AI generated - may have errors

Strategic context:

Standardized Medical Name: Platinum-Resistant Ovarian Cancer (PROC) (Inclusive of epithelial ovarian, fallopian tube, and primary peritoneal cancer recurring ≤6 months after completion of platinum-based chemotherapy)

Target Patient Profile:

- **Temporality:** Prevalent disease state defined by treatment history, characterized by an incident recurrence or progression event occurring within 6 months of the last platinum-based chemotherapy administration.
- **Disease Stage/State:** Advanced or Metastatic (FIGO Stage III-IV). Patients must have confirmed platinum-resistant status and are typically heavily pre-treated, often including prior exposure to PARP inhibitors and anti-angiogenics (e.g., bevacizumab).

Strategic Rationale: Pharmaceutical Relevance (2025-2026):

Platinum-Resistant Ovarian Cancer (PROC) represents the most significant unmet medical need in advanced ovarian cancer, characterized by poor prognosis and low response rates to standard single-agent chemotherapy. The 2025-2026 timeframe is a critical inflection point for PROC, marked by pivotal Phase III readouts and regulatory decisions that are rapidly shifting the standard of care away from cytotoxic therapies toward novel modalities and biomarker-driven segmentation.

The strategic landscape is defined by the following key R&D imperatives:

1. **Introduction of Novel, Broadly Applicable Mechanisms:** The industry is successfully introducing new mechanisms that apply broadly across biomarker subgroups.

    - *Evidence (Glucocorticoid Modulation):* Corcept Therapeutics' **Relacorilant** (a selective glucocorticoid receptor antagonist), combined with nab-paclitaxel, demonstrated improved PFS and OS in the Phase 3 ROSELLA trial. An NDA has been accepted by the FDA with a PDUFA date of July 11, 2026, signaling a near-term shift in the standard of care.
    - *Evidence (Immunotherapy Breakthrough):* After years of limited success, immunotherapy is poised to enter the PROC landscape. Merck announced that the Phase 3 KEYNOTE-B96 trial (**Pembrolizumab** + chemotherapy) met its primary PFS endpoint and showed an OS improvement. Data presentation is anticipated (e.g., ESMO 2025), potentially making it the first PD-1 inhibitor approved in this setting. (Note: The challenges in this space are highlighted by the recent failure of the Phase 3 ARTISTRY-7 trial for Nemvaleukin Alfa, which did not meet OS endpoints at interim analysis).

2. **Expansion and Diversification of Antibody-Drug Conjugates (ADCs):** Following the validation of the ADC approach with mirvetuximab soravtansine (Elahere) in Folate Receptor-Alpha (FRα)-high PROC, the industry is aggressively expanding the ADC footprint to address FRα-low/negative populations and overcome resistance.

    - *Evidence (Next-Generation FRα):* Competition is intensifying with agents designed for broader FRα expression or utilizing different payloads. Eli Lilly's **LY4170156** showed activity across FRα levels at ASCO 2025 and is advancing toward Phase 3. Genmab's **Rinatabart sesutecan (Rina-S)** is proceeding with randomized Phase 3 studies following positive data at SGO 2025.
    - *Evidence (Novel Targets):* Investment in alternative targets is critical. Tubulis announced plans to present initial Phase I/IIa data for **TUB-040** (targeting NaPi2b) at ESMO 2025.

3. **Targeting Replication Stress and DNA Damage Response (DDR):** As most patients developing PROC have progressed on PARP inhibitors, overcoming this resistance by targeting alternative DDR pathways (e.g., WEE1, ATR) is a major strategic focus, particularly in molecularly defined populations.

    - *Evidence (WEE1 Inhibition):* Zentalis Pharmaceuticals is advancing **azenosertib** (a WEE1 inhibitor). The registration-intent DENALI Part 2 study in Cyclin E1+ PROC is on track to initiate in 1H 2025, with topline data anticipated by year-end 2026.

Intended Clinical Application Research Utility:

Epidemiological research on the contemporary (2025-2026) PROC population is essential to support the clinical development and commercialization of these emerging pipelines. As the landscape rapidly evolves with the introduction of ADCs, potential immunotherapies, and novel mechanisms (e.g., Relacorilant), historical benchmarks are inadequate.

