Annals of Research in Oncology
Vol. 5(1), 7-17, 2025

PERSPECTIVE

REAL WORLD EVIDENCE IN ONCOLOGY: AN ITALIAN EXAMPLE-BASED EXPERTS OPINION ON ADVANCING CLINICAL AND REGULATORY DECISION-MAKING

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ABSTRACT: Real World Evidence (RWE) is transforming oncology by integrating insights from randomized clinical trials (RCTs) with real-world data, enhancing personalized care, optimizing treatments, and informing clinical and regulatory decisions. This expert opinion, based on a multidisciplinary Italian project, demonstrates RWE's ability to address gaps in RCTs, especially for complex or underrepresented populations, using case studies from the Fondazione Ricerca e Salute (ReS) healthcare database.
While RWE shows transformative potential, challenges remain in data quality, accessibility, and regulatory integration. Experts emphasize standardizing data collection and harmonizing methodologies across healthcare systems to ensure actionable insights. RWE is also crucial for pricing, reimbursement, and regulatory approvals, particularly in cases where large-scale trials are infeasible or raise ethical concerns. The integration of artificial intelligence tools is highlighted as essential for advancing data processing and analysis, enabling RWE to provide more nuanced insights. Collaboration among healthcare providers, researchers, and policymakers is critical to harness RWE's full potential. By addressing these challenges, RWE can improve patient outcomes, streamline resource allocation, and enhance decision-making in oncology, driving progress toward more efficient and personalized cancer care.

Doi: 10.48286/aro.2025.104

Impact statement: This study highlights how real-world evidence complements clinical trials, advancing precision oncology and supporting regulatory and healthcare decision-making for improved patient outcomes.

Key words: *Real World Evidence; oncology; decision-making; regulatory submissions; precision medicine.*

Received: Jan 23, 2024/**Accepted:** Mar 4, 2025/

Published: Mar 31, 2025

INTRODUCTION

The use of Real World Evidence (RWE) in oncology has rapidly expanded over the past decade, driven by its ability to complement and extend beyond the controlled findings of randomized clinical trials (RCTs) (1-3). While RCTs are the gold standard for assessing the efficacy and safety of therapies, they are conducted in highly controlled environments, often excluding key patient populations such as those with comorbidities, elderly individuals, or those on complex medication regimens. This limits the generalizability of RCT results to real-world clinical settings, where patient variability and treatment adherence fluctuate (4).

RWE, derived from sources like healthcare administrative databases, electronic health records, patient registries, and insurance claims, fills these gaps by providing insights into how treatments perform in everyday clinical practice. It offers a comprehensive view of long-term treatment effectiveness, safety, and patient outcomes across broader and more diverse populations. By integrating RWE with RCT data, healthcare providers and regulators gain a more nuanced understanding of therapeutic performance over extended periods, capturing real-world factors such as patient adherence, comorbid conditions, and varying treatment regimens (3). Regulatory bodies, including the Food and Drug Administration (FDA) and the European Medicine Agencies (EMA), have increasingly integrated RWE into their frameworks to support both pre- and post-approval decisions for new drugs and indications (5, 6). According to a recent landscape review, RWE has played a significant role in regulatory submissions, with over 36.5% of identified use cases in oncology (7). RWE has been particularly valuable in cases where traditional RCTs are not feasible, such as rare diseases or where conducting large-scale trials may pose ethical concerns. These regulatory submissions have demonstrated the utility of RWE in areas such as label expansions, dose modifications, and supporting single-arm trials in oncology (8, 9).

