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Volume 2: Real World Evidence (RWE): Paths to Enhancing Patient Access to New Medications

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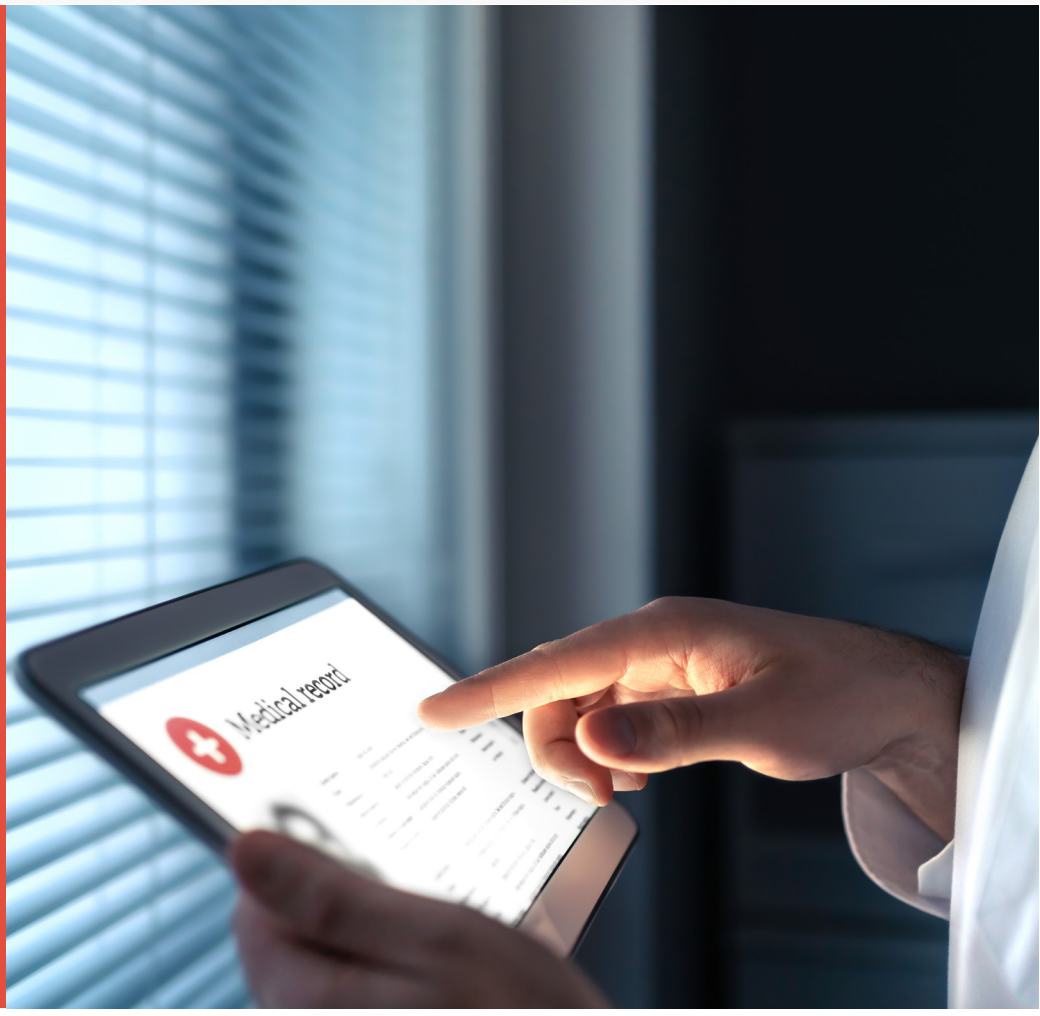

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Volume 2: Real World Evidence (RWE): Paths to Enhancing Patient Access to New Medications

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The growing availability of real-world data (RWD)—from electronic health records, claims databases, patient support programs, and disease registries—together with major advances in analytical methodologies, including artificial intelligence, has reshaped the generation and application of real-world evidence (RWE). High-quality RWE is increasingly recognized as a critical complement to traditional clinical trial data for informing healthcare decision-making.

Building on the foundation established in Volume 1, which addressed key methodological challenges in RWE generation, Volume 2 of this Special Issue focuses on the pragmatic use of RWE to improve and accelerate patient access to medicines. With recent guideline updates from regulatory authorities, reimbursement agencies, and advertising control boards explicitly endorsing the use of robust RWE, its role in supporting regulatory approval, reimbursement decisions, and communication is rapidly expanding.

This eBook brings together six peer-reviewed articles published in Volume 2, highlighting practical applications of RWE in regulatory and access contexts. Collectively, these contributions provide timely insights for researchers, regulators, and industry stakeholders navigating the evolving RWE landscape.

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Editorial: Volume 2: real world evidence (RWE): paths to enhancing patient access to new medications

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KEYWORDS

Canada, drugs, FAST, pCPA, reimbursement, market access, patient access

Editorial on the Special Issue
Volume 2: real world evidence (RWE): paths to enhancing patient access to new medications

NEW PATHWAYS, OLD PROBLEMS: IS PATIENT ACCESS TO NEW MEDICATIONS IMPROVING IN CANADA?

Timely and equitable access to innovative medicines is the cornerstone for improving patient health outcomes and the overall quality of healthcare. Canada's public reimbursement system for new medicines is widely recognized as complex and challenging, and Canada ranks among the slowest Organization for Economic Co-operation and Development (OECD) countries for patient access to novel medications, taking more than 1.5 years after regulatory approval for a new drug to be listed on the public plans in Canada [1]. This slow pace is recognized as a result of the multi-layered drug reimbursement processes involving federal, pan-Canadian, and provincial reviews, which are frequently opaque and difficult to navigate, and cause significant delays in access to urgently-needed treatments [2, 3].

