Cancer Treatment Guidelines Need a Reality Check — RWE Can Help

Asieh Golozar[1, 2], Patrick Alba[3], Henry Morgan Stewart[1], Dan Smith[4], Salma Rachidi[5], Eric Fey[5], Valtteri Nieminen[5], Alexey Ryzhenkov[5], Tommi Kauko[6], Pia Tajanen-Doumbouya[6], Mikael Högerman[6], Sampo Kukkurainen[7], Harri Rantala[7], Åslaug Helland[8], Åsa Ôjlert[8], Wei Hai Deng[8], Zarah Van Schoor[9], Jonas Minne[10], Stelios Theophanous[11], Geoff Hall[11], John Methot[12], Thejas Bharadwaj[12], Roshanthi Weerasinghe[13], Andrew Nute[13], Martin Koch[14], Ines Reinecke[14], Katja Hoffmann[14], Jasmin Carus[15], Stefan Bartels[15], Michael Franz[16], Fabian Prasser[16], Jonathan Jeutner[16], Álvaro MartÌnez Pèrez[17], Carlos López Gómez[17], Ben Gerber[18], Jung Ae Lee[18], Thamir Alshammari[19], Jared Houghtaling[20], Paul Nagy[21], Ben Martin[21], Raivo Kolde[22], Marek Oja[22], Sirli Tamm[22], Miguel-Angel Mayer[23], Juan Manuel Ramirez-Anguita[23], Angela Leis[23], Sam T Patnoe[24], Deran A Mckeen[24], Patricia L Mabry[24], Seng Chan You[25], Subin Kim[25], Chang Jun Koc[25], Jason C. Hsu[26], Phung Anh Nguyen[26], Nguyen Thi Kim Hien[26], Phan Thanh Phuc[26], Qi Yang[27], Kees Ebben[28], Maaike van Swieten[28], Jelle Evers[28], Agnes Moesgåard Eschen[29], Andreas Bjerrum[29], Irina Veytsman[30], Dalia Mobarek[30], Espen Enerly[31], Joelle Thonnard[32], Emmanuel Seront[32], Cedric van Marcke[32], Dries Hens[33], Clara L. Oeste[33], Mikaela Bruhammar[33], Loretta Zsuzsa Kiss[34], Mészáros Ágota[34], Zsolt István Bagyura[34], Ruochong Fan[35], Linying Zhang [35], Alberto Moreno Conde[36], Jesus Moreno Conde[36], Tomoni Kimura[37], Justin Matthew Petucci[38], Matteo Pontuni[39], Pantelis Natsiavas[40], Chytas Achilleas[40], Rekkas Alexandros[40], Farmaki Anastasia[40], Elad Sharon[12], Kimmo Porkka[5], Annelies Verbiest[9], Otto Ettala[6], Christian Reich[1,2]

[1]Nemesis Health, [2]OHDSI Oncology WG, [3]VINCI, Veteran Affairs, USA, [4]Emory University Hospital, Atlanta, USA, [5]Helsinki University Hospital Comprehensive Cancer Center, Finland, [6]The wellbeing services county of Southwest Finland, Auria Clinical Informatics (VARHA), [7]Tampere University Hospital, Finland (PIRHA), [8]Oslo University Hospital Comprehensive Cancer Centre, Norway, [9]Antwerp University Hospital, University of Antwerp, Belgium, [10]Institute of Analytics for Health (INAH), Brussels, Belgium,[11] Leeds Teaching Hospitals NHS Trust, UK, [12]Dana Farber Cancer Institute, USA, [13]Providence St. Joseph Health, USA, [14]University Hospital Dresden, National Cancer Center, Germany, [15]University Medical Center Hamburg-Eppendorf (UKE), Germany, [16]Germany, Charité Universitätsmedizin, Germany, [17]Health Research Institute Hospital La Fe, Valencia, Spain, [18]University of Massachusetts Chan Medical School, USA, [19] College of Pharmacy, Jazan University, Saudi Arabia, [20]Tufts University School of Medicine, Tufts Medical Center, Boston MA, [21]School of Medicine, Johns Hopkins University, [22]University of Tartu, Estonia, [23]Hospital del Mar, Barcelona, Spain, Hospital del Mar Research Institute, Barcelona, Spain, [24]HealthPartners Institute, USA, [25]Yonsei University Hospital, South Korea, [26]Taipei Medical University, Taiwan, [27]IQVIA, USA, [28]Netherlands Comprehensive Cancer Organization, Utrecht, The Netherlands, [29]Copenhagen University Hospital – Rigshospitalet, Copenhagen, Denmark, [30]Veterans Affairs, [31]Cancer Registry Norway, [32]UC Louvain, Belgium, [33]LynxCare, Belgium, [34]Semmelweis University, [35]Washington University in St. Louis, USA, [36]Virgen Macarena University Hospital, Spain, [37]Astellas, Japan, [38]Penn State Health, USA, [39]Azienda Ospedaliero-Universitaria di Parma, Italy, [40]Institute of Applied Biosciences, Centre for Research & Technology Hellas (INAB|CERTH)

Background:
Clinical guidelines form the foundation of evidence-based medicine and are typically based on outcomes from randomized controlled trials (RCTs). These trials deliver the highest level of evidence by evaluating the efficacy and safety of treatments within a carefully selected trial population. However, RCTs often fail to address matters concerning generalizability, adherence, or applicability to real-world clinical practice. As a result, without any feedback mechanism, recommendations based on these trials may not be ideal for treating patients in standard clinical settings.

Real-world evidence (RWE) offers a significant opportunity to address this gap, as it uses data derived from real-world environments. However, to possess clinical relevance and effectively inform guidelines,

RWE must meticulously replicate recommended treatments and patient populations while adhering to the highest standards of methodological rigor.