In oncology, RWE plays a pivotal role in addressing the gaps left by RCTs, particularly in the era of precision medicine (10). Beyond genomic and molecular profiling, patient outcomes are influenced by a range of real-world factors, including the tumor microenvironment, pharmacological interactions, and lifestyle choices (11). For example, RWE studies have revealed how proton pump inhibitors can reduce the efficacy of immune checkpoint inhibitors by altering the gut microbiome, an insight that was not captured in clinical trials but is critical for optimizing treatment in diverse patient populations (12). Moreover, RWE is increasingly important for healthcare systems transitioning toward value-based care models. RWE allows policymakers to evaluate the real-world cost-effectiveness of therapies, optimize resource allocation, and forecast future healthcare needs (13). Large-scale databases such as the Fondazione Ricerca e Salute (ReS) database (14) in Italy provide invaluable data on treatment patterns, healthcare resource use, and patient outcomes, offering a comprehensive view that informs both clinical practice and health policy.

This expert opinion aims to explore the growing role of RWE in oncology decision-making, particularly within the Italian healthcare system. Drawing on insights from the 'RWE Oncology and Territorial Care Planning' project, this article examines how RWE is being used to support personalized oncology care, optimize treatment pathways, and inform regulatory and healthcare decisions to improve patient outcomes and system efficiency.

The opinion was based on practical examples from the Fondazione ReS database of the identification of populations affected by specific cancers and the analyses that can be performed to generate RWE in oncology to suggest how these data can be used for different analytical purposes. The examination of these examples allowed the multidisciplinary group of experts to express their opinions and suggestions on the role of RWE in the decision-making process for oncological drugs.

METHOD

This expert opinion was developed through the insights gathered during the 'RWE Oncology and Territorial Care Planning' project. The project aimed to explore how RWE can support clinical and regulatory decision-making in oncology, aligning not only with Mission 6 of Italy's National Recovery and Resilience Plan (PNRR), which focuses on enhancing healthcare systems by improving access to care, strengthening prevention, and integrating innovative technologies to advance patient outcomes, but also with Italy's National Oncology Plan and the Europe's Beating Cancer Plan, reinforcing a coordinated approach to cancer prevention, treatment, and research at both national and European levels (15-17).

The core of the project was a co-creation event held on July 16, 2024, in Rome, organized by Edra and Fondazione ReS. The event brought together a multidisciplinary panel of Italian experts from oncology, pharmacology, health policy, and healthcare management. Participants included representatives from organizations such as the Italian Medicines Agency (AIFA), oncology networks, and academic institutions. The co-creation methodology facilitated collaborative discussions among the experts, promoting a structured exchange of knowledge and perspectives.

During the event, the panel has been engaged in interactive sessions of co-creation divided into two working groups: one focusing on clinical and organizational aspects, and the other on managerial and economic aspects. Case studies from the Fondazione ReS database (data source description in **Box 1**) were presented to demonstrate the practical application of RWE in identifying target populations, analyzing treatment pathways, and understanding the economic impact of oncology therapies (**Supplementary Material**). These case studies, involving cancers such as breast, prostate, lung, and lymphoma, formed the foundation for the discussions.

The co-creation process also involved analyzing how RWE can inform pricing and reimbursement decisions, especially through its application in regulatory processes. The event's discussions generated key insights into how RWE can fill gaps in traditional clinical trials by providing data on long-term effectiveness, real-world safety, and patient outcomes. The outcomes of these discussions and the insights drawn from the Fondazione ReS database have been integrated into this expert opinion to offer a comprehensive overview of the role of RWE in advancing oncology care in Italy.

IDENTIFYING TARGET POPULATIONS THROUGH RWE

Real World Evidence plays a crucial role in oncology, not only for identifying target populations but also for enhancing patient stratification and customizing treatments (26). While RCTs provide essential efficacy data, they are often limited in their ability to capture the complexity of real-world patient populations. By utilizing real-world data (RWD) from sources such as healthcare administrative databases, electronic health records, national registries, and insurance claims, RWE offers a more comprehensive view of patient variability. This allows healthcare providers to stratify patients based on more detailed characteristics such as comorbidities, adherence patterns, and genetic profiles, which directly influence treatment outcomes.

During the event, experts highlighted how RWE has revolutionized patient characterization by providing insights into not only demographic data but also

BOX 1. Description of the ReS administrative healthcare data source.