Health Canada does not significantly contribute to these delays, as it has modernized its regulatory processes and positioned itself among the top tier international review agencies, following on the footsteps of leading regulatory agencies such as FDA and EMA [4]. Health Canada's three pathways for drug approvals – Standard Reviews, Priority Reviews and Notice of Compliance with Conditions (NOC/c) – provide flexible options for the submission of new medicines, including those supported by preliminary evidence, treatments for rare (orphan) conditions, and drugs with exceptional efficacy [5]. Health Canada also was among the first regulators to participate in Project Orbis [6], an FDA-led international joint review initiative for promising oncology drugs, underscoring its reputation as a science-driven, evidence-based regulator.

So where does the slowdown come from? After Health Canada grants regulatory approvals, approximately half of drugs [7] face additional scrutiny through health technology assessments (HTA) by Canada's Drug Agency (CDA-AMC) or Quebec's Institut national d'excellence en santé et en services sociaux (INESSS), followed by price negotiations with the pan-Canadian Pharmaceutical Alliance (pCPA) and, finally, each provincial jurisdiction independently decides whether to include the medication on its public drug formulary [8]. These steps can stretch out the time between approval and actual patient access, leading to inconsistent availability of medications across different regions [9]. The typically sequential HTA, pCPA and provincial formulary processes have been identified as main contributors to delays in patient access.

Recent reforms to accelerate access: early impact and remaining gaps

From 2023 to 2025, Canada introduced three new processes to accelerate access to novel medicines [10, 11]. (Other processes, such as Pharmaceuticals with Anticipated Comparable Efficacy and Safety (PACES) and Targeted Negotiation Process (TNP), are not being mentioned here as they are not pertinent to novel medicines). These are:

- TLR-pTAP: Canada's Drug Agency's Time-limited recommendation (TLR) category, which established a mechanism to provide time-limited HTA recommendations to drugs with evidence uncertainties approved under NOC/c, and the corresponding pan-Canadian Pharmaceutical Alliance's Temporary Access Process (pTAP), were introduced in September 2023 [12, 13].
- pCPA ENP: The pan-Canadian Pharmaceutical Alliance's (pCPA) Early Negotiation Process (ENP), introduced in October 2025, provides an expedited negotiation pathway for cancer drugs that are part of Project Orbis, whereby the negotiation process begins when a HTA body accepts a submission [14].
- Ontario FAST: Also in October 2025, Ontario launched the Funding Accelerated for Specific Treatments (FAST) 3-year pilot program for selective oncology drugs approved by the Orbis process, and provides early public funding while the pCPA and drug manufacturer negotiate the drug price [15].

These processes enable concurrent reviews by 2-3 agencies – an approach already adopted for more than a decade by various European agencies – and signal the emergence of an important continuous improvement mindset across organizations as well as a convergence of institutional silos. However, it remains uncertain whether they will lead to a tangible reduction in delays to drug access. Early results from the TLR-pTAP processes suggest that the stringent criteria for acceptance into these pathways have limited uptake [16]. As the pCPA's ENP and Ontario's FAST programs have only recently launched, more time will be required to analyse their impact.

Proposed strategies towards tangible timely access solutions

- Continuing to prioritize operational efficiencies at the pCPA: Recent performance improvements at the pCPA illustrate how strengthening core operational timelines can yield meaningful access gains at scale. Total negotiation times across all drugs declined from approximately 11 months in 2020 to 6.5 months in 2025, representing a 41% reduction, with similar improvements observed for oncology therapies [17]. Although less conspicuous than newly introduced pathway initiatives, these efficiency gains affect the largest number of medicines and directly shorten the time to patient access. Establishing and maintaining a reliable baseline performance at the pCPA can create the capacity needed to address more complex files, using targeted pathways and innovative approaches such as outcomes-based agreements or other innovative access models requiring real-world data to address remaining uncertainties.
- Protected funding for innovation: Building on the Ontario FAST program, it is critical to further establish Canada-wide dedicated funding mechanisms to support innovative and equitable reimbursement strategies, especially for high-cost and rare disease therapies. The National Strategy for Drugs for Rare Diseases, which launched in 2023, has "yet to translate into improvements in access to treatments for patients with rare diseases" [18].
- Continuous policy and process evolution: Guidelines and policies for enabling timely public access to innovative medicines need to align with advancements in medical practice and emerging real-world evidence. This includes, for example, broadening the scope of accelerated reimbursement pathways to include a broader range of high-priority therapies. Currently, the three paths described in this paper focus solely or primarily on oncology.
- Establishing a pathway for joint pricing models for high-cost therapies and drugs for rare diseases: Proactive collaboration between pharmaceutical companies, HTA agencies, the pCPA and public payers will enable the development realistic, value-based pricing models that

link reimbursement to real-world clinical outcomes for high-cost treatments such as CAR-T, gene therapies, and other drugs for rare diseases, tailored to the Canadian funding environment.

Conclusion: moving toward timelier access, slowly but surely

The introduction of novel pathways brings hope to Canadian patients that "more equitable access to life-saving treatments" can be achieved [19]. Although these approaches have led to some improvements in patient access, significant hurdles persist. In addition to the challenges noted above, gaps in health-system readiness for the implementation of new drugs have recently emerged as a potential obstacle [20]. The growing influence of artificial intelligence in drug discovery and development is expected to transform therapies entering the market, which may further strain current access pathways. As such, those championing the early, timely and equitable availability of new medicines in Canada must balance forward-thinking ambition with pragmatic solutions, recognizing the complex relationships between government agencies, pharmaceutical companies, and patient communities.

