

# 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

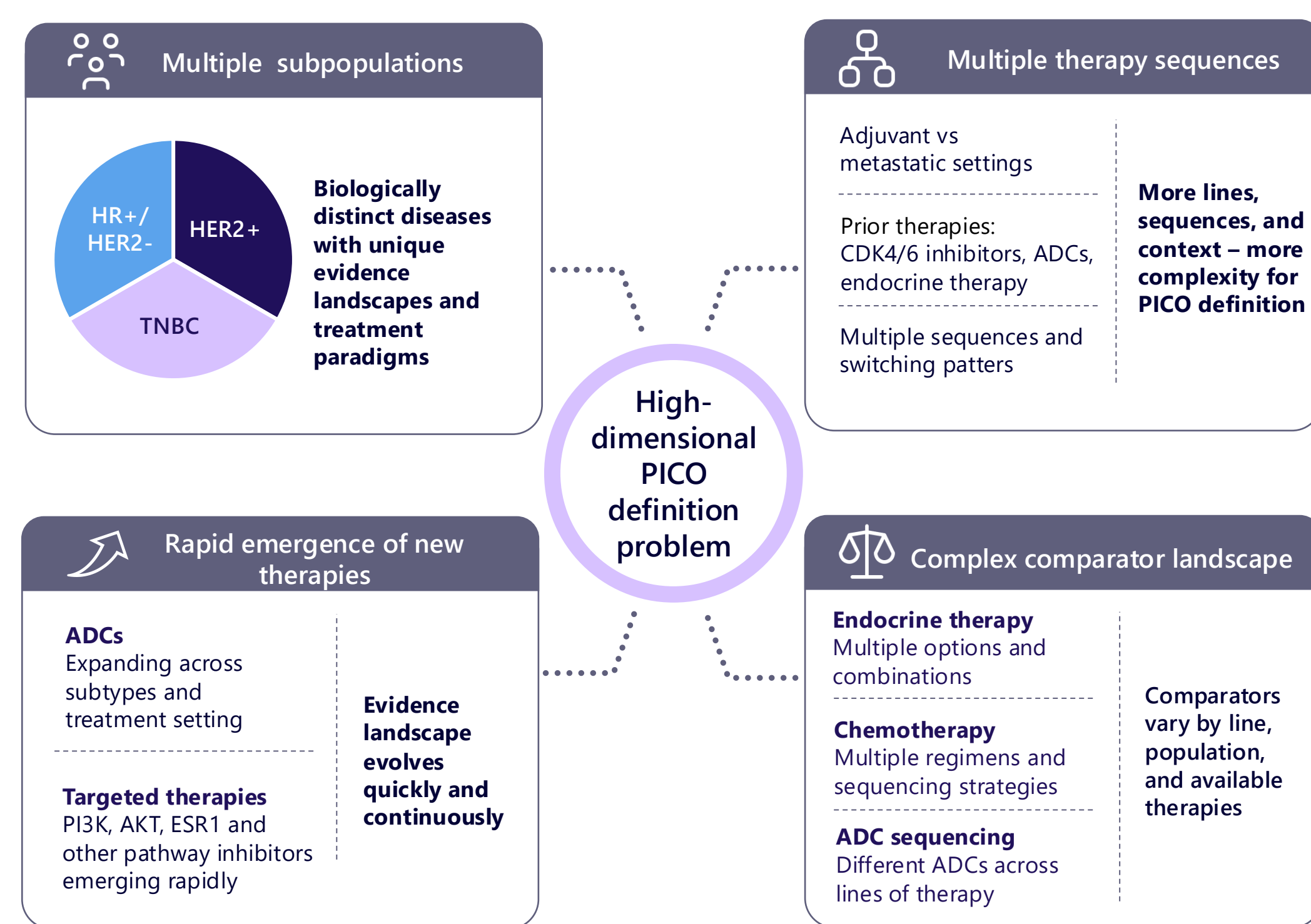
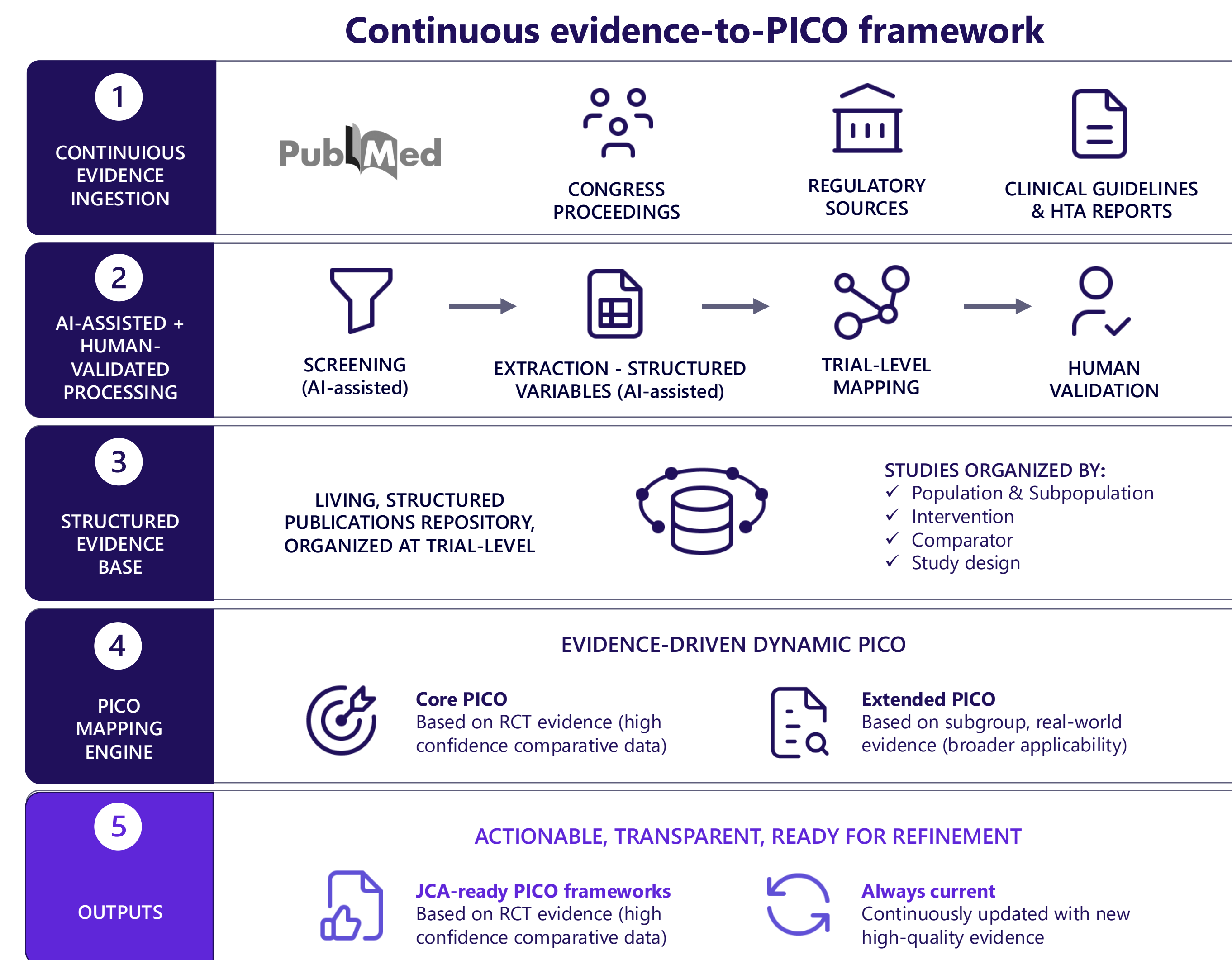