Fondazione ReS is a non-profit foundation working on Italian healthcare real-world data with the aim of planning and monitoring healthcare policy issues, for different stakeholders and in various clinical fields since its establishment in 2018 (18-20). Through the collaboration with Cineca (Interuniversity Consortium (REF (21)), which guarantees quality and security of the data management (international standard certifications), the Fondazione ReS database, after further quality and accuracy data checks, collects and integrates the administrative healthcare data that Italian Local and Regional Healthcare Authorities (HAs) annually convey to the Italian Ministry of Health. Data from some HAs, owners of these data, are made available to Fondazione ReS under specific agreements, to be analyzed in aggregated form, after anonymization. Demographics (age, sex, local HA of residency and disease waiver claim for co-payment) of each patient are completely anonymized at the source according to European privacy rules. (22) The pharmaceuticals' database contains drugs reimbursed by the SSN and supplied from local and hospital pharmacies (Italian marketing code, ATC code, dose, number of packages and dispensing date). The hospitalizations' database contains in-hospital diagnoses and procedures, according to the Italian version of the 2007 ICD-9-CM (International Classification of Diseases – 9th version – Clinical modification (23), accessible through the hospital discharge forms of overnight and daily in-hospital stay. The outpatient specialist care database (visits, diagnostic and invasive/non-invasive procedures charged to the SSN) is analyzed based on the current national classification system, 2017 version (24). Administrative healthcare databases also provide direct costs incurred by the SSN, due to reimbursement purposes.

molecular and clinical characteristics. For example, the Fondazione ReS database has been instrumental in tracking cases of breast cancer, specifically hormone receptor-positive (HR+), HER2-negative subtypes (example 4 in **Supplementary Material**). By analyzing RWD on receptor expression, clinicians are better equipped to customize hormonal and targeted therapies based on the likelihood of patient response. This ensures that therapies are directed at the right patients, enhancing treatment efficacy and reducing unnecessary exposure to ineffective treatments.

Moreover, RWE allows for the identification of comorbidities that may influence treatment selection. For instance, in the case of uterine and prostate cancer, a high percentage of patients present with chronic conditions such as hypertension or diabetes, which can alter treatment outcomes (example 3 in **Supplementary Material**) (26-29). By capturing these comorbidities, RWE facilitates more tailored treatment approaches that account for the broader clinical picture of each patient.

One of the key advantages of RWE is its ability to stratify patients into subgroups that are not typically represented in RCTs. For example, in metastatic prostate cancer, RWE data revealed that around 4.9% of prostate cancer cases in 2022 involved metastasis, highlighting the need for more targeted therapies for these patients (example 2 in **Supplementary Material**). By identifying such subgroups in the real-world setting, RWE helps to optimize treatment pathways, ensuring that advanced therapies are applied where they are most likely to be effective.

Additionally, RWE's capacity to track healthcare resource utilization and treatment adherence plays a pivotal role in customizing treatment strategies. For example, in the case of lung cancer, RWD can monitor adherence to complex treatment regimens, allowing clinicians to adjust care plans in response to patient behaviors and outcomes. It is also essential to understand the various treatment lines and trajectories to ascertain the progression of a tumor. To illustrate, in the case of diffuse large b cell lymphoma (DLBCL), 15.4% of patients were treated with a third or subsequent line of therapy (example 6 in **Supplementary Material**). This dynamic approach, informed by real-world insights, ensures that treatments are continuously optimized based on the patient's real-world experience, rather than relying solely on RCT-derived protocols.

In summary, RWE significantly enhances patient stratification by providing detailed insights into the molecular, clinical, and behavioral aspects of patient populations. This ability to customize treatments based on real-world patient characteristics leads to better outcomes, more efficient resource utilization, and a more personalized approach to oncology care.

HIGHLIGHTS BOX

The experts' opinion: RWE is pivotal in identifying and stratifying target populations in oncology, enabling more precise and personalized treatments that better reflect the complexities of real-world clinical practice.