Post Submission Note: It was announced on January 22, 2026, that since October 2025 six cancer drugs have been accelerated for funding through the FAST pilot [21].

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A systematic review of real-world evidence on the clinical relevance, characterization, and utility of *CYP2D6* biomarker testing

Patrick Rodriguez[1], Emma Kikerkov[1], Nora Emmott[1], Christine Y. Lu[2,3,4†] and Rachele M. Hendricks-Sturrup[1*†]

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Pharmacogenomic (PGx) research investigates how an individual's genetic make-up impacts their drug metabolism. PGx testing can therefore inform therapeutic decision-making, especially as compelling evidence develops over time to substantiate its clinical and personal utility across a range of therapeutic areas. PGx biomarker *CYP2D6*, in particular, is widely implicated in drug metabolism and across several therapeutic areas. Real-world evidence (RWE) derived intentionally using electronic health record (EHR) and insurance claims data presents an opportunity to explore clinical-behavioral outcomes and implementation barriers and facilitators for PGx testing in real-world clinical settings. In this systematic review, we explored these areas with a focus on PGx biomarker *CYP2D6*, investigating drug-gene pairs with strong evidence (Level A, Final classification by the Clinical Pharmacogenetics Implementation Consortium [CPIC]). Across 25 studies that met our study inclusion criteria, nine (9) drug-gene pairs that met the CPIC Level A, Final, strong evidence category for *CYP2D6* were described. Overarching qualitative themes across studies were 1) variation in CYP2D6 biomarker testing and interpretation, and 2) PGx test implementation and data considerations. CYP2D6-drug pairs were reported across four therapeutic areas (analgesia [n = 21], psychiatry [n = 17], oncology [n = 7], gastroenterology [n = 6]) with the two most researched drugs being codeine (n = 21) and tramadol (n = 18). Six (6) of 25 articles reported PGx clinical outcomes, considered to be a "measurable change in symptoms, overall health, ability to function, quality of life, or survival outcomes" in relation to PGx testing. Special EHR and claims data considerations for future work include but are not limited to addressing inconsistent phenotype categorizations

(i.e., natural genotype versus phenoconversion); lack of reliable racial, ethnic, and genetic ancestry data within EHR and claims data sources; and data inoperability issues between PGx test results and EHRs.

KEYWORDS

electronic health records, pharmacogenomics, precision medicine, *CYP2D6*, biomarker testing, claims data, real-world data, real-world evidence

Introduction

CYP2D6 is a key enzyme and biomarker involved in the metabolism of may commonly prescribed medications, particularly in older adults [1–3]. A large and growing body of evidence demonstrates the clinical importance of *CYP2D6* in precision medicine research and practice. The Clinical Pharmacogenomics Implementation Consortium (CPIC), a pharmacogenomics (PGx) organization with implementation guidance on *CYP2D6*, reviews evidence around the implications of different genes to adversely affect drug metabolism. To date, CPIC has assigned four evidence levels to drug-gene pairs: A, B, C, and D [4]. Drug-gene pairs assigned to "CPIC Level A, Final" are accompanied or followed by in-depth reviews of evidence to guide the practice of prescribing/de-prescribing based on PGx biomarker status. CPIC recommends prescribing action for Level A medications and that alternative medications are likely safe and effective. Currently, ten *CYP2D6*-drug pairs are assigned to CPIC Level A, Final [5].

Similarly, the U.S. Food and Drug Administration (FDA) Table of Pharmacogenomic Biomarkers in Drug Labeling associates *CYP2D6* with 73 different medications [6]. Of all biomarkers within the Table, and thus of regulatory concern, *CYP2D6* holds the highest number of labeling sections (~13% of 570 total) [6]. As seen in Figure 1, *CYP2D6* holds special pharmacological potential and significance in psychiatry, a therapeutic area holding 50% of all its labeling sections, followed by cardiology (10%), neurology (8%), and urology (7%). Among the ten *CYP2D6*-drug pairs in CPIC, nine have FDA PGx drug labeling sections (see Figure 1).

Evidence is often generated through randomized, controlled clinical trials. However, such trials face structural and systemic challenges that interfere with accurate, generalizable, and efficient investigation of critical research questions spanning various therapeutic areas. Some of these challenges are limited trial availability, access barriers, and eligibility issues for prospective trial participants, especially racial/ethnic minorities and populations with comorbidities, contributing to systemic barriers that impede participation in research and institutional mistrust. In fact, a recent National Academies report showed that despite making up 39% of the U.S. population, historically underrepresent racial and ethnic groups represent between 2%