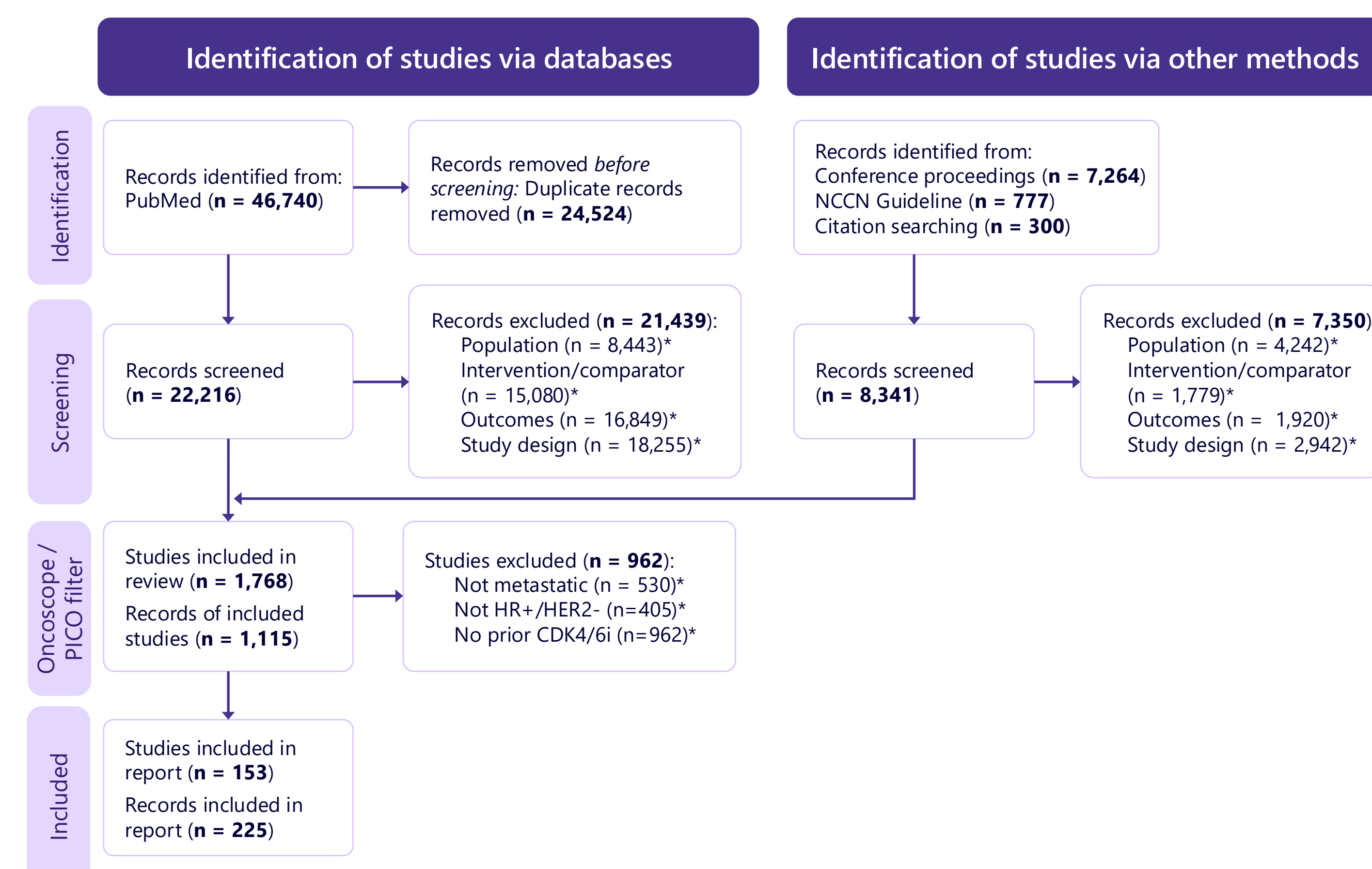
Figure 2. REAL-SLR for JCA PICO mapping



## 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 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"> <li>Adults with metastatic Breast Cancer</li> <li>HR+ / HER2-negative</li> <li>Biomarker – any</li> <li>Line of therapy – progressed on CDK4/6 inhibitor therapy</li> </ul> | <ul style="list-style-type: none"> <li>Derived from RCTs identified from REAL-SLR in metastatic HR+/HER2-negative Breast Cancer in post CDK4/6 setting</li> </ul>   |
| Interventions / Comparator | <ul style="list-style-type: none"> <li>Treatment strategies evaluated in RCTs:</li> <li>ADCs</li> <li>endocrine therapy (ET)</li> <li>targeted therapy +/- ET</li> <li>Chemotherapy</li> </ul>                 | <ul style="list-style-type: none"> <li>ADCs (Datopotamab deruxtecan, Sacituzumab govitecan, Sacituzumab tirumotecan, Trastuzumab deruxtecan)</li> <li>ET (Capivasertib+fulvestrant, Ipatasertib+fulvestrant, Camizestrant, Elacestrant, Giredestrant)</li> <li>Targeted (AKT-Targeted, HER2-Targeted, PI3K-Targeted, PARPi)</li> <li>Chemo (Paclitaxel, Vinorelbine, Eribulin, Physician's choice)</li> </ul> |
| Outcomes                   | OS, PFS, ORR, Grade 3/4 AEs, Treatment discontinuation, QOL  | <ul style="list-style-type: none"> <li>OS, PFS, DOR, ORR</li> <li>EORTC-QLQ-C30; EORTC QLQ-BR45; EORTC QLQ-BR23, PRO-CTCAE; PGI-TT; EQ-5D-5L</li> <li>Grade 3/4 AEs, Treatment discontinuation; Neutropenia</li> </ul>  |
| 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 reflects biomarker-defined populations, HER2 expression subgroups, sites of metastases, and prior treatment patterns

