] Observational data in cervical cancer populations further explore outcome associations.[33,34] In endometrial cancer, observational evidence has also been synthesized in meta-analytic form, although interpretation remains limited by confounding.[35] These clinical and mechanistic intersections are summarized in Table 2 and contextualized across tumor types in Table S6.

6.2 | Incretin-based biology

Preclinical diabetic mouse models suggest GLP-1–related signaling may exert antitumor effects.[36] These findings justify structured

TABLE 1 Gynecologic cancer prognostic genes with established diabetes mechanisms ($n = 11$).

Gene	Diabetes-related process	Role in gynecologic cancers	Primary immunometabolic axis (Figure 1)	Evidence source
CDKN2A	Cell cycle dysregulation in insulin resistance	Risk gene in cervical/endometrial cancer	Cell cycle regulation/p53 pathway interface	COSMIC, RNA-seq
STAT3	Chronic inflammation, insulin resistance	Oncogenic, immune evasion	IL-6 /JAK/STAT3 inflammatory axis	Reviews, functional studies
PPARG	Insulin sensitivity, lipid metabolism	Context-dependent tumor suppressor	Adipokine signaling/lipid metabolism axis	GWAS, functional literature
HNF1A	β-cell function, insulin regulation	Modulator of differentiation	β-cell regulation/insulin secretion axis	DIAGRAM, Broad RNA-seq
TCF7L2	Strongest T2DM susceptibility locus	Wnt-driven proliferation	Wnt signaling–metabolic cross-talk axis	GWAS, COSMIC
SIRT1	Oxidative stress, metabolic memory	Protective effect in endometrial cancer	SIRT1/FOXO1 metabolic memory axis	RNA-seq, functional studies
ESR1	Hormone receptor signaling, obesity link	Prognostic in gynecologic tumors	Hormone–metabolic integration axis	Functional literature
IGF1	Insulin/IGF axis, growth factor signaling	Tumor growth, proliferation	Insulin/IGF–PI3K/AKT/mTOR axis	COSMIC
INS	Hyperinsulinemia, insulin resistance	Mitogenic effect in tumors	Insulin signaling/PI3K–AKT axis	Functional studies
MTOR	Nutrient sensing, insulin pathway	Oncogenic driver	PI3K/AKT/mTOR nutrient-sensing axis	COSMIC, pathway databases
AKT1	Insulin signaling	Cell survival, progression	PI3K/AKT survival signaling axis	COSMIC, Broad RNA-seq

Note: Genes implicated in type 2 diabetes pathogenesis (β-cell function, insulin resistance, immunometabolic memory) that also demonstrate prognostic associations in gynecologic cancers. Columns include gene identifier, diabetes-related mechanism, gynecologic cancer role (oncogene, tumor suppressor, or prognostic marker), primary data source (e.g., GWAS, RNA-seq, cancer driver catalogs, functional literature), and key supporting evidence. Associations are hypothesis-generating and require functional validation under diabetic-relevant conditions. Inclusion criteria required evidence from genome-wide association studies, curated cancer gene catalogs, or functional immunometabolic literature. Gene roles may be context-dependent across tumor types. The table integrates cross-domain evidence and does not imply direct mechanistic causality within diabetic tumor microenvironments.

clinical investigation but should not be interpreted as established clinical efficacy.

6.3 | SGLT2 inhibitors

SGLT2 inhibitors have emerging oncology-relevant mechanistic plausibility,[37] and observational data report lower cervical cancer incidence among T2DM patients receiving SGLT2 inhibitors in one study context.[38] These translational intersections are incorporated into the therapeutic mapping shown in Figure 3 and detailed in Table S6.

6.4 | Ovarian cancer, metabolic phenotype, and PARP inhibitor efficacy

In ovarian cancer, PARP inhibitors (PARPi) are established components of maintenance therapy, particularly in homologous recombination–deficient tumors.[26–29] However, no prospective studies have systematically evaluated whether host metabolic factors—including type 2 diabetes, glycemic control, or antidiabetic medication exposure—modify PARPi efficacy or toxicity profiles.

Chronic hyperglycemia and systemic inflammation may plausibly interact with DNA damage response pathways and treatment tolerance; however, this interaction has not been evaluated in PARPi maintenance cohorts stratified by homologous recombination status. Future studies should prospectively collect baseline metabolic variables (e.g., HbA1c, fasting glucose, body mass index [BMI, calculated as weight in kilograms divided by the square of height in meters], antidiabetic medication exposure) in PARPi-treated populations and evaluate progression-free survival on maintenance therapy, dose interruptions, treatment discontinuation due to toxicity, and time to resistance. These considerations represent a clinically actionable research gap rather than an established therapeutic interaction. No current clinical guidelines recommend modification of PARP inhibitor use based on metabolic status.