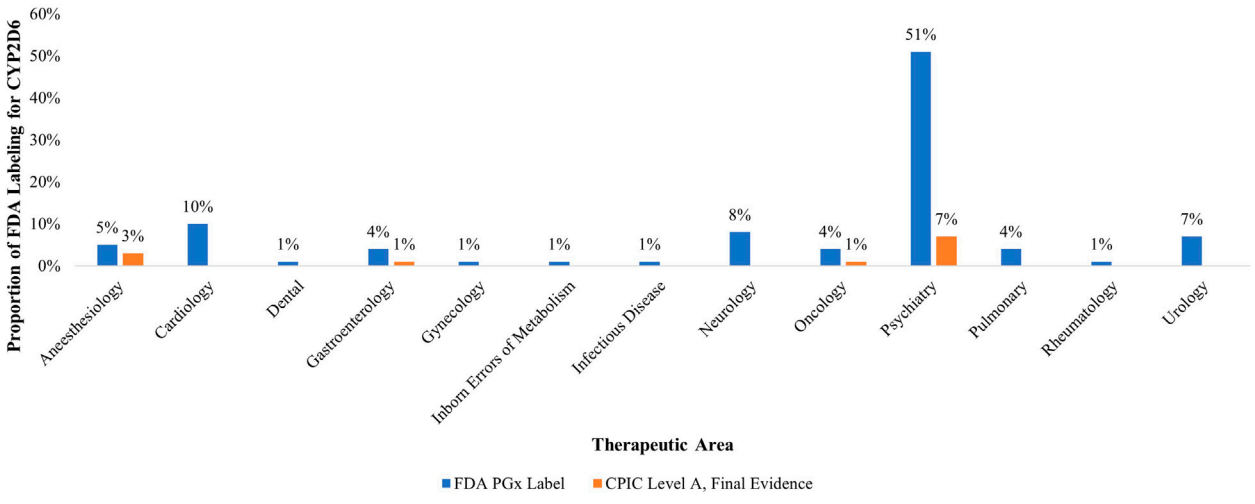

FIGURE 1
Proportion of therapeutic areas with US FDA labels for pharmacogenomic biomarker CYP2D6 and CPIC Level A, Final Evidence drugs (n = 73). Legend: This figure demonstrates both the regulatory and clinical significance of PGx biomarker *CYP2D6*. *CYP2D6* accounts for the highest proportion of all FDA PGx labeling sections (~13%) and is disproportionately demonstrated in psychiatry (51%), followed by cardiology, neurology, and anesthesiology respectively. Of the thirteen therapeutic areas which have FDA PGx labeling sections, only four of these therapeutic areas also have CPIC Level A final evidence, illustrating misalignment between clinical guidance and regulatory acknowledgement.

and 16% of trial participants [7]. Underrepresentation becomes even more prevalent in cases where participant characteristics become even more diversified beyond race/ethnicity (i.e., sex/gender, pregnancy status, comorbidity status, and age).

To address these challenges, real-world evidence (RWE) on the clinical utility of *CYP2D6* biomarker testing across each of these therapeutic areas can be generated through the analysis of real-world data (RWD) deriving from a diverse array of data sources [8, 9]. This includes, but is not limited to, electronic health record (EHR) data and claims data, to help better characterize, clarify, and/or establish RWE on the therapeutic (un)importance of *CYP2D6* biomarker testing. Doing so among and across demographically diverse (sub)populations would be vitally important to maximize potential therapeutic benefit and reducing the likelihood of potential serious adverse events associated with biological variation in *CYP2D6*-mediated drug metabolism among patients. Regulators, payers, and health technology assessment (HTA) bodies leveraging insights from EHR and claims data to evaluate new and/or existing drugs across several therapeutic areas with *CYP2D6* biomarker implications also stand to benefit from understanding the therapeutic applications of *CYP2D6* biomarker testing in real-world settings.

To date, no systematic review has been published exploring the utility and impact of *CYP2D6* testing to anticipate drug-gene interactions in real-world clinical settings and with an intentional focus on such insights derived from EHR and/or claims data. Here, we present our review of such evidence to help inform regulators, payers/HTA bodies, clinicians, and patients or patient advocates.

Methods

PICO assessment

Our PICO assessment was as follows:

Patient: Patients of any age with or without PGx testing to guide therapeutic options or decisions, discernable from EHR and/or insurance claims data.

Intervention: *CYP2D6* PGx biomarker testing implementation among and across various types of health care service providers.

Comparison: Patients and health care service providers not undergoing *CYP2D6* PGx biomarker testing) were compared to those who underwent testing.

Outcome: PGx clinical implementation strategies, patient-level outcomes (e.g., improved well-being, disease progression), patient health behavior (e.g., medication adherence), and health care service provider treatment decisions following *CYP2D6* PGx testing.

Search strategy

Four authors (RH-S, NE, PR, and EK) conducted a literature search in June 2024 for original articles or research published at any time in the English language and indexed in Google Scholar, PubMed, Scopus, and Semantic Scholar. No specific filters or search limits were applied. The following search strategies were used:

- cyp2d6 AND drug interaction AND ("electronic health record" OR "electronic medical record")
- cyp2d6 AND drug interaction AND ("electronic health record" OR "electronic medical record") AND "drug-gene interaction"
- cyp2d6 AND drug interaction AND ("electronic health record" OR "electronic medical record") OR ("claims data" OR "administrative data") AND "drug-gene interaction"

Inclusion/exclusion criteria

Papers were included in our analysis if they presented, measured, and/or described real-world clinical or patient and/or provider behavioral outcomes based on an assessment of EHR or insurance claims data following PGx testing for the *CYP2D6* biomarker, included PGx biomarker(s)-drug pairs with CPIC Level A and Final Evidence designations, and were published in the English language (inclusion criteria). Papers were excluded if they were not published in the English language, did not present real-world clinical or patient and/or provider outcomes based on an assessment of EHR or insurance claims data following PGx testing for the *CYP2D6* biomarker, did not include PGx biomarker(s)-drug pairs with CPIC Level A and Final Evidence designations, contained duplicates, or were located online at broken links.

Article screening and selection

One senior author (RH-S.) initially and manually reviewed a subset of article titles and abstracts to facilitate further review among the co-authors. Subsequent manual reviews were conducted by three authors (NE, PR, and EK) for all remaining articles to identify articles for inclusion/exclusion. In cases of uncertainty among the three authors (NE, PR, and EK) concerning inclusion/exclusion following their reviews of titles, abstracts, and/or full papers, a fourth author (RH-S) was consulted to render a final decision to include/exclude any article.