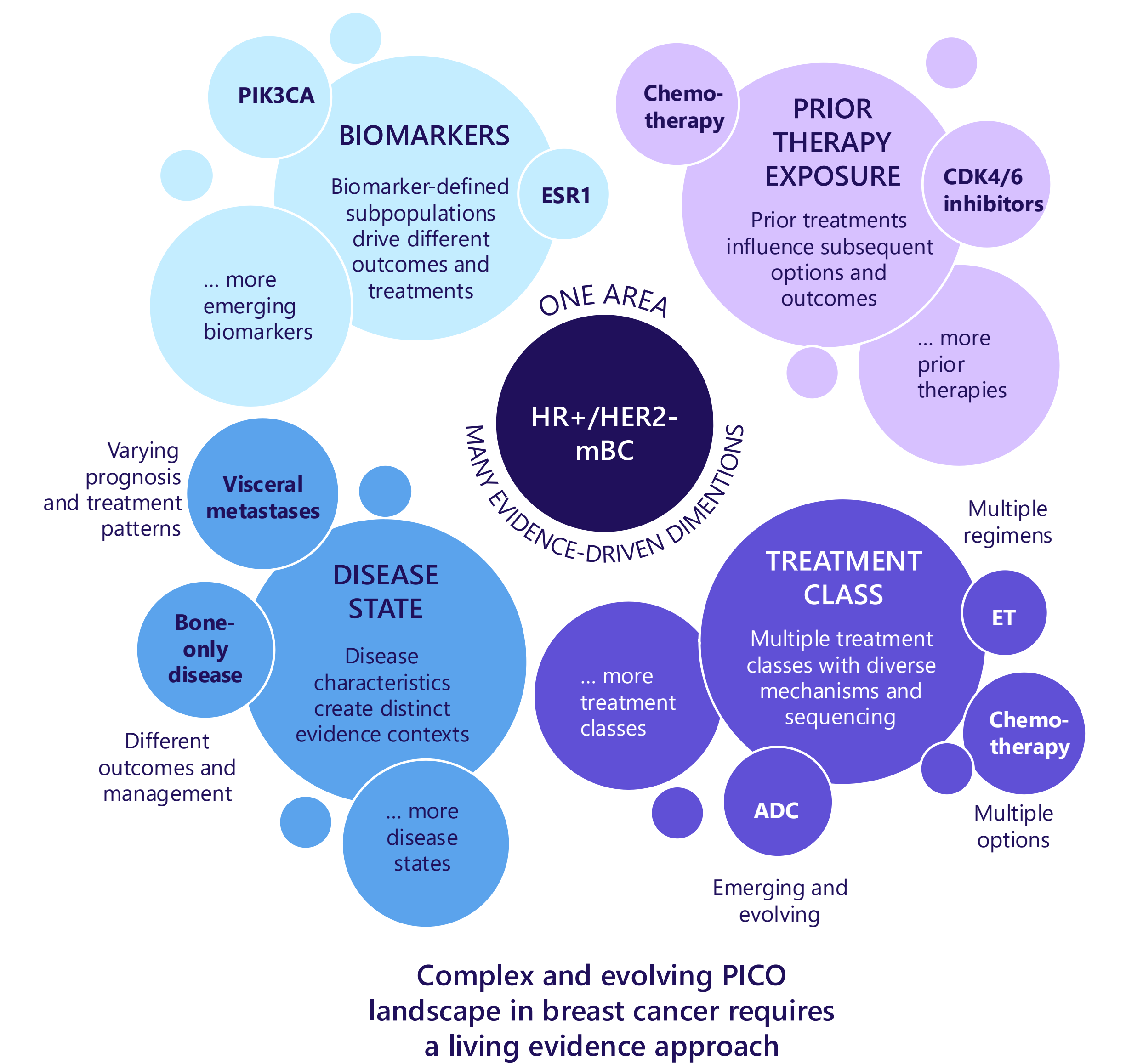
→ Multidimensional PICO expansion required for JCA in breast cancer to ensure JCA-relevant subgroup analyses and evidence interpretation across member states

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

## 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-Dimension 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