7 | IMMUNOMETABOLIC MEMORY AND TUMOR IMMUNITY

Hyperglycemia-induced trained immunity and metabolic memory provide a coherent framework linking systemic metabolic dysfunction to persistent immune remodeling.[12,13] In HPV-driven

TABLE 2 Clinical trials of antidiabetic agents in gynecologic cancer.

Agent/C class	Primary signaling axis /mechanistic rationale	Cancer setting	Combination partners	Rationale vs. score axes	Clinical stage/ status	Predictive biomarker	Key safety notes	Key reference (NCT)
Metformin	AMPK activation → mTOR inhibition → metabolic stress signaling	Endometrial cancer	NA	Metabolic–mTOR axis	COMPLETED	Yes (molecular endpoints)	Not specified (clinicaltrials.gov)	https://clinicaltrials.gov/study/NCT01205672
Metformin	AMPK activation → mTOR inhibition → metabolic stress signaling	Ovarian, fallopian tube, and primary peritoneal cancer	NA	Metabolic–mTOR axis	COMPLETED	Not specified	Not specified (clinicaltrials.gov)	https://clinicaltrials.gov/study/NCT01579812
HPV vaccine, Imiquimod, metformin	Immune activation (HPV-specific response) + AMPK-mediated metabolic modulation	Cervical, vaginal, vulvar, HPV-associated carcinoma	NA	Inflammation–metabolism	RECRUITING	Not specified	Not specified (clinicaltrials.gov)	https://clinicaltrials.gov/study/NCT06686043
Metformin + Paclitaxel + Carboplatin	AMPK activation → mTOR inhibition; chemotherapy sensitization	Epithelial ovarian carcinoma	Chemotherapy	Metabolic–mTOR axis	UNKNOWN	Not specified	Not specified (clinicaltrials.gov)	https://clinicaltrials.gov/study/NCT02437812
Metformin + Levonorgestrel	AMPK activation → mTOR inhibition; hormonal pathway interaction	Complex endometrial hyperplasia/ grade 1 endometrial adenocarcinoma	Hormonal therapy	Metabolic–mTOR axis	ACTIVE, not recruiting	Not specified	Not specified (clinicaltrials.gov)	https://clinicaltrials.gov/study/NCT01686126
Metformin + Carboplatin + Paclitaxel	AMPK activation → mTOR inhibition; metabolic–cytotoxic cross-talk	Endometrial adenocarcinoma (multiple histologies, recurrent/ advanced uterine corpus cancer)	Chemotherapy	Metabolic–mTOR axis	UNKNOWN	Not specified	Not specified (clinicaltrials.gov)	https://clinicaltrials.gov/study/NCT02065687
Metformin + Zimberelimab	AMPK activation → mTOR inhibition; immunometabolic modulation (PD-1/PD-L1 axis)	Ovarian clear cell carcinoma	ICI (anti-PD-1)	Metabolic–mTOR axis	UNKNOWN	Not specified	Not specified (clinicaltrials.gov)	https://clinicaltrials.gov/study/NCT05759312

Note: Ongoing and completed interventional studies evaluating metformin and other metabolic agents in gynecologic malignancies. Columns include agent or class, primary signaling axis, cancer setting, combination partners, mechanistic rationale, trial phase or status, predictive biomarkers (if available), safety considerations, and supporting sources. Trial details reflect publicly available registry information. Trial status reflects registry information at the time of data extraction (August–December 2025). Inclusion does not imply demonstrated clinical efficacy. Mechanistic rationales are derived from pathway convergence models presented in Figures 1 and 3.

