

Evidence-Based PICO Mapping for EU Joint Clinical Assessment (JCA) Using a Real-Time AI-assisted Living Systematic Literature Review (REAL-SLR): A Metastatic Breast Cancer Case Study

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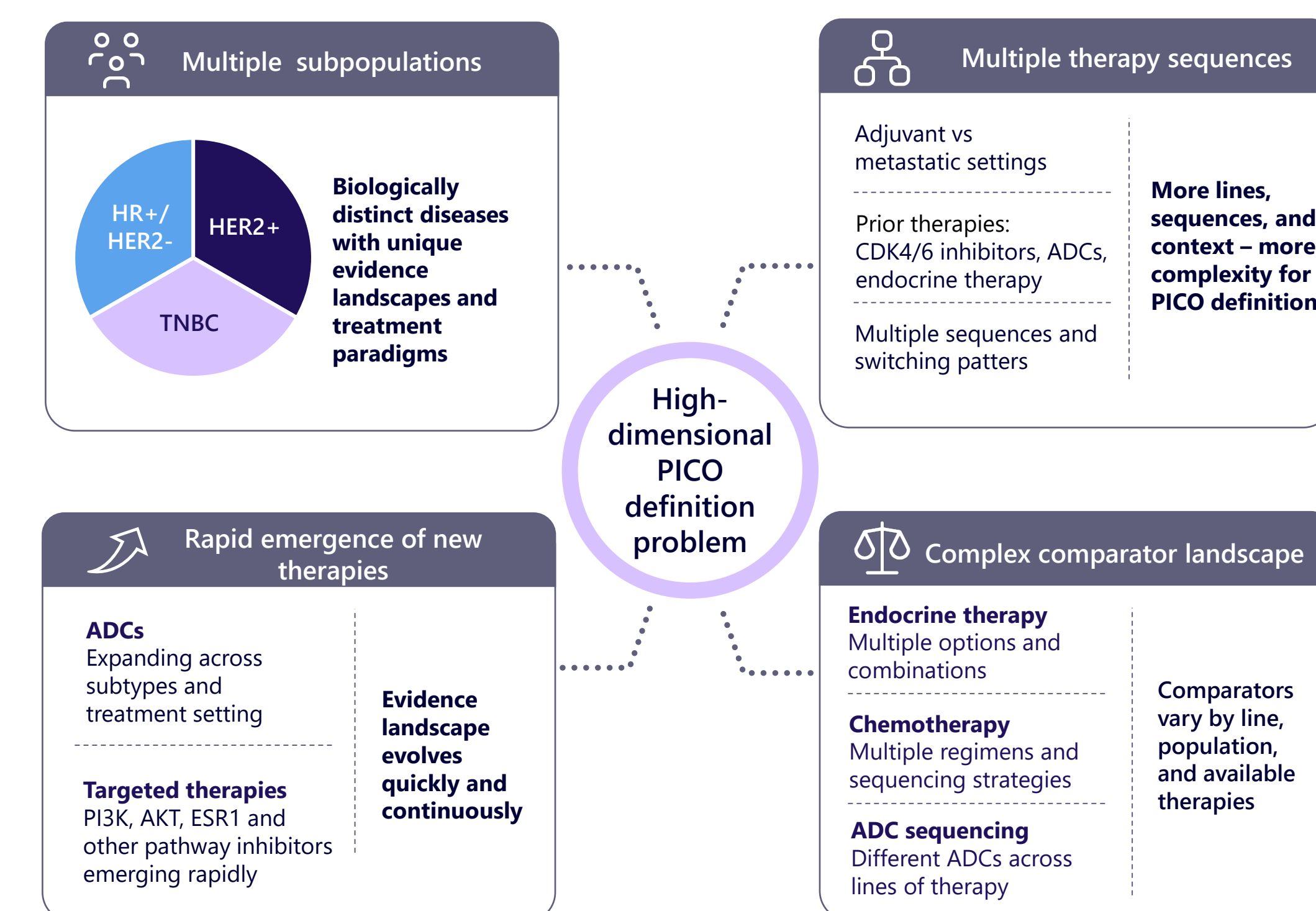
OBJECTIVES