Experts' suggestion: to enhance the identification of target populations through RWE, experts recommend developing standardized methodologies for data collection, fostering cross-institutional data sharing, and integrating advanced analytics such as Artificial Intelligence (AI) to better process complex datasets. They also emphasize the need for greater collaboration between healthcare providers, researchers, and regulatory authorities to ensure that RWE is consistently applied.

REGULATORY DECISION-MAKING AND RWE

RWE is increasingly recognized as a vital tool for regulatory decision-making, particularly in the pre- and post-marketing stages of drug development (7, 30). Its ability to provide insights into the long-term safety, effectiveness, and real-world impact of therapies has made it indispensable in bridging the gaps that traditional clinical trials often leave unaddressed.

Application of RWE in pre- and post-marketing stages of drug development

RWE is used extensively in both pre- and post-marketing contexts to inform regulatory decisions. In the pre-marketing stage, RWE can provide supplementary data when RCTs are not feasible or when patient populations are too small or specific to conduct a large-scale trial. RWE can also be used in single-arm trials, where it serves as a comparison group based on real-world outcomes. This is especially useful for rare diseases or in cases where ethical or logistical constraints limit the feasibility of a traditional control arm.

In the post-marketing stage, RWE plays a crucial role in monitoring long-term safety and effectiveness. It

allows regulatory authorities and healthcare providers to track how therapies perform across diverse, real-world patient populations over time, providing valuable data that cannot be captured in the controlled environment of an RCT. For example, real-world data helps to identify adverse events or long-term effects that may not become evident during the initial phases of drug development. This ongoing monitoring ensures that any new risks are promptly identified and mitigated. Furthermore, RWE can be useful to verify the effectiveness of a drug, as shown in the case of DLBCL where 72% of patients treated with at least one line of therapy survive 12 months after the first diagnosis (example 7 in **Supplementary Material**).

Support for pricing and reimbursement decisions

RWE has also become instrumental in pricing and reimbursement decisions, particularly in the context of Italy's regulatory environment. The pricing and reimbursement dossier, which can be compiled using real-world data, enables AIFA to assess the real-world value of new therapies and determine their pricing and reimbursement status. By analyzing treatment outcomes in the real world − such as patient survival rates, healthcare resource utilization, and quality of life improvements − AIFA can make more informed decisions regarding which treatments to reimburse and at what price point.
In cases where the clinical trial data are insufficient to justify the high cost of a new therapy, RWE can provide the necessary evidence to demonstrate the therapy's cost-effectiveness in real-world use. For example, treatments for conditions like advanced cancer often carry significant price tags. Using RWE to assess their long-term effectiveness and impact on overall healthcare costs helps regulators, such as AIFA, negotiate appropriate pricing and ensure that resources are allocated efficiently.

Addressing clinical trial gaps

A key advantage of RWE is its ability to address gaps left by clinical trials, particularly regarding long-term safety and effectiveness. Clinical trials are typically limited by time constraints and focus on narrowly defined patient populations, which can exclude individuals with comorbidities or those from underrepresented groups. RWE provides an ongoing source of data that reflects the full spectrum of patient experiences, capturing how therapies perform over longer periods and in more diverse populations.
This RWD can help fill the evidence gaps in areas such as drug safety in elderly populations, treatment adherence in complex regimens, and long-term survival outcomes. By integrating RWE into regulatory frameworks, healthcare providers and regulators can ensure that decisions are based on comprehensive data that reflects the realities of patient care, ultimately leading to more effective and safer treatments for oncology patients.

HIGHLIGHTS BOX

The experts' opinion: RWE is crucial for supplementing traditional clinical trial data, offering vital insights into long-term safety and effectiveness that guide regulatory decisions, particularly in pricing, reimbursement, and monitoring the real-world performance of oncology therapies.
Experts' suggestion: to fully harness the potential of RWE in regulatory decision-making, experts recommend fostering closer collaboration between regulatory agencies, healthcare providers, and pharmaceutical companies, while standardizing data collection and analysis processes to ensure consistent and actionable outcomes.