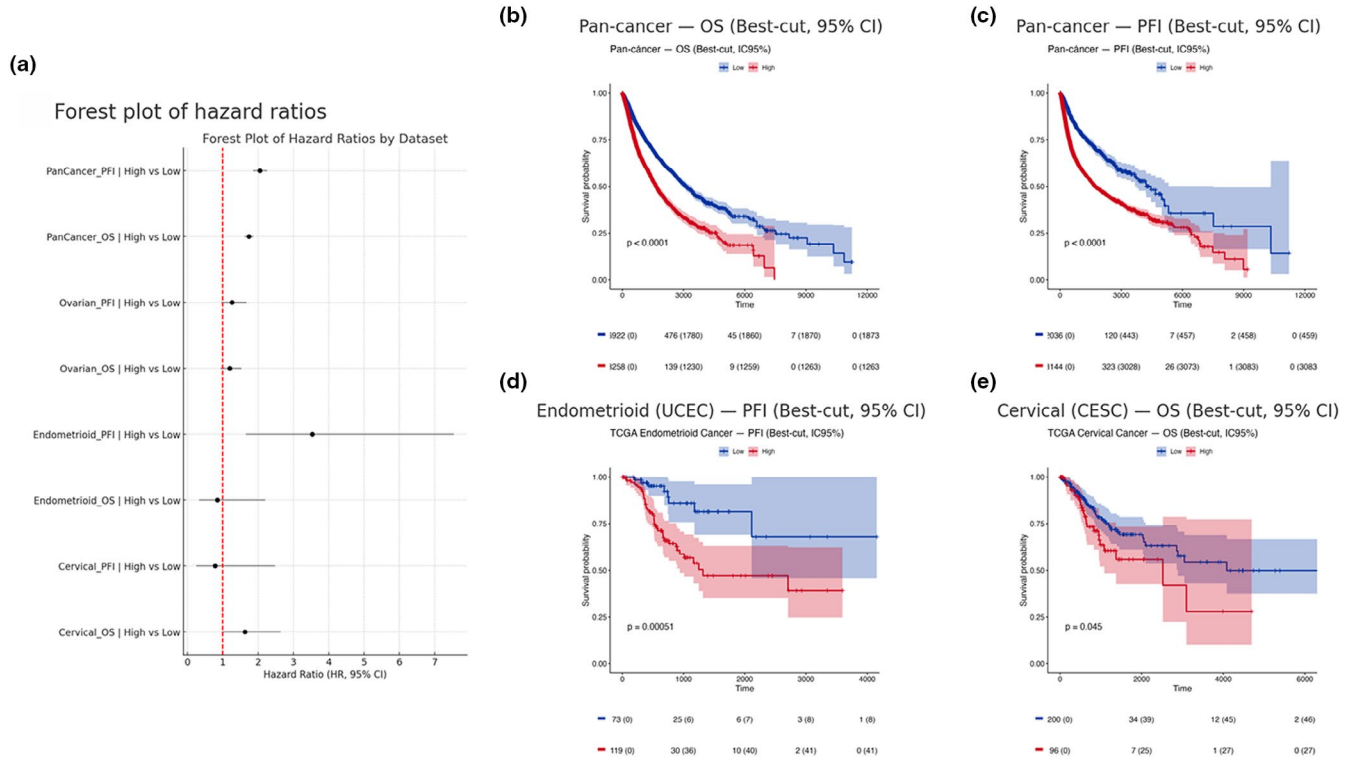

FIGURE 4 Survival associations of the diabetes-associated transcriptional score (DATS). (a) Forest plot of hazard ratios (hazard ratio [HR], 95% confidence interval [CI]) for overall survival (OS) and progression-free interval (PFI) across pan-cancer and gynecologic cohorts. (b–c) Kaplan–Meier curves demonstrate significant stratification in >10 000 tumors (log-rank $p < 1 \times 10^{-4}$). (d) Endometrial cancer (UCEC) shows strong association with PFI ($p = 0.00051$). (e) Cervical cancer (CESC) shows modest OS significance ($p = 0.045$). No significant survival effect was detected in ovarian cancer (OV). DATS groups were defined using median stratification unless otherwise specified. Hazard ratios were estimated using univariable Cox proportional hazards models. Survival analyses are unadjusted and no correction for multiple testing was applied. No adjustment was performed for stage, grade, molecular subtype, body mass index (BMI), diabetes status, or treatment variables. Accordingly, findings are exploratory and hypothesis-generating and should not be interpreted as independent prognostic validation.

malignancies, immune escape programs intersect with these host factors.[10,11] The integrated model of immunometabolic memory and tumor immune escape is illustrated in Figure 2, which conceptualizes how durable immune reprogramming may influence responsiveness to immunotherapy and DNA-damage–targeted strategies.

7.1 | Immune checkpoint inhibitors and metabolic host factors

Immune checkpoint inhibitors (ICIs) have introduced new complexity into the metabolic management of cancer patients. ICI-associated dysglycemia and insulin-dependent diabetes have been increasingly recognized.[39–41] Although data remain limited in gynecologic oncology specifically, these observations underscore the bidirectional interaction between cancer therapy and metabolic homeostasis.

Two clinically relevant dimensions warrant distinction: (i) therapy-induced dysglycemia or insulin-dependent diabetes as an immune-related adverse event, and (ii) the possibility that baseline metabolic phenotype modifies immunotherapy efficacy. Evidence remains limited in gynecologic oncology, warranting prospective trials that include baseline metabolic assessment and longitudinal glucose monitoring. In clinical practice, baseline HbA1c assessment and coordination with endocrinology may be considered for patients receiving ICIs. This suggestion reflects pragmatic clinical coordination rather than evidence of altered immunotherapy efficacy.