→ To utilize a Real-Time AI-assisted Living SLR (REAL-SLR) approach for evidence-based JCA PICO mapping in HR+/HER2-mBC

BACKGROUND

- The EU Joint Clinical Assessment (JCA) requires early, transparent, and evidence-based definition of Population-Intervention-Comparator-Outcome (PICO) frameworks.
- In hormone receptor-positive, HER2-negative (HR+/HER2-) metastatic breast cancer (mBC), rapid therapeutic innovation following progression on CDK4/6 inhibitors, expanding treatment classes, and increasing reliance on subgroup analyses challenge traditional static systematic literature reviews (SLRs) for JCA planning (Figure 1)

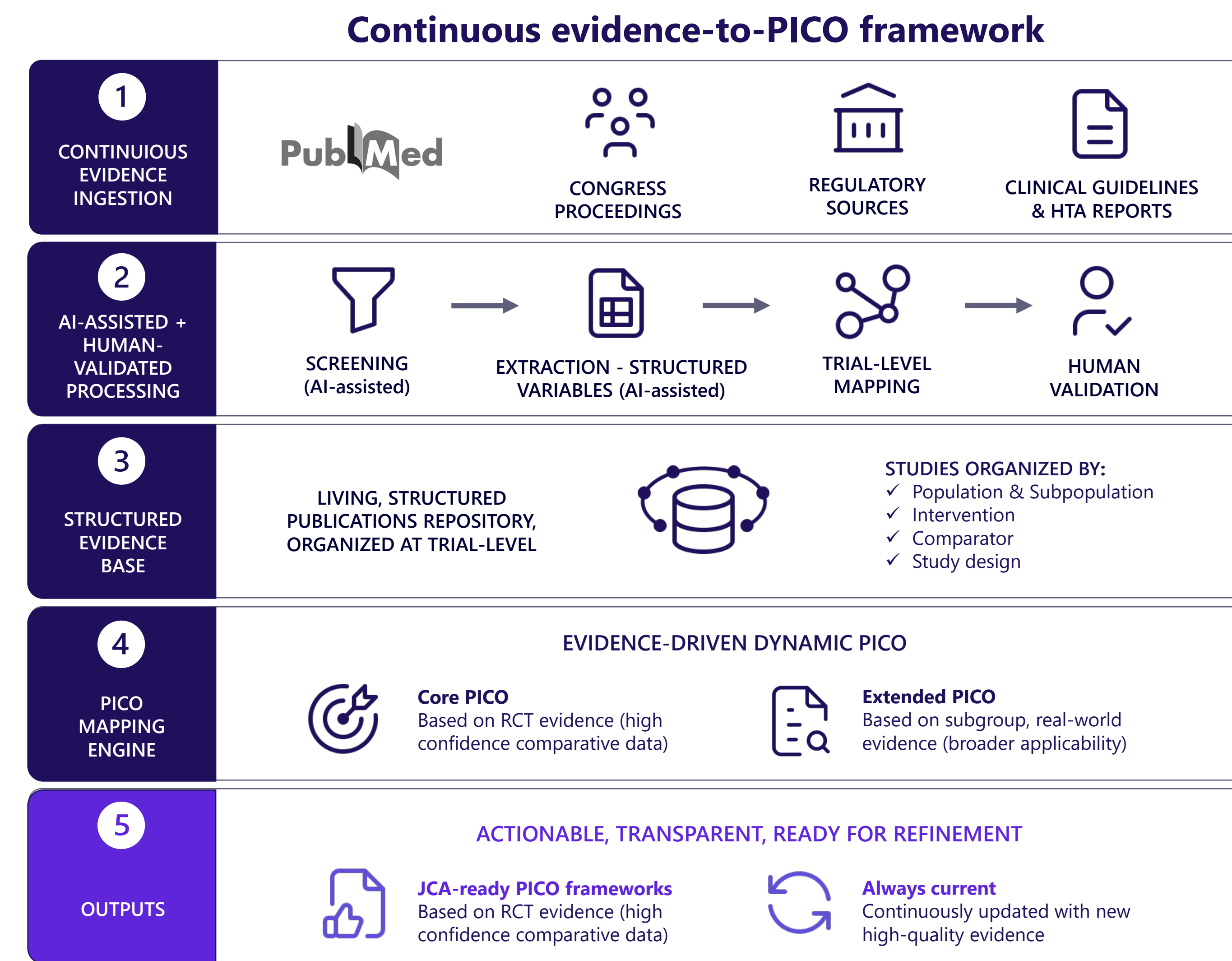
Figure 1. Why breast cancer is a challenge for JCA