The intended research utility includes characterizing real-world treatment patterns, sequencing strategies (particularly post-PARPi and post-ADC), and utilization of biomarker testing (e.g., FRα, PD-L1, emerging markers like Cyclin E1). Furthermore, characterizing clinical outcomes (rwPFS, OS) with the current standard of care, especially in high-unmet-need subgroups (e.g., FRα-low/negative), will provide critical contemporary benchmarks for comparative effectiveness research, support market access negotiations, and inform the design of subsequent pivotal trials.

Phenotype Description: Platinum-Resistant Ovarian Cancer (PROC)

1. Clinical Condition

Recommended Phenotype: Platinum-Resistant Ovarian Cancer (PROC) (Inclusive of epithelial ovarian, fallopian tube, and primary peritoneal cancer recurring ≤6 months after completion of platinum-based chemotherapy)

Common Synonyms:

- Recurrent Ovarian Cancer (ROC) with a platinum-free interval (PFI) of <6 months.
- Platinum-refractory ovarian cancer (a subset characterized by progression *during* platinum therapy; typically included within the broader PROC definition for clinical research and management purposes).

---

2. Detailed Presentation

Platinum-Resistant Ovarian Cancer (PROC) defines an advanced and aggressive disease state characterized by a lack of durable response to standard platinum-based chemotherapy. It encompasses high-grade epithelial ovarian, fallopian tube, and primary peritoneal cancers. The defining feature of PROC is temporal: disease recurrence or progression documented within six months of completing the last dose of a platinum-containing regimen (e.g., carboplatin, cisplatin).

Clinical Presentation and Assessment Patients presenting with PROC have a history of advanced or metastatic disease (typically FIGO Stage III-IV). This population is characteristically heavily pre-treated, often having undergone primary cytoreductive surgery and subsequent lines of therapy, including maintenance therapy with PARP inhibitors (e.g., olaparib, niraparib) and anti-angiogenic agents (e.g., bevacizumab).

Symptoms of recurrence are often non-specific, including abdominal bloating, pelvic pain, early satiety, or changes in bowel habits. Clinical findings may include ascites, pleural effusion, or palpable abdominal masses. Assessment requires evaluation of the patient's performance status (e.g., ECOG) and the impact of cumulative toxicities from prior therapies.

Diagnostic Criteria, Laboratory, and Imaging Findings The diagnosis of PROC requires:

1. Histopathological confirmation of epithelial ovarian, fallopian tube, or primary peritoneal cancer.
2. A documented history of treatment with a platinum-based chemotherapy regimen.
3. Evidence of recurrence or progression ≤6 months after the last platinum administration.

Recurrence is established via:

- **Imaging:** CT scans (chest, abdomen, pelvis) are the standard modality for detecting radiographic progression (new lesions or growth of existing lesions, often assessed by RECIST criteria).
- **Laboratory:** Serum Cancer Antigen 125 (CA-125) is routinely monitored; rising levels often indicate biochemical relapse.
- **Biomarker Testing:** Molecular profiling is essential for guiding therapy in the contemporary (2025-2026) landscape:
    - **Folate Receptor-Alpha (FRα):** Assessed via immunohistochemistry (IHC); expression levels (high, low, negative) are critical for Antibody-Drug Conjugate (ADC) eligibility.
    - **Emerging Biomarkers:** PD-L1 expression (relevant for immunotherapy) and markers of replication stress such as Cyclin E1 amplification (relevant for DDR-targeting agents) are increasingly critical for therapeutic segmentation.

Common Treatments and Medications Re-challenge with platinum agents is ineffective. Management focuses on extending progression-free survival and palliation.

- **Standard Cytotoxic Chemotherapy:** Management has historically relied on sequential single-agent chemotherapy (e.g., pegylated liposomal doxorubicin (PLD), topotecan, weekly paclitaxel), often combined with bevacizumab.
- **Evolving Landscape (2025-2026):** The standard of care is rapidly shifting toward novel modalities:
    - **Antibody-Drug Conjugates (ADCs):** Mirvetuximab soravtansine is utilized for FRα-high patients. The landscape is expanding with next-generation ADCs designed for broader FRα expression or novel targets (e.g., NaPi2b).
    - **Novel Broad Mechanisms:** Glucocorticoid modulation (e.g., Relacorilant) in combination with chemotherapy is an emerging standard of care.
    - **Immunotherapy:** PD-1 inhibitors (e.g., Pembrolizumab) in combination with chemotherapy are emerging as a new standard of care.
    - **DNA Damage Response (DDR) Inhibitors:** Agents targeting alternative pathways to overcome PARP resistance, such as WEE1 inhibitors (e.g., azenosertib), are utilized in molecularly defined populations (e.g., Cyclin E1+).