8 | IN SILICO MULTIOMIC INTEGRATION

Exploratory transcriptomic and spatial analyses further support a diabetes-linked transcriptional axis in gynecologic cancers.

Score-based survival stratification is shown in Figure 4, single-cell lineage distribution patterns in Figure 5, ecotype and immune–stromal remodeling in Figure 6, and spatial transcriptomic validation in cervical cancer in Figure 7. Single-cell RNA sequencing datasets were normalized using log-transformed counts per million, and cell-type annotations were based on original study classifications.

Spatial transcriptomic data were analyzed using publicly available processed matrices; diabetes-associated transcriptional activity was projected using the same predefined gene panel applied to bulk analyses. These projections represent relative expression patterns and are not direct measures of patient-level metabolic status.

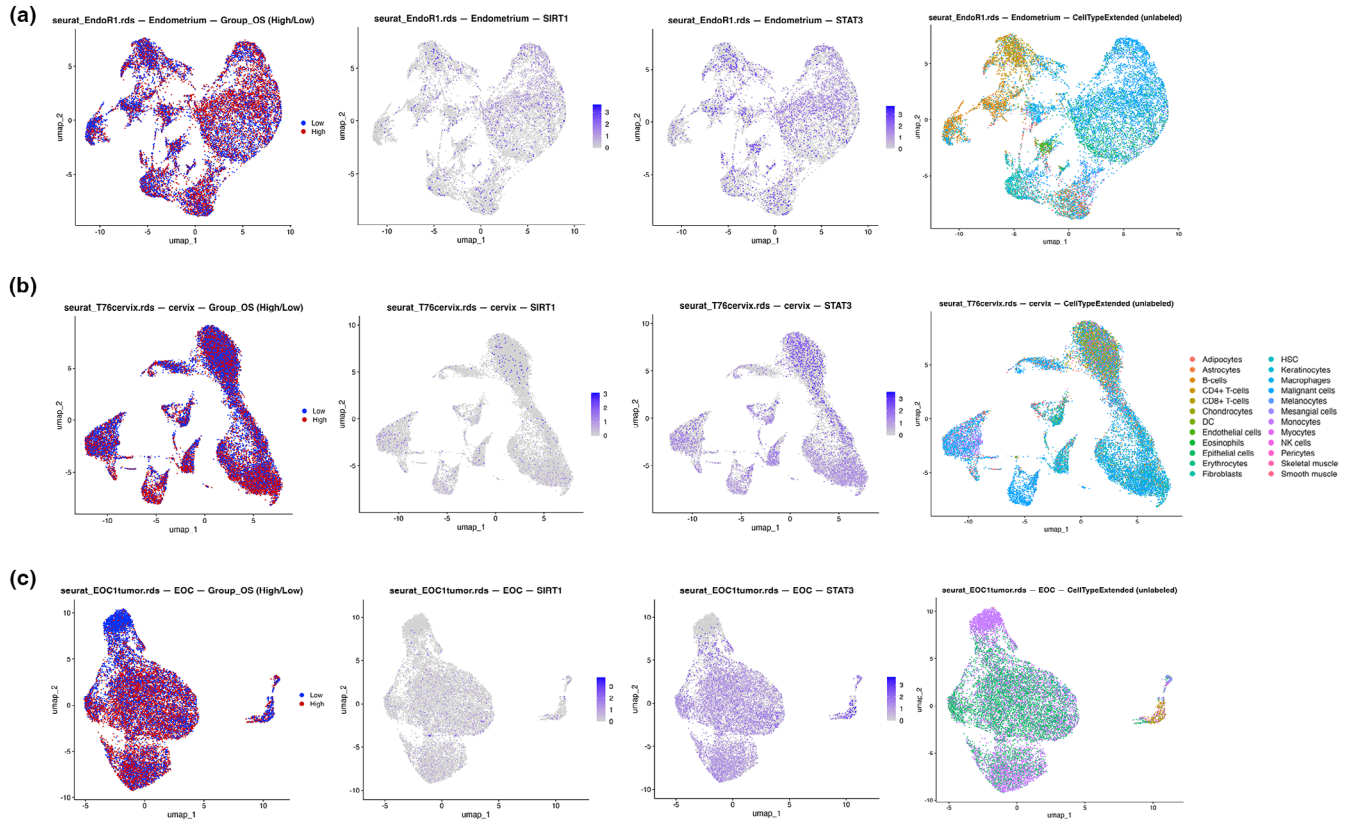

FIGURE 5 Single-cell transcriptomic distribution of diabetes-linked genes. (a) Endometrial cancer: High versus low diabetes-associated transcriptional score (DATS) groups show SIRT1 enrichment in stromal and epithelial compartments, broad STAT3 expression, and ESR1 localized to tumor epithelium. (b) Cervical cancer: SIRT1 minimally expressed, STAT3 broadly distributed across malignant and immune clusters, CDKN2A enriched in malignant populations. (c) Ovarian cancer: Diffuse STAT3 expression with limited prognostic association; SIRT1, ESR1, and CDKN2A minimally represented. These lineage-specific patterns may help explain tumor-type heterogeneity in prognostic impact (single-cell transcriptomic analysis). Single-cell data were derived from publicly available datasets processed using standardized Seurat workflows. Gene expression values are displayed as normalized and scaled expression (z-score). Cell-type annotations reflect reference-based labeling and may vary according to clustering resolution and dataset-specific preprocessing parameters.