METHODS

- A PRISMA-compliant REAL-SLR was conducted using protocol-driven searches updated daily for metastatic breast cancer
- Evidence from interventional clinical trials, regulatory sources, clinical guidelines, selected high-quality real-world evidence, and technology assessments was continuously identified, screened, and structured
- For each eligible study, data were extracted on study design, population, intervention, comparator, endpoints, and reported subgroup analyses
- Real-Time AI-assisted Living SLR (REAL-SLR) (Figure 2) is a continuously maintained evidence system that:
 - Updates evidence through protocol-driven, ongoing searches
 - Structures studies at trial-level (not publication-level)
 - Enables instant re-querying of evidence without re-running the SLR
 - Preserves PRISMA traceability, auditability, and methodological consistency
- This continuously updated evidence-base REAL-SLR was used to define both core and extended JCA PICO frameworks without re-running searches, enabling dynamic refinement while preserving auditability and methodological consistency

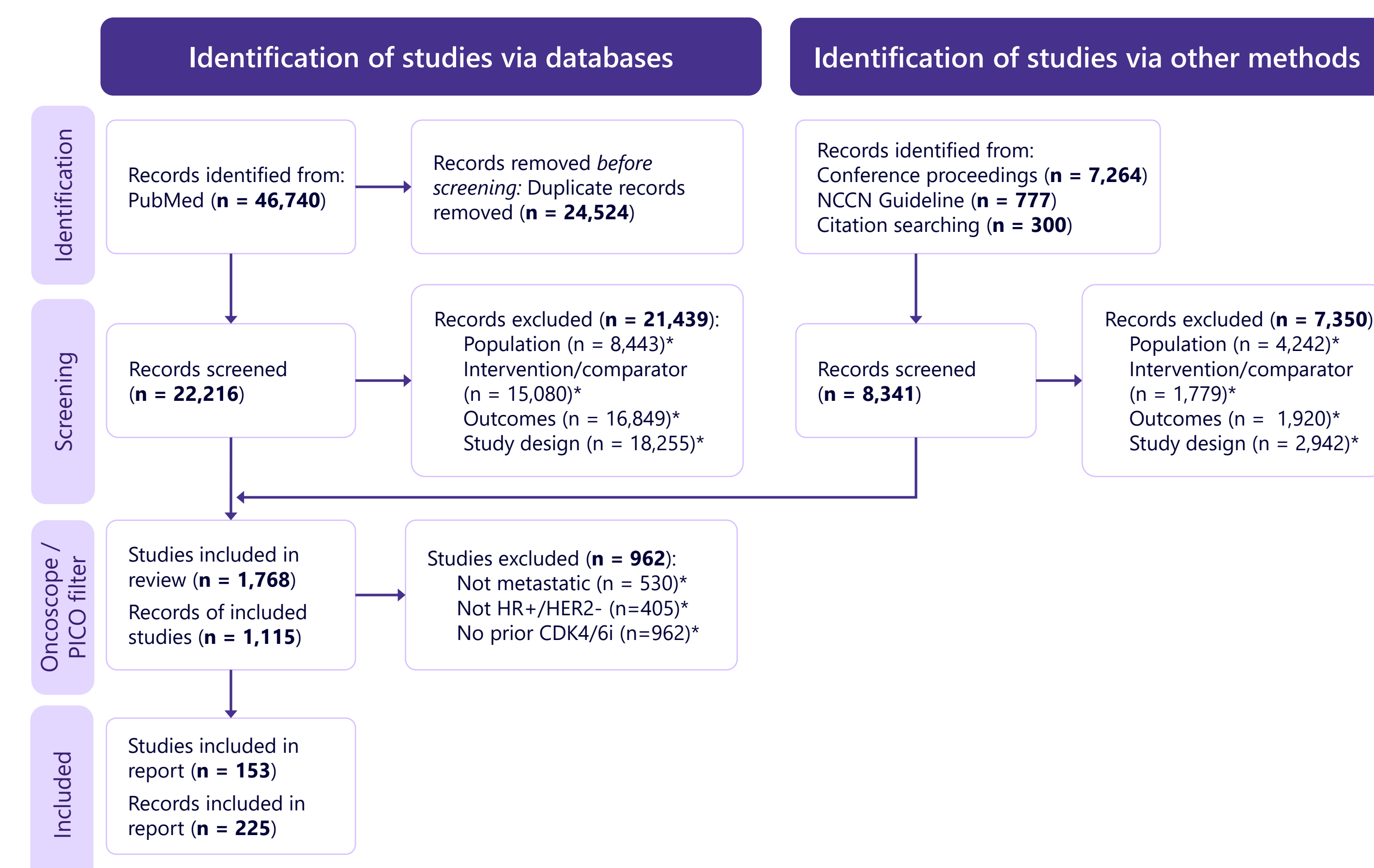
Figure 2. REAL-SLR for JCA PICO mapping



RESULTS

- As of April 16, 2026, the REAL-SLR identified 153 published studies in HR+/HER2- mBC following progression on CDK4/6 inhibitor therapy (Figure 3)
- Thirty-seven Phase 2 or Phase 3 randomized controlled trials defined the evidence-anchored core PICO (Table 1)
- Interventions/comparators across these studies included endocrine therapy (ET), targeted therapy with/without ET, chemotherapy, and antibody-drug conjugates.
- Extended PICO frameworks were mapped using (Table 2, Figure 4):