Prognosis and Complications PROC carries a poor prognosis and represents the most significant unmet medical need in ovarian cancer. Common complications include malignant bowel obstruction, intractable ascites, venous thromboembolism, and progressive cachexia.

---

3. Phenotype Boundaries and Granularity

This phenotype is designed to capture a specific, high-unmet-need population defined primarily by their response to prior therapy in the context of advanced disease.

General Exclusions

- Platinum-Sensitive Ovarian Cancer (recurrence >6 months after last platinum therapy).
- Non-epithelial ovarian cancers (e.g., germ cell tumors, sex cord-stromal tumors).
- Ovarian tumors of low malignant potential (borderline tumors).
- Early-stage disease (FIGO Stage I-II).

Temporal Context

- **Target State:** Prevalent disease state (advanced/metastatic cancer). The phenotype is defined by an **Incident** event of recurrence or progression that specifically occurs within the 6-month window following the completion of platinum exposure.

Clinical Granularity

- **Severity:** Required. Restricted to Advanced or Metastatic disease (FIGO Stage III-IV).
- **Acuity:** A chronic condition characterized by an acute event of progression/resistance.
- **Etiology:** Required. Must be of epithelial origin (ovarian, fallopian tube, or primary peritoneal).
- **Manifestation and History:** High granularity is essential for:
    - **Timing:** Precise documentation of the platinum-free interval (≤6 months).
    - **Prior Treatment History:** Documentation of prior exposure and sequencing of key drug classes (PARP inhibitors, anti-angiogenics, and increasingly, prior ADCs).
    - **Biomarker Status:** Ability to stratify by FRα expression level is essential. Granularity regarding PD-L1 and Cyclin E1 is highly desired due to emerging therapeutic segmentation.

Population Context

- Adult patients with a confirmed history of the included cancer types and prior platinum chemotherapy.

---

4. Intended Clinical Application Research Utility

The strategic focus for this phenotype is to support the clinical development and commercialization of emerging therapeutic pipelines during the critical 2025-2026 timeframe. This period marks an inflection point in PROC management, characterized by the introduction of

novel, broadly applicable mechanisms (e.g., Relacorilant, Pembrolizumab), diversified ADCs (addressing FRα-low/negative populations), and novel DDR targets (e.g., WEE1 inhibitors). Due to this rapid evolution away from cytotoxic therapies, historical outcome benchmarks are obsolete.

The intended research utility is to generate contemporary (2025-2026) real-world evidence to:

1. **Establish Contemporary Clinical Benchmarks:** Characterize real-world progression-free survival (rwPFS) and overall survival (OS) with the current standard of care. This data is critical for comparative effectiveness research, supporting market access negotiations, and informing the design of pivotal trials, especially in high-unmet-need subgroups (e.g., FRα-low/negative).
2. **Characterize Treatment Patterns and Sequencing:** Describe real-world utilization and sequencing strategies, particularly in the post-PARP inhibitor and emerging post-ADC settings.
3. **Assess Biomarker Utilization:** Evaluate the uptake and impact of testing for FRα, PD-L1, and emerging markers like Cyclin E1 on treatment decisions.

Clinical Description: Advanced/Metastatic Ovarian Cancer (Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer)

Synonyms: Advanced EOC (Epithelial Ovarian Cancer), Metastatic Ovarian Cancer, Stage III Ovarian Cancer, Stage IV Ovarian Cancer, Advanced Fallopian Tube Cancer, Advanced Primary Peritoneal Cancer.