Quality assurance assessment

The PRISMA checklist and reporting guideline was used to support our analysis and guide our reporting of studies evaluating the effects of *CYP2D6* PGx testing as an intervention (see Supplementary Figure S1). Due to the differences in study objective, design, and reporting strategies,

two distinct tools were applied to assess study quality and risk of bias, each suited to different study types. The Newcastle-Ottawa Scale (NOS) was used for non-randomized studies [10]. The A comprehenSive tool to Support rEporting and critical appraiSal of qualitative, quantitative, and mixed methods implementation reSearch outcomes (ASSESS) tool was also used for the remaining studies that did not fit the NOS criteria [11]. This dual approach ensured that each study was evaluated using the most appropriate criteria based on its methodological design. While individual studies' sample size information was extracted as part of data analysis, sample sizes were not used to evaluate evidence-strength of studies nor did evidence-strength formally impact studies' individual influence on final recommendations.

Evaluation of selected studies

We assessed studies both quantitatively (descriptive analysis using Microsoft Excel) through weighted average comparisons of extracted data elements, described below, and qualitatively (single layer, bottom-up topic modeling) to identify categorical themes collectively across all studies. Weighted, as opposed to unweighted, averages were used to account for variance in sample size across studies. Two authors (PR and EK) conducted an initial assessment of descriptive statistical information presented in each study. Those two authors developed categorical themes for discussion first with a third author (NE) following final discussion with a fourth author (RH-S). Themes and subthemes were refined until >95% agreement was reached among all four authors.

Data extraction

The following data, when present, were extracted from each study:

- Author/year;
- Aims and purpose of the study;
- Drug-biomarker pairs along with associated drug classes and therapeutic areas;
- Genes researched in conjunction with the biomarker of interest;
- Number of participants within each study, including those who received PGx testing;
- Participant/patient *CYP2D6* metabolizer phenotype;
- Demographic information: gender/sex, age, race, ethnicity, and genetic ancestry;
- Clinical outcomes following PGx testing implementation;
- Provider and/or patient behavioral outcomes following PGx testing implementations;
- PGx qualitative themes and subthemes.

Three authors (NE, PR, and EK) extracted data from all studies that met the inclusion criteria. Where possible, we calculated weighted averages across extracted data to account for variance in study sample sizes. The accuracy and clarity of qualitative and quantitative findings from extracted data were then confirmed by two senior authors (RH-S and CL).

Results

Study selection and broad characteristics

We identified a total of 218 articles across Google Scholar (n = 188), PubMed (n = 8), Scopus (n = 12), and Semantic Scholar (n = 10; see PRIMSA flow diagram in Figure 2). Upon excluding duplicate articles and articles at broken links, 192 articles remained for initial title and abstract screening. A total of 133 articles were excluded after reviewing titles and abstracts for relevance to the study question, leaving 59 articles sought for retrieval and full text review. Following full text review, 33 articles were out of scope, leaving 25 for final analysis [12–36]. No study presented randomized controlled trial evidence. One study was open-label, non-randomized [23] and five were retrospective, observational in nature [22, 29, 31, 34, 35]. The remaining studies focused on lessons learned from implementing PGx into clinical systems or reported phenotype prevalence in different patient cohorts (e.g., managed care, advanced, cancer, etc.).

Quality assessment of selected studies

NOS scores ranged from four to seven (maximum possible score of eight) with an average score of 6.4 across all selected studies. Two studies, Aka et al. and Bertholim-Nasciben et al., scored at 4 and were the only two studies scoring below 7 [12, 17]. This was due to point reductions on the Comparability (inadequate or lack of study controls) and Outcome (no long-term outcomes follow-up) metrics. ASSESS scores ranged from one to five (maximum possible score of five)—higher scores represent lower risk of bias—with an average score of 4.5. Individual study scores for NOS and ASSESS are available in the Supplemental (Supplementary Tables S1, S2).

Overall quantitative and qualitative assessment

Across all selected studies quantitative data categories were metabolizer phenotypes (n = 10), gender/sex (n = 17), age (n = 14), race (n = 13), ethnicity (n = 4), genetic ancestry (n = 1), and PGx implementation outcomes (n = 7). Qualitative findings comprised of seven subthemes across two overarching themes. Theme 1 comprised of four (4) *CYP2D6-Specific* subthemes centered on genes researched alongside *CYP2D6* (n = 20), metabolizer phenotypes (n = 17), gene sequencing strategies