This study seeks to develop a scalable, systematic method for incorporating real-world evidence into clinical guideline development, demonstrated using the 2024 European Association of Urology (EAU) guideline on metastatic bladder cancer (mBC). The primary aims are to assess the relevance, adherence and generalizability of guideline-defined treatment pathways in real-world settings, and to identify areas where further research is necessary. Specific research questions include evaluating the congruence between patient populations and trial-based eligibility criteria, determining the degree to which recommended treatments are implemented in practice, and examining whether clinical outcomes correspond with those reported in trials.

Methods:
This initiative provides a structured framework for incorporating real-world evidence (RWE) into guideline development. The methodology is based on three key components: (1) breaking down guideline recommendations into structured decision nodes with clearly defined populations, criteria, outcomes, and recommended treatments; (2) assessing the feasibility and validity of addressing these questions using observational data available in standardized networks; and (3) conducting targeted studies to inform only those recommendations where high-quality RWE can fill significant evidence gaps or identify inconsistencies between guidelines and practice.

To achieve this, the initiative utilizes a network of federated observational healthcare data, standardized to the OMOP Common Data Model (CDM). Guideline recommendations are broken down into structured decision nodes to define multiple patient cohorts, including those eligible for treatment, those treated as recommended, and those receiving alternative regimens. Outcomes include time to treatment discontinuation, time to next treatment, and overall survival, with additional analyses on treatment patterns, adherence, and demographic comparability. All analytics are executed locally by data partners to ensure patient privacy, and results are aggregated for cross-database analysis. Detailed methodology is available here: GDE_Bladder Cancer Protocol FINAL_25JUN2025.docx.

Results:
Guideline decision nodes have been successfully extracted and structured, resulting in the following decision tree (link: node criteria extraction-EAU mBC.xlsx):

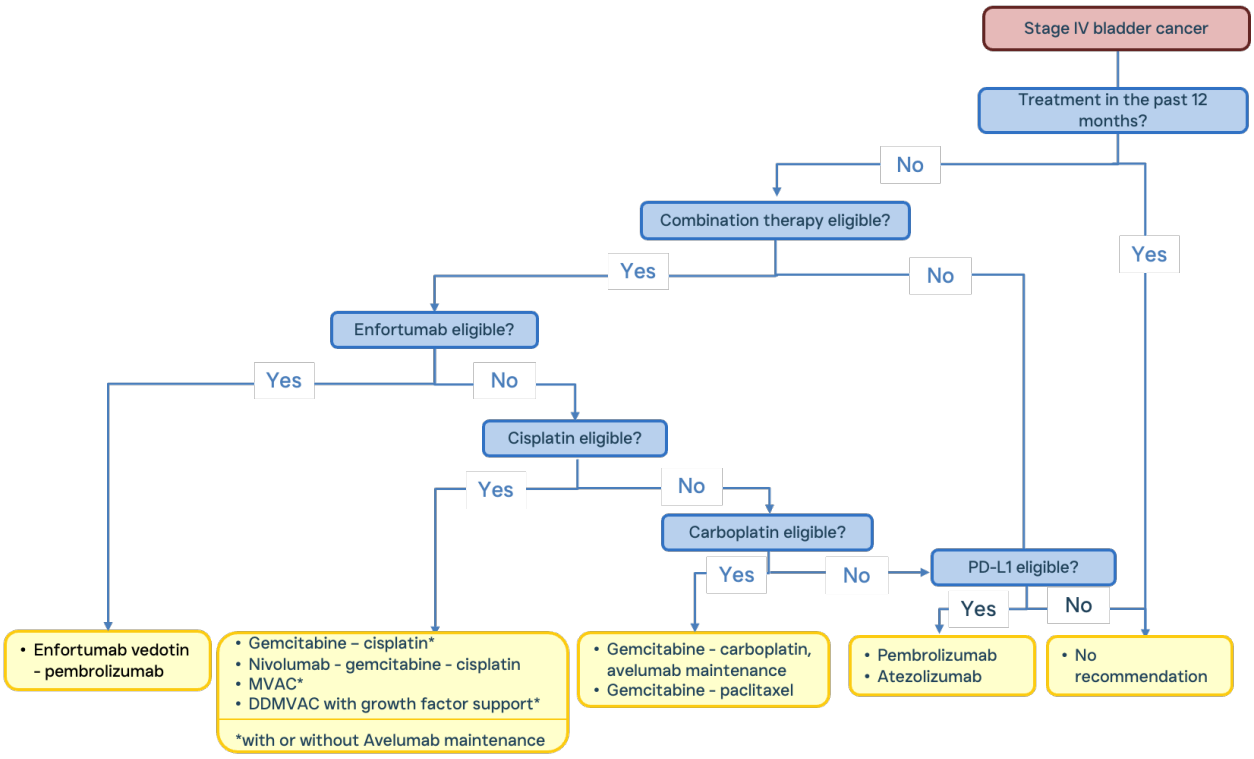

Figure. Schematic representation of the Guideline decision tree. This tree starts with the overall mBC cohort (red) and, after evaluating all eligibility nodes (blue), results in subpopulations with specific treatment recommendations (yellow).

These have been translated into 26 cohorts. As of now, 31 data partners from 12 countries have enrolled in the study. All sites are currently undergoing a data readiness assessment (link) to evaluate the completeness and conformance of oncology-specific mappings. Any identified issues are being addressed through targeted vocabulary updates or local ETL patches. Data partners who pass the assessment will proceed to execute the standardized analytics package. The study protocol has been submitted for IRB review and approval. A detailed overview of project milestones and timelines is available here: GDEG mBC milestones and timelines_May 23.xlsx. Final study results will be presented at the upcoming OHDSI symposium.