These analyses are hypothesis-generating and grounded in curated diabetes and cancer gene resources.[14,15] They do not adjust for clinical covariates and therefore should not be interpreted as a clinically validated risk model. They are intended to prioritize convergent biological pathways and candidate nodes for future investigation rather than to define a diabetes-specific tumor subtype or establish clinically actionable molecular stratification.

8.1 | Methodological considerations regarding the DATS framework

The DATS should not be interpreted as a validated prognostic signature. The score was constructed using a predefined gene panel and applied without multivariable adjustment for tumor stage, grade, treatment exposure, or metabolic clinical variables. No correction for multiple hypothesis testing was performed given the exploratory design. Therefore, observed associations are intended to highlight convergent biology rather than define clinically actionable stratification. Prospective validation in metabolically annotated cohorts with pre-specified endpoints would be required before any clinical application.

9 | DISCUSSION

Understanding the relationship between type 2 diabetes and gynecologic cancers requires moving beyond the description of individual pathways toward an integrated biological perspective. In this context, we propose an immunometabolic convergence framework in which systemic metabolic alterations—including hyperglycemia, hyperinsulinemia, and adiposity—interact with key intracellular signaling hubs such as PI3K/AKT/mTOR, IL-6/STAT3, NF-κB, and SIRT1/FOXO1, ultimately shaping tumor microenvironment dynamics, immune regulation, and treatment response. Within this framework, metabolic disturbances act as upstream drivers that propagate through interconnected signaling networks, influencing both oncogenic programs and host immune behavior.

In this context, the intersection between T2DM and gynecologic malignancies becomes clinically relevant, as metabolic dysfunction