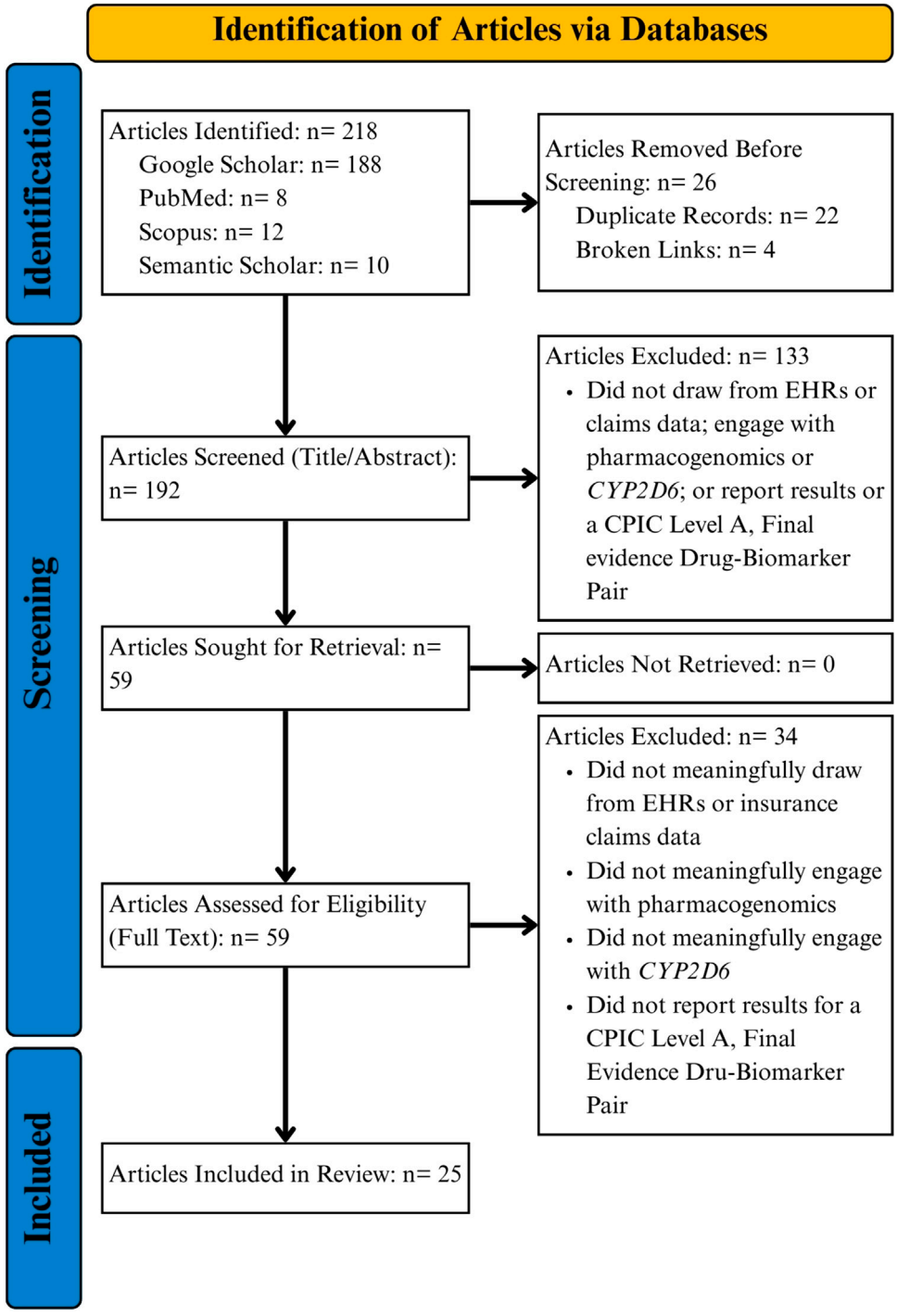

FIGURE 2
PRISMA flowchart.

(n = 9), and phenoconversion (n = 3). Theme 2 comprised of three *PGx and RWD Specific* subthemes centered on patient sub-groups in retrospective RWD analysis (n = 19), PGx implementation considerations (n = 8), and the range of health care provider decisions following PGx testing (n = 6). Ancillary quantitative and qualitative summaries for selected articles are provided the Supplementary Tables S3–S5.

TABLE 1 *CYP2D6*-Impliacted Therapeutic Areas and Drug Classes Mentioned Across 25 studies published as of June 2024.

Therapeutic areas (n)	Drug classes (n)	Drugs (n)
Analgesia (21)	Opioid (21)	Codeine* (21)
		Tramadol* (18)
Psychiatry (17)	Selective Serotonin Reuptake Inhibitor (SSRI) (11)	Paroxetine* (11)
		Vortioxetine* (1)
	Tricyclic Antidepressant (TCA) (11)	Amitriptyline* (11)
		Nortriptyline* (8)
	Selective Norepinephrine Reuptake Inhibitor (SNRI) (5)	Atomoxetine (5)
Oncology (7)	Selective Estrogen Receptor Modulator (SERM) (7)	Tamoxifen* (7)
Gastroenterology (6)	5-HT3 Receptor Antagonist (6)	Ondansetron* (6)

TABLE 2 Articles reporting PGx clinical outcomes.

Author	Study purpose	Outcome description	Study size	Study design	Therapeutic area
Chanfreau-Coffinier et al. [22]	Determining DGI risk among opioid users	Veterans with chronic opioid use were more likely to have higher care utilization. Veterans with chronic opioid use were more likely to receive CYP2D6-implicated medications	2,438,534	Observational, retrospective	Analgesia
Dorfman et al. [23]	Impact of PGx medication management	Following PGx testing, medications were changed and drug-therapy problems (DTPs) resolved	985	Open label, non-randomized	Psychiatry and Analgesia
Michaud et al. [29]	Assessment of PGx variants and medication risk scores impact on healthcare costs	High medication risk score with PGx variant increases risks of treatment failure, health care expenditure, and increased opioid doses	4,088	Observational, retrospective	Agnostic
Nichols et al. [31]	Calculates potentially avoidable adverse drug events with PGx	Several adverse events for ondansetron (nausea/vomiting), codeine (hypoanalgesia/sedation), and paroxetine (persistent depression)	193	Observational, retrospective	Oncology
St Sauver et al. [19]	Assessed *CYP2D6* phenotypes with adverse drug events	UM and PM patient were more likely to experience poor pain control and experience adverse symptoms, which disrupted treatment regimens and undercutting prescriptions	257	Observational, retrospective	Analgesia
Takahashi et al. [35]	Assessed hospitalization risk for UM *CYP2D6* phenotype	In a patient cohort, found 47% of UM were hospitalized compared to 30% NMs and 62% of UM visited emergency departments compared to 49%	929	Observational, retrospective	Agnostic

Identified drugs, therapeutic areas, and clinical outcomes

The foundational results from the analyzed literature are the drugs (and associated drug classes and therapeutic areas) implicated in *CYP2D6* PGx testing. Studies were summarized according to each drug, drug class, and therapeutic area associated with *CYP2D6* testing. Therapeutic areas were tabulated based on drugs and drug classes associated with *CYP2D6*, rather than all therapeutic areas mentioned within a given article.