 - biomarker-defined subpopulations (PIK3CA/AKT1/PTEN alterations, HER2-low/ultra-low disease)
 - subgroup evidence, including:
 - brain/bone/liver metastases,
 - prior CDK4/6-inhibitor use (adjuvant vs metastatic), and
 - prior treatment exposure patterns including concurrent vs sequential ET/CDK4/6-inhibitor therapy

Figure 3. Continuously updated PRISMA (REAL-SLR framework) in Breast Cancer (updated Apr 16, 2026)



*Reasons for exclusion were not mutually exclusive.

Table 1.

Evidence-anchored core PICO (derived from REAL-SLR)

PICO element	Core definition	Evidence anchor from REAL-SLR
Population	<ul style="list-style-type: none"> Adults with metastatic Breast Cancer HR+ / HER2-negative Biomarker – any Line of therapy – progressed on CDK4/6 inhibitor therapy 	<ul style="list-style-type: none"> Derived from RCTs identified from REAL-SLR in metastatic HR+/HER2-negative Breast Cancer in post CDK4/6 setting
Interventions / Comparator	<ul style="list-style-type: none"> Treatment strategies evaluated in RCTs: <ul style="list-style-type: none"> ADCs endocrine therapy (ET) targeted therapy +/- ET Chemotherapy 	<ul style="list-style-type: none"> ADCs (Datopotamab deruxtecan, Sacituzumab govitecan, Sacituzumab tirumotecan, Trastuzumab deruxtecan) ET (Capivasertib+fulvestrant, Ipatasertib+fulvestrant, Camizestrant, Elacestrant, Giredestrant) Targeted (AKT-Targeted, HER2-Targeted, PI3K-Targeted, PARPi) Chemo (Paclitaxel, Vinorelbine, Eribulin, Physician's choice)
Outcomes	OS, PFS, ORR, Grade 3/4 AEs, Treatment discontinuation, QOL	OS, PFS, DOR, ORR, EORTC-QLQ-C30; EORTC QLQ-BR45; EORTC QLQ-BR23, PRO-CTCAE; PGI-TT; EQ-5D-5L
Study design	RCTs	37 Phase 2 / Phase 3 RCTs (14 Phase 2 RCTs, and 23 Phase 3 RCTs)