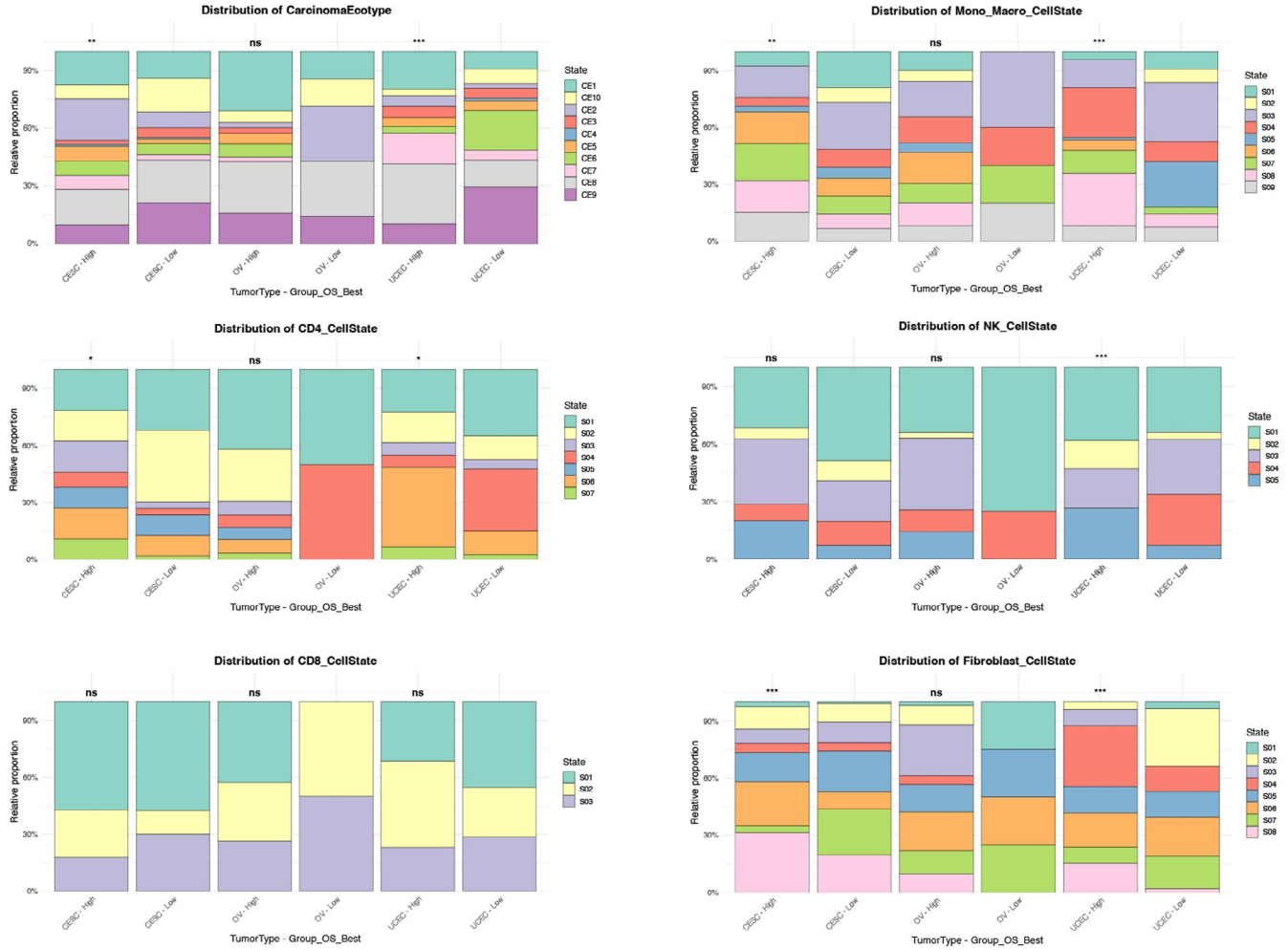

FIGURE 6 Ecotype and immune–stromal cell-state remodeling by diabetes-associated transcriptional score (DATS). Bar plots display relative abundance of carcinoma ecotypes and immune/stromal cell states stratified by DATS (high vs. low). In UCEC, high-score tumors are enriched for CE1/CE8 ecotypes, fibroblasts, and monocyte/macrophage states. In CESC, high-score tumors show shifts in $CD4^+$ T cells, NK cells, and fibroblasts consistent with immune remodeling. No consistent changes were observed in OV. Statistical comparisons: $^{***}p < 0.001$, $^{**}p < 0.01$, $^{*}p < 0.05$; ns, not significant. Group comparisons were performed using Wilcoxon rank-sum testing without correction for multiple comparisons. Exploratory multiomics integration. No adjustment was applied for tumor purity, stage, molecular subtype, or treatment exposure. Results represent descriptive comparative patterns within integrated datasets and should be interpreted as hypothesis-generating.

may influence tumor biology, treatment tolerance, survivorship trajectories, and potentially therapeutic responsiveness.[1,3,41] Observational signals linking diabetes to adverse outcomes, particularly in cervical cancer,[16,17] support consideration of metabolic risk within comprehensive oncologic assessment.

Mechanistic convergence across insulin/IGF, PI3K/AKT/mTOR, and inflammatory IL-6/JAK/STAT3 networks provides biological plausibility for tumor-promoting effects in metabolically dysregulated contexts.[3–5,7,8] The trained immunity and metabolic memory frameworks further contextualize how durable immune reprogramming could interact with HPV-driven carcinogenesis.[10,12,13] Translational evidence remains strongest for metformin,[30,32] while broader metabolic drug classes require rigorous, biomarker-stratified evaluation.[37,38] Future trials should integrate oncologic endpoints with metabolic phenotyping and survivorship outcomes within comprehensive host–tumor frameworks.[24] This integrative perspective differs from prior reviews that have examined these pathways in isolation, by emphasizing their convergence within a unified biological and translational context.

The integration of bulk transcriptomic, single-cell, and spatial analyses (Figures 4–7) provides cell-type–resolved support for the proposed immunometabolic convergence model, although these findings remain exploratory and require validation in metabolically annotated clinical cohorts.