RWE IN PERSONALIZED ONCOLOGY CARE

RWE plays a transformative role in personalized oncology care, enabling clinicians to tailor treatments to the unique needs of individual patients. During the event, experts emphasized how RWE supports real-time adjustments to care strategies, filling in the gaps left by traditional RCTs which often exclude patients with comorbidities or those who don't adhere perfectly to treatment protocols.
The shift toward truly personalized care involves moving beyond predictive models and stratified medicine. In oncology, we are witnessing a broadening of treatment and patient management models, which is leading to changes in the research and drug development process: the mutational model has recently been added to the previous histological and agnostic models (31). The latter requires RWD to be implemented in the best possible way. Such data can be derived from studies, the results of which can then be passed on to pharmaceutical companies for authorization and reimbursement procedures, according to a specific Decree of the

Italian Ministry of Health for facilitating non-profit studies (32).

Although numerous molecular targets and innovative therapies have been developed, translating these advances into everyday practice remains challenging. RWE provides a framework to bridge this gap by incorporating complex data such as tumor microenvironment interactions and pharmacological effects. For instance, it can be used to evaluate how the gut microbiome influences therapy outcomes or how drug interactions impact progression-free survival (PFS) (33).

In the context of precision oncology, RWE supports the customization of treatments by utilizing genetic and molecular data from various real-world sources like patient registries and administrative databases. This integration allows clinicians to identify trends in treatment response not evident in controlled trials, guiding the selection of targeted therapies for specific patient subgroups.

In conclusion, RWE allows healthcare providers to adopt a more flexible and personalized approach to oncology care, continuously adapting treatments based on real-world patient data. This ensures that therapies are not only effective but also aligned with the complexities of individual patient profiles, resulting in better overall outcomes.

HIGHLIGHTS BOX

The experts' opinion: RWE is crucial for tailoring precision oncology treatments to real-world patient needs, capturing vital data on patient diversity and comorbidities that clinical trials often overlook, making it indispensable for personalized cancer care.

Experts' suggestion: to fully capitalize on RWE in personalized oncology, experts advocate for the integration of advanced platforms and AI tools to manage and analyze complex data sets.

ECONOMIC IMPACT AND RESOURCE PLANNING

RWE offers critical insights into the cost-effectiveness of cancer treatments, allowing for better planning and optimization of healthcare resources. Integrating RWE with real-world data can provide a more comprehensive understanding of treatment costs, particularly for complex conditions like lung cancer.

An important example discussed by the experts was the cost analysis of lung cancer treatments based on data from the Fondazione ReS database. According to this analysis, the average cost of treating a newly diagnosed lung cancer patient within the first 12 months is approximately € 21,000, with the largest share of expenses attributed to chemotherapy and surgical interventions (example 8 in **Supplementary Material**). This real-world cost analysis can provide healthcare systems with a clear understanding of the financial impact, aiding in the development of more efficient resource allocation strategies.

The integration of AI-driven forecasting tools with RWE was also highlighted as a transformative approach in cancer research, with the potential to not only anticipate future resource needs but also enhance predictive insights into patient outcomes and treatment efficacy. As recent studies underscore, AI applications in oncology are advancing rapidly, offering unprecedented opportunities for optimizing patient management and tailoring interventions in real time (34). By analyzing demographic trends and treatment patterns, AI can predict the evolution of patient populations and help healthcare systems plan more accurately for future demands. This approach was presented as a key to ensuring sustainable healthcare systems, where resources are directed toward the most cost-effective treatments and interventions.

In addition, RWE plays a crucial role in planning healthcare systems and resource allocation, particularly in stratifying patient needs and optimizing treatment pathways. By capturing real-world treatment outcomes and healthcare resource utilization, RWE enables policymakers to design more efficient, patient-centered healthcare models. This approach allows for better forecasting of hospitalization rates, long-term care needs, and drug reimbursement strategies, ultimately ensuring that healthcare resources are used where they can have the most impact.