Table 2. Extended PICO mapping for JCA (evidence-based stratification)

Extended PICO frameworks reflect biomarker-defined populations, HER2 expression subgroups, sites of metastases, and prior treatment patterns

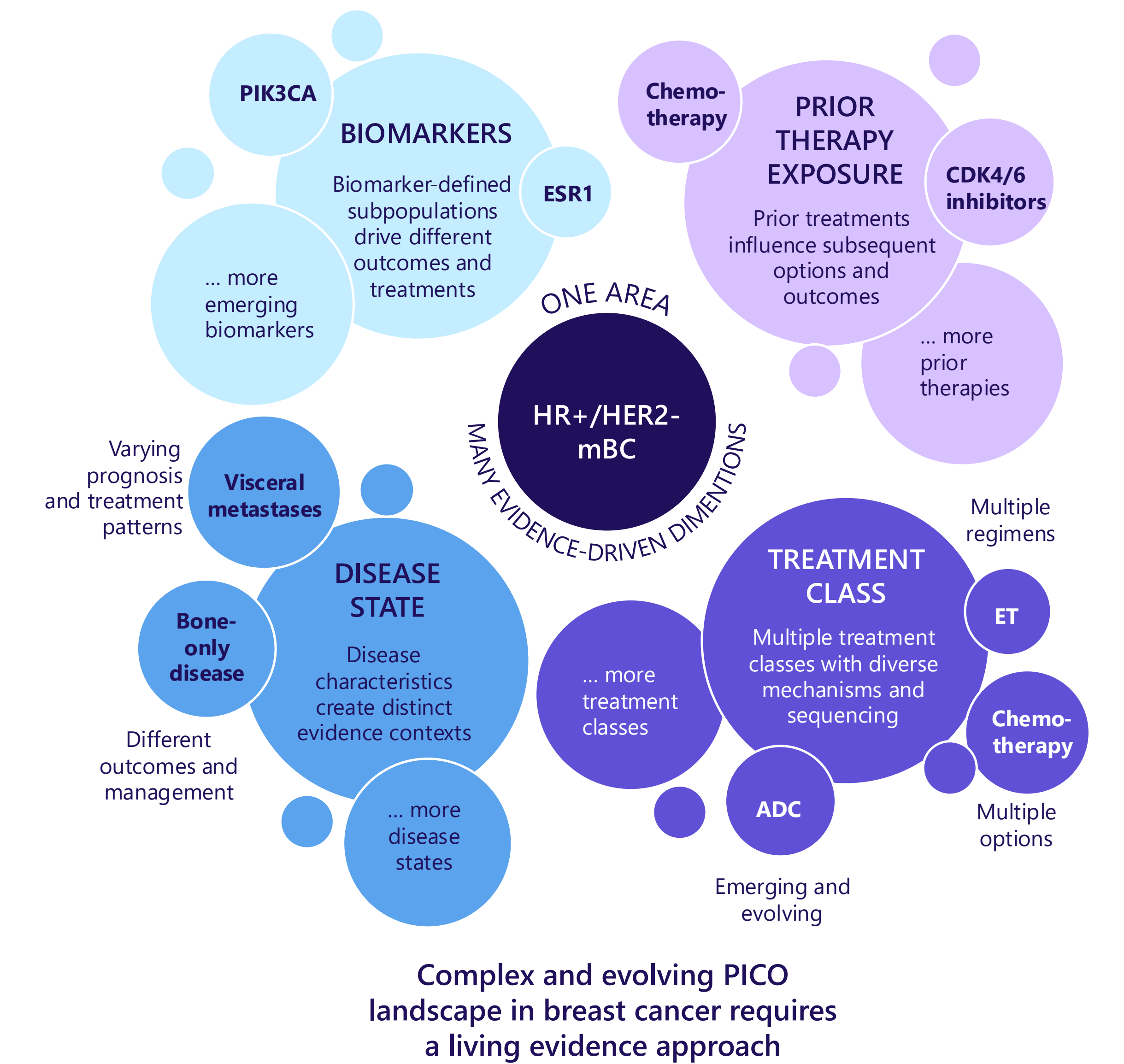
- Multidimensional PICO expansion required for JCA in breast cancer to ensure JCA-relevant subgroup analyses and evidence interpretation across member states