Importantly, no prospective interventional data currently demonstrate that modification of metabolic parameters improves gynecologic cancer–specific survival or alters therapeutic efficacy in a causal manner. The present framework therefore should be

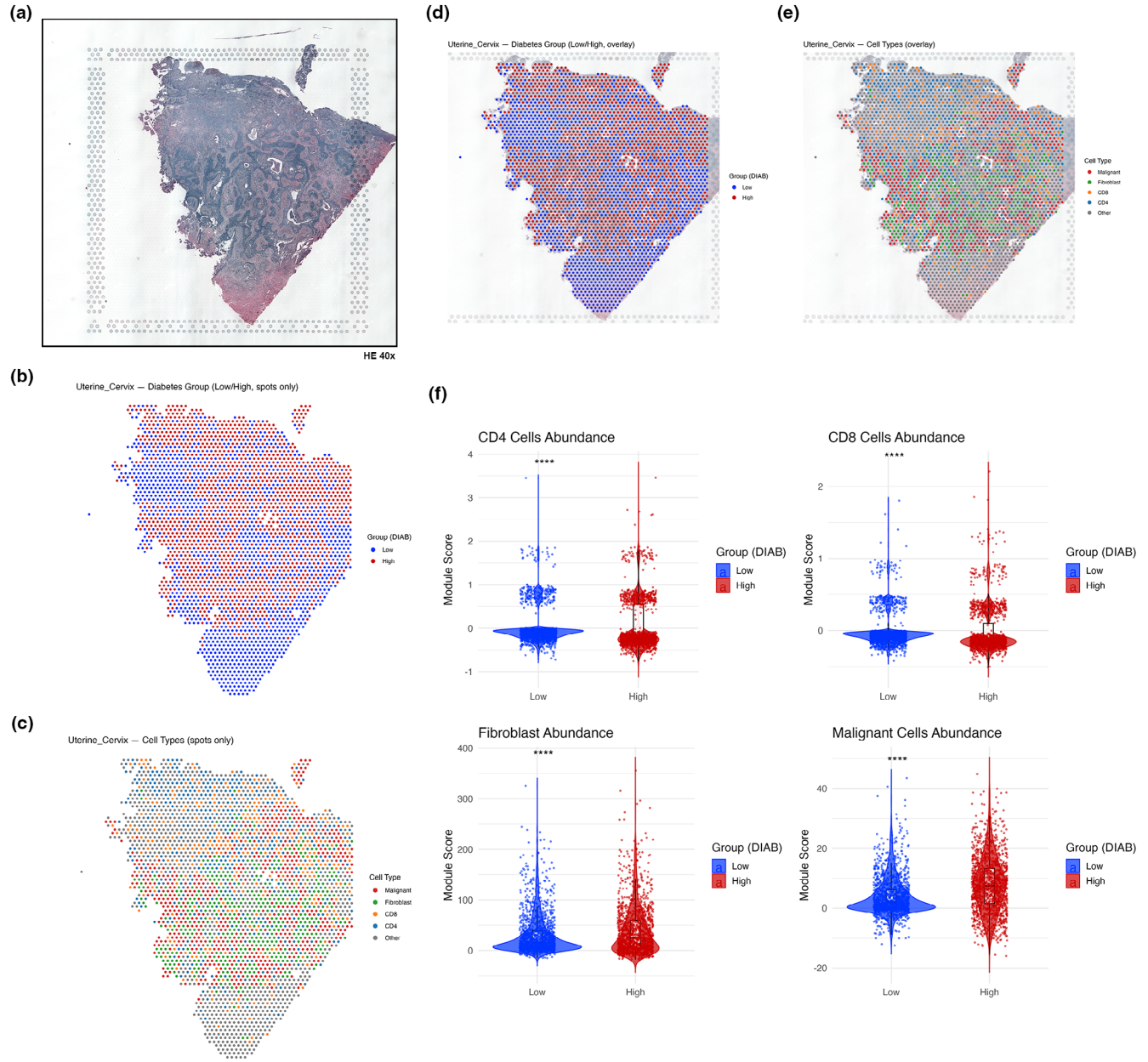

FIGURE 7 Spatial transcriptomic validation of the diabetes-associated transcriptional score (DATS) in cervical cancer. (a) Hematoxylin & eosin (H&E) section of representative cervical tumor. (b) Spatial mapping of DATS groups. (c) Cell-type annotations. (d–e) Overlays demonstrating co-localization of high-score regions with immune and stromal compartments. (f) Violin plots show enrichment of $CD4^+$ T cells, $CD8^+$ T cells, fibroblasts, and malignant cells in high-score regions ($p < 1 \times 10^{-4}$). These findings suggest spatial encoding of diabetes-associated transcriptional risk within fibro-immune niches. DATS grouping reflects relative transcriptional enrichment within the analyzed dataset and does not correspond to clinically documented diabetes status. Spatial associations were evaluated at the spot level without patient-level metabolic annotation. Statistical comparisons represent exploratory module score differences and were not adjusted for spatial autocorrelation. Spatial projections represent transcriptional patterns rather than direct measurement of systemic metabolic phenotype.

interpreted as a structured hypothesis-generating model rather than as evidence supporting immediate therapeutic modification based on metabolic status alone. This conceptual integration may help explain heterogeneity in treatment response and provides a rationale for exploring combined metabolic and oncologic therapeutic strategies in future studies.