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TABLE 3 Genes Researched in Conjunction with *CYP2D6* across 25 studies published as of June 2024.

Other genes	*n*
CYP2C19	17
CYP2C9	13
SLCO1B1	8
CYP3A5	7
CYP3A4	6
VKORC1	6
TPMT	5
HLA-B	5
CYP4F2	3
CYP1A2	3
DPYD	3
CYP2B6	3
NUDT15	2
CYP4F1	2
Other biomarkers[a]	1

[a]*ATM, F5, UGT1A1, CYP1A1, CYP2A13, CYP2A4, CYP2A6, CYP2C8, CYP2E1, CYP2J2, CYP2R1, CYP2S1, CYP2W1, CYP3A43, CYP3A7, HLA-A, SLC15A2, SLC22A2, SLCO2B1.*

CYP2D6-drug pairs with CPIC Level A, Final evidence were identified across studies selected for in our literature search across four therapeutic areas: analgesia (n = 21), psychiatry (n = 17), oncology (n = 7), and gastroenterology (n = 6). Nine (n = 9) drugs implicated in *CYP2D6* PGx testing were explored. Of these nine *CYP2D6*-drugs, eight had existing FDA PGx Biomarker labeling section. The two most researched drugs were codeine (n = 21) and tramadol (n = 18)—both opioids. Five drugs across three drug classes were within the therapeutic area of psychiatry: selective serotonin reuptake inhibitors (SSRIs, n = 11), tricyclic antidepressants (TCAs, n = 11), and selective norepinephrine reuptake inhibitor (SNRIs, n = 5). All other therapeutic areas had drugs belonging to one drug class (see Table 1). Atomoxetine, a psychiatric SNRI evaluated in five (5) studies, was the only drug without an FDA PGx Biomarker labeling section.

Six (6) of 25 articles reported PGx clinical outcomes, considered to be a "measurable change in symptoms, overall health, ability to function, quality of life, or survival outcomes" in relation to PGx testing [37] Table 2). Of these six studies, three (3) focus on analgesia, with other investigated therapeutic areas being psychiatry and oncology. There was no consistent clinical outcome of interest investigated. All but one were observational, retrospective studies.

Theme 1: variation in CYP2D6 biomarker testing and interpretation

Theme 1 comprises subthemes that are: 1.1, Single gene sequencing vs. gene panel sequencing for PGx analysis (n = 9); 1.2, Genes researched along with CYP2D6 (n = 20); 1.3, Metabolizer phenotypes and inconsistent phenotype categorization (n = 17); and 1.4, Drug-gene interactions (natural genotype) vs. drug-drug-gene interactions (phenoconversion) (n = 3).

Subtheme 1.1: single gene sequencing vs. gene panel sequencing for PGx analysis

Across nine (9) studies, investigators alternated between relying on single gene sequencing vs. gene panel sequencing for PGx analysis [13, 14, 16, 17, 22, 24–26, 33]. Seven studies relied solely on panel sequencing [14, 16, 17, 24–26, 33] and one only on single-gene sequencing [13]. The last studies reviewed a dataset with both kinds of tests, within which 48 of 90 tests were single-gene [22]. Some studies highlighted benefits and drawbacks of testing strategies. On one hand, single gene sequencing allowed for targeted assessment of individual genes, typically performed after adverse drug events had been observed. On the other hand, gene panels provided researchers with a broader understanding of participants' overall PGx situation. Panels were most often performed as a part of pre-emptive—before adverse drug events occurred—PGx testing. When gene panels were used, other genes were researched along with *CYP2D6* because of PGx evidence within guidelines and/or literature, rather than because those genes happened to be on the same panel as *CYP2D6*.

Subtheme 1.2: biomarkers researched along with CYP2D6

Twenty (20) studies researched other biomarkers alongside *CYP2D6* [12–20, 22–26, 29–33, 36]. Across all studies, 33 distinct biomarkers were reported (see Table 3). Biomarker testing outcomes most frequently researched alongside *CYP2D6* were *CYP2C19* (n = 17), *CYP2C9* (n = 13), and *SLCO1B1* (n = 8). Across the 33 genes, Cytochrome P450 genes were researched more often (n = 20) than those outside the CYP family (n = 13).

Subtheme 1.3: metabolizer phenotypes and inconsistent phenotype categorization

Of the 25 studies, 17 [15, 17–19, 21–24, 26–28, 30, 31, 33–36] qualitatively discussed *CYP2D6* phenotypes and 10 [14, 17, 22, 23, 26–28, 33, 35, 36] provided quantitative data. There were four primary phenotype categories. Importantly, these categories represent general metabolizer phenotypes rather than specific 'at-risk' phenotypes for specific biomarker-drug pairs. Individuals with abnormally low drug metabolism levels were Poor Metabolizers (PM). Intermediate Metabolizers (IM) had higher drug metabolism than PMs but did not metabolize at

TABLE 4 Weighted average percentage of patients with each CYP2D6 phenotype across all drugs.