HIGHLIGHTS BOX

The experts' opinion: RWE is indispensable for understanding the true cost-effectiveness of cancer therapies, providing healthcare systems with RWD to inform smarter resource allocation and long-term planning for complex diseases like lung cancer.

Experts' suggestion: to fully leverage RWE in economic planning, experts suggest integrating

AI tools with RWE data to predict future healthcare demands more accurately. Additionally, they emphasize the importance of stronger collaboration between healthcare providers and policymakers to standardize data collection across systems. By aligning strategies and leveraging real-world evidence, this partnership can ensure more efficient resource allocation, prioritize the most effective cancer treatments, and minimize unnecessary healthcare expenditures.

CHALLENGES AND LIMITATIONS

Despite the potential of RWE in oncology, several challenges limit its full integration into clinical and regulatory frameworks. One key issue is the quality and consistency of data. The variability in how data is collected across different health-information systems often results in incomplete or inconsistent datasets, making it difficult to ensure reliability in real-world insights. These inconsistencies can undermine the value of RWE when applied to clinical decision-making.

Another challenge involves regulatory alignment. While RWE is gaining recognition, regulatory bodies often have differing standards on how RWE can be incorporated into their processes. The experts discussed the need for greater harmonization of regulatory requirements to facilitate the integration of RWE into approval processes, particularly in complex areas like oncology where evidence from traditional clinical trials may be limited.

Additionally, there are significant gaps in clinical data variables. Many databases are lacking essential details such as molecular profiling, patient adherence data, or longitudinal outcomes, which are critical for robust RWE analyses. This problem is exacerbated by privacy regulations, which restrict access to patient-level data, making it more difficult to conduct comprehensive analyses while ensuring patient confidentiality.

Addressing these challenges will require strategies to improve RWE data collection and integration. During the event, experts emphasized the need for more structured data collection protocols that can be uniformly applied across different healthcare environments. Furthermore, enhancing the technological infrastructure, such as deploying advanced data integration platforms, will be key to overcoming current limitations and unlocking the full potential of RWE in oncology.

HIGHLIGHTS BOX

Experts' opinion: the quality, consistency, and accessibility of RWE data are major challenges, particularly given the gaps in key clinical variables and the differing standards across regulatory bodies.
Experts' suggestion: to overcome these challenges, experts recommend enhancing the infrastructure for RWE data collection by standardizing data across health-information systems. Additionally, they suggest integrating more advanced data management tools and increasing collaboration between institutions to ensure comprehensive, high-quality datasets that support better patient outcomes.

CONCLUSIONS

RWE has proven to be a transformative tool in oncology decision-making, enabling more comprehensive patient stratification, treatment customization, and long-term outcome analysis. Its ability to capture real-world patient experiences, particularly for populations often excluded from randomized clinical trials, has made RWE indispensable in complementing traditional clinical data. By providing critical insights into treatment effectiveness, safety, and resource allocation, RWE supports both clinical and regulatory advancements in oncology.

Moving forward, it is essential to focus on improving RWE methodologies, particularly by standardizing data collection across health-information systems. The integration of datasets from various real-world sources, such as healthcare administrative data, electronic health records and patient registries, will further enhance the robustness of RWE. Additionally, fostering collaboration between healthcare providers, researchers, and policymakers is critical to overcoming current limitations related to data quality, privacy, and regulatory alignment.

The work of the experts has led to the identification of key actions aimed at maximizing the use of RWE in oncology, focusing on improving data collection, regulatory integration, and economic planning (**Table 1**). The experts call for the broader adoption of RWE in oncology to advance both clinical practice and regulatory processes. By addressing existing challenges and integrating innovative technologies such as AI, the potential for RWE to revolutionize oncology care, ensuring more precise, personalized, and efficient treatment pathways, becomes increasingly clear.