9.1 | Strength of evidence across domains

The evidence supporting the proposed immunometabolic convergence framework is heterogeneous in strength and maturity.

Level A (direct clinical interventional evidence): randomized presurgical metformin studies in endometrial cancer.

Level B (robust observational associations): population-based registry data linking diabetes with HPV-related anogenital disease incidence and selected survival analyses in cervical cancer cohorts.

Level C (mechanistic plausibility and translational hypothesis): interactions involving SGLT2 inhibitors, incretin-based therapies, PARP inhibitor resistance modulation, and trained immunity frameworks.

This hierarchical distinction is essential to avoid overinterpretation and underscores that most domains remain hypothesis-generating rather than practice-changing.

Importantly, the present framework is intended to stimulate structured investigation rather than to redefine therapeutic standards.

9.2 | Limitations

Several limitations should be acknowledged. Much of the available evidence linking diabetes and gynecologic cancers derives from observational cohorts and preclinical models. Residual confounding by obesity, treatment heterogeneity, and comorbidity burden is likely. The in silico analyses presented here are exploratory and do not account for tumor stage, systemic therapy exposure, or direct metabolic measurements. Accordingly, the proposed immunometabolic convergence framework should be considered hypothesis-generating and should not be used to guide therapeutic modification outside prospective study settings. Reverse causation cannot be excluded in observational datasets. Additionally, the absence of direct glycemic measurements in most oncologic cohorts limits the ability to infer metabolic state at the tumor level.

The clinical implications of this immunometabolic framework and the key research priorities for gynecologic oncology are summarized in Box 1, anchored in the observational and therapy-related metabolic toxicity literature[18,39–41] and intended to be implemented in context of local protocols and comorbidity burden.

These implications are pragmatic considerations and not clinical practice guidelines. Implementation should follow local oncology/endocrinology protocols and patient-level risk–benefit assessment.

BOX 1 Clinical implications and research priorities in gynecologic oncology implications for current practice.

- Structured baseline metabolic assessment (HbA1c, fasting glucose, body mass index [BMI], antidiabetic medication exposure) may be considered within multidisciplinary care models, according to local protocols and resource availability.
- Recognize increased risk of dysglycemia during systemic therapies, particularly corticosteroids and immune checkpoint inhibitors.[39–42]
- Encourage adherence to cervical cancer screening in women with diabetes.[18] Integrate survivorship care models addressing cardiovascular and metabolic health.
- Document metabolic phenotype and antidiabetic drug exposure in prospective clinical trials to enable stratified analyses of therapeutic efficacy and toxicity.

9.3 | Research priorities

- Prospective studies stratifying oncologic outcomes by metabolic phenotype.
- Evaluation of diabetes status and glycemic control as modifiers of PARP inhibitor and immunotherapy efficacy.
- Biomarker-driven trials integrating metabolic, inflammatory, and tumor genomic parameters.
- Investigation of antidiabetic agents as adjunctive therapies in selected populations.
- Incorporation of standardized metabolic phenotyping frameworks into cooperative group trials in gynecologic oncology.

The proposed immunometabolic framework may be particularly relevant in low- and middle-income settings, where the burden of type 2 diabetes is rapidly increasing alongside cervical cancer incidence. Integrating metabolic assessment into gynecologic oncology pathways may therefore represent a scalable strategy to address intersecting noncommunicable disease burdens in resource-constrained environments.

10 | CONCLUSIONS

Immunometabolic convergence provides a biologically coherent and clinically relevant framework for integrating metabolic disease assessment into gynecologic oncology care. While current evidence does not support immediate therapeutic modification solely based on metabolic status, rigorously designed prospective biomarker-driven studies with integrated metabolic phenotyping are warranted.

AUTHOR CONTRIBUTIONS

Mauricio A. Cuello: Conceptualization; methodology; literature synthesis; in silico analyses; writing—original draft; writing—review and editing. **Carolina Ibañez**: Literature synthesis; clinical interpretation; writing—review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

The datasets analyzed in this study are publicly available from the sources cited in the Supplementary Methods and analytic notes. Any additional code used to generate the in silico analyses is available from the corresponding author upon reasonable request.

ORCID

Mauricio A. Cuello https://orcid.org/0000-0003-2812-0015

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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