Dimension	Stratification approach	Evidence basis
Biomarker-defined populations	Patients with actionable mutations	<ul style="list-style-type: none"> AKT1 activating mutation (2 studies) DDR/HRD mutations (1 studies) ESR1 mutation (7 studies) gBRCA1/2 mutation (3 studies) PIK3CA activating mutation (6 studies) PTEN alteration (2 studies)
HER2 expression subgroups	HER2-low and HER2-ultralow disease	<ul style="list-style-type: none"> HER2-low/HER2-ultra low (3 studies)
Metastatic site / disease burden	Presence of brain or bone metastases	<ul style="list-style-type: none"> Bone metastases (1 study) Brain metastases (1 study) Liver metastases (2 studies) ctDNA dynamics (3 studies)
Prior treatment exposure patterns	Prior CDK4/6i exposure patterns, Prior other therapies	<ul style="list-style-type: none"> Duration of prior CDK4/6i therapy (2 studies) Prior CDK4/6i use in adjuvant vs. metastatic setting (1 study) Concurrent vs. sequential use of CDK4/6i and ET (2 studies) Prior ADC (1 study)

ABBREVIATIONS

ADC, antibody-drug conjugate; AEs, adverse events; AKT, protein kinase B; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ctDNA, circulating tumor DNA; DDR, DNA damage repair; DOR, duration of response; EQ-5D-5L, EuroQol 5-Level questionnaire; ESR1, estrogen receptor 1; ET, endocrine therapy; EORTC, European Organization for Research and Treatment of Cancer; QLQ-BR23, Quality of Life Questionnaire Breast Cancer 23; QLQ-BR45, Quality of Life Questionnaire Breast Cancer 45; QLQ-C30, Quality of Life Questionnaire Core 30; gBRCA1/2, germline breast cancer gene 1/2; HER2, human epidermal growth factor receptor 2; HR+, hormone receptor-positive; HRD, homologous recombination deficiency; NSCLC, non-small cell lung cancer; ORR, overall response rate; OS, overall survival; PARPi, poly(ADP-ribose) polymerase inhibitor; PFS, progression-free survival; PGI-TT, Patient Global Impression of Treatment Tolerability; PI3K, phosphoinositide 3-kinase; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PRO-CTCAE, Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events; QOL, quality of life; RCTs, randomized controlled trials

Figure 4. PICO explosion in Breast Cancer



CONCLUSIONS

- REAL-SLR-enabled PICO mapping anchors JCA scoping in the evolving metastatic breast cancer evidence landscape rather than a static SLR
- Evidence-driven PICO definition increases transparency, allows flexibility, reduces rework and overall enhances preparedness for JCA in complex and rapidly evolving indications, compared to traditional reiterative approach (Figure 5)

Figure 5. Defining PICO: What changes with REAL-SLR