Phenotype	Percentage without Verma et al. [36]	Percentage with Verma et al. [36]	Impact of including Verma et al. [36]Δ
PM	4.9%	3.6%	−1.3%
IM	35.5%	24.9%	−10.6%
NM	56.8%	37.9%	−18.9%
UM	7.1%	Not applicable	Not applicable

Changes represented with a delta symbol.

normal levels. Those who did metabolize normally were Normal or Extensive Metabolizers (NM or EM)—this review uses the more common classification of NM. The last major phenotype category was Ultrarapid Metabolizer (UM), when individuals metabolized drugs at a much higher rate than normal.

Outside the common categorizations, two studies included three intermediary categories: poor-to-intermediate, intermediate-to-extensive, and extensive-to-ultrarapid [26, 35]. Other studies outlined a Rapid Metabolizer (RM) category but only one reported numbers and percentages for that category—3 of 91 participants (4.4%) [14]. Studies that recognized the RM phenotype, but did not present corresponding data, experienced technical limitations which prevented the analysis of copy number variants (CVNs) and could not identify or differentiate between UMs and RMs. Because RM data was only reported once within the literature, and other intermediary categories only twice, they are considered outlier categories.

Excluding outliers, we calculated weighted averages for PM, IM, NM, and UM groups among study groups (see Table 4). Using weighted averages accounted for the wide range of study sizes and mitigated outsized impacts from any one study. Approximately 92% of participants had normal or intermediate metabolism for *CYP2D6*-implicated drugs and 12% were either poor or ultrarapid metabolizers. Importantly, due to inconsistent reporting of metabolizer phenotype across studies, the phenotype percentages do not add up to 100%.

Despite weighting, the total results were evaluated with and without findings from Verma et al., because 66.3% (n = 28,778) of participants in Verma et al. had incomplete phenotype data [36]. This percentage was calculated by combining three of the study's *CYP2D6* result categories: 2,701 (6.2%) ambiguous results, 12,541 (28.9%) indeterminate results, and 13,536 (31.2%) participants with no results. When included, the missing data dramatically decreased the weighted average calculations for each metabolizer category (Table 4). The study did not report UM rates or any outlier categories.

Subtheme 1.4: drug-gene interactions (natural genotype) vs. drug-drug-gene interactions (phenoconversion)

DGIs are when a specific drug interacts with a gene by either inhibiting or inducing it [15, 28]. In this case, implicated drugs taken by individuals with a *CYP2D6* variant resulted in abnormal or adverse drug responses due to altered drug metabolism by the CYP2D6 protein. Alternatively, DDGIs occur when one drug inhibits or activates a given gene, altering the efficacy or safety profile of a second drug [22]. Importantly, an individual may not necessarily have a variant form of *CYP2D6* but, because of a DDGI, may phenotypically experience variant-like drug metabolism. This is also known as phenoconversion. We identified DGIs and DDGIs as important, but distinct, areas of PGx research and treatment. Because phenoconversion leads to genotypically wild-type patients expressing variant phenotypes, PGx testing was considered useful for clearly distinguishing between these two sub-groups. One study determined phenoconversion is responsible for a majority of PM phenotypes, reporting an increase by "at least 2-fold" in PMs "after considering phenoconversion" [14].

Theme 2: PGx test implementation and data considerations

Studies along Theme 2 (n = 22) comprised of three (3) subthemes [12–20, 22, 25–36]. Theme 2.1 describes the range of healthcare provider decisions following PGx testing. These include accepting PGx-based recommendations generally, specific medication modifications, and no changes in prescribing behavior. Theme 2.2 addresses patient sub-groups in retrospective RWD analysis, identifying trends regarding three sub-group identifiers: gender and sex (2.2.1); race, ethnicity, and genetic ancestry (2.2.2); and age (2.2.3). Theme 2.3 focuses on results about PGx implementation into clinical care, decision-making, and EHRs. From this theme, three common barriers to PGx implementation were identified: data inoperability (2.3.1), cost and reimbursement (2.3.2), and limited PGx knowledge (2.3.3). Additionally, Subtheme 2.3.4 outlines different implementation strategies between pharmacists and physicians.

Subtheme 2.1: range of healthcare provider decisions following PGx testing

Six studies under Subtheme 2.1 described provider responses to PGx-based recommendations [13, 14, 16, 22, 24, 30]. All studies assessed at least one other gene in addition to *CYP2D6*

TABLE 5 Articles reporting proportion of acceptance of pharmacogenomic test-based recommendations.

Article title	Prescribing recommendations	Accepted (%)
Arwood et al. [14]	62	54 (87%)
Bain et al. [16]	436	388 (89%)
Mills & Massmann [30]	170	153 (90%)
Total:	668	595 (89.1)

and do not differentiate between them when discussing recommendations. Within the literature, "recommendations" were suggested clinical actions based on a patient's PGx profile, their prescribed medications, and established PGx medical research and guidelines. If studies specified what kind of recommendation was given, it was for a medication change. In some studies, recommendations were pharmacist-provided, whereas other studies involved computer-assisted or -prompted recommendations based on pre-defined rules (e.g., CPIC guidelines for specific medications) [16]. A provider's "acceptance" of a recommendation referred to whether or not they followed the clinical suggestion. The study involved an assessment of EHR and claims data before and after a given recommendation to determine if a physician accepted or did not accept a PGx recommendation. One study, which relied solely on insurance claims, noted this methodology limited their ability to definitively confirm "whether the result of the. . .test guided the treatment choice" [13].

Three studies provide quantitative data on general acceptance of PGx-based recommendations [14, 16, 30]. In total, 668 PGx-based recommendations were made and 595 (89.1%) were accepted (see Table 5). Two studies (n = 2) researched how PGx testing