1. Clinical Case Definition

This phenotype defines advanced or metastatic malignant neoplasms arising from the epithelial cells of the ovary, the fallopian tube, or the peritoneum. Due to their shared embryologic origin (Müllerian epithelium), similar histological features (most commonly high-grade serous carcinoma), and overlapping clinical management, these three malignancies are clinically grouped and treated as a single entity.

The phenotype specifically targets advanced disease, corresponding to Stage III or Stage IV according to the International Federation of Gynecology and Obstetrics (FIGO) staging system.

- **Stage III** is characterized by tumor involvement of one or both ovaries/fallopian tubes, or primary peritoneal cancer, with confirmed cytological or histological spread to the peritoneum outside the pelvis (e.g., omental caking, peritoneal implants) and/or metastasis to the retroperitoneal lymph nodes.
- **Stage IV** is characterized by distant metastasis beyond the peritoneal cavity (e.g., liver parenchyma, lungs, pleural effusion with positive cytology, extra-abdominal lymph nodes).

Diagnosis requires definitive histologic confirmation from tissue biopsy (e.g., surgical specimen, core biopsy) or cytological analysis of malignant cells (e.g., from ascites). Radiographic imaging (CT/MRI) is essential for staging, and elevated serum tumor markers (e.g., CA-125) are characteristic and supportive.

2. Phenotype Scope & Granularity

- **Temporal Context:** Prevalent disease state. Intended to identify patients with an existing diagnosis of advanced or metastatic disease, regardless of treatment status (e.g., newly diagnosed, recurrent, or actively treated).
- **Severity:** Advanced (Stage III) or Metastatic (Stage IV) only. This scope is not inclusive of localized or early-stage (Stage I-II) disease.
- **Acuity / Chronicity:** Chronic condition.

- **Etiology:** Primary malignant neoplasm of epithelial origin (ovary, fallopian tube, or peritoneum). Includes both sporadic cases and those associated with hereditary syndromes (e.g., BRCA1/2 mutations).
- **Population Context:** Primarily the adult population.

3. Related Conditions & Scope Boundaries

This phenotype is defined by specific primary site, histology, and stage. The following conditions and contexts are clinically related but are not within the scope of this phenotype:

- **Treatment Response Status (Platinum Sensitivity/Resistance):** This phenotype defines the anatomical and histological presence of advanced cancer. The classification of the disease as "Platinum-Sensitive" or "Platinum-Resistant" describes the tumor's response relative to prior chemotherapy exposure and requires specific temporal logic (e.g., time from last platinum dose to recurrence). These are separate clinical constructs and are explicitly not defined within this core clinical description.
- **Early-Stage Ovarian Cancer (FIGO Stage I-II):** Disease confined to the ovaries or pelvis is not within the scope of this advanced phenotype.
- **Non-Epithelial Ovarian Cancers:** Cancers with different histologies (e.g., Germ cell tumors, Sex cord-stromal tumors) have distinct biology and treatment paradigms and are not within the scope of this epithelial-focused phenotype.
- **Ovarian Tumors of Low Malignant Potential (Borderline Tumors):** These tumors are distinct from invasive epithelial cancer and are not within scope.
- **Secondary Metastases to the Ovary:** Cancers metastasizing *to* the ovary from other primary sites (e.g., colorectal cancer, gastric cancer [Krukenberg tumor], breast cancer) are not within the scope of this primary ovarian/fallopian/peritoneal phenotype.

4. Key Complications & Common Comorbidities

The following are common complications associated with advanced and metastatic ovarian cancer, but they are distinct from the definition of the core malignancy:

- Malignant Ascites
- Bowel Obstruction (Malignant)
- Malignant Pleural Effusion
- Venous Thromboembolism (VTE)
- Cachexia and Malnutrition
- Hydronephrosis (due to pelvic mass effect)

5. Intended Data Sources

This clinical description is intended for building concept sets against real-world administrative claims, electronic health record (EHR) databases, and patient registries. The target data should

be standardized to the OMOP Common Data Model. Examples of licensable data sources where this concept set would be applied include:

- **Optum®** (Clinformatics® Data Mart, SES, Pan-Therapeutic)
- **Merative™** (MarketScan® Commercial Claims and Encounters)
- **Veradigm** (Health Verity, Practice Fusion EHR)
- **IQVIA** (AmbEMR, PharMetrics Plus)
- **HealthVerity**