Table 1. *Key actions identified by experts for maximizing the use of RWE in oncology.*

	ACTIONS
Identifying target populations through RWE	• Develop reproducible algorithms to identify patients with specific conditions using available data sources (*e.g.*, ReS database, cancer registries). • Ensure transparency by publishing algorithms that define how target populations are identified. • Use demographic and administrative health data to fill gaps where clinical data is missing (*e.g.*, staging and disease progression). • Implement tracking mechanisms for follow-up visits and treatment adherence to improve patient monitoring. • Censor all available data sources and implement codification systems to track patient entry into oncological treatment pathways. • Integration of pathology data into RWE to provide a more comprehensive source of real-world data.
Regulatory decision-making and RWE	• Leverage RWE to fill gaps where randomized clinical trials (RCTs) are impractical, providing critical evidence for pricing, reimbursement, and regulatory approval. • Use RWE pre-marketing to analyze target populations, defining eligibility criteria, prevalence, incidence, and associated costs. • Integrate RWE into regulatory frameworks to improve dossier submissions for new drug approval and reimbursement processes (*e.g.*, analysis of costs and effectiveness). • Utilize RWE to monitor the real-world performance of treatments over time and adjust regulatory decisions accordingly.
RWE in personalized oncology care	• Emphasize the use of RWE to tailor treatment strategies based on real-world patient outcomes, addressing complexities like comorbidities and pharmacological interactions. • Explore AI integration for analyzing complex patient data (*e.g.*, tumor microenvironment, drug interactions) to refine treatment approaches. • Promote the use of RWE in identifying high-risk populations for early intervention and personalized care pathways. • Build advanced platforms to collect and analyze complex RWE datasets, with AI support to enhance clinical decision-making in oncology.
Economic impact and resource planning	• Use RWE to perform cost-effectiveness analyses in real-world settings, particularly for high-cost treatments such as cancer therapies. • Integrate AI tools with RWE to forecast future healthcare resource needs based on epidemiological trends and treatment patterns. • Quantify the impact of cancer treatments on healthcare resources (*e.g.*, hospitalization rates, outpatient care) to guide resource allocation decisions. • Develop RWE-based strategies for re-negotiating drug prices and reimbursement rates, using real-world performance data.

ACKNOWLEDGEMENTS

The Authors thank the Fondazione ReS team (Giulia Ronconi, Leonardo Dondi, Silvia Calabria, Irene Dell'Anno, Immacolata Esposito, Alice Addesi, Aldo P. Maggioni) for the examples provided and described in the supplementary material.

COMPLIANCE WITH ETHICAL STANDARDS

Funding

This project has received unconditional funding from AstraZeneca S.p.A., Glaxosmithkline S.p.A., Pfizer S.r.l., Roche S.p.A.

Conflict of interests

This project was conceptualized by Edra S.p.A. and made possible thanks to an unconditional contribution of: AstraZeneca S.p.A., Glaxosmithkline S.p.A., Pfizer S.r.l., Roche S.p.A. All the activities for the realization of the article (choice of topics, selection of contents, drafting of texts, choice of sources, selection and involvement of Authors) were carried out in full autonomy by Authors without any interference.

Availability of data and materials

The data underlying this article are available within it and in the Supplementary Material available at the following link: https://www.annals-research-oncology.com/wp-content/uploads/2025/03/Supplementary-Material.pdf.

Authors' contributions

NM, GR, LB made substantial contributions to the conception or design of the work. NM, CP, and LD contributed to the acquisition, analysis, or interpretation of data for the work. All Authors were involved in drafting the work or revising it critically for important intellectual content, approved the final manuscript for publication, and agreed to be accountable for all aspects of the work to ensure that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethical approval

Human studies and subjects

N/A.

Publication ethics

Plagiarism

Authors declare no potentially overlapping publications with the content of this manuscript and all original studies are cited as appropriate.

Data falsification and fabrication

All the data corresponds to the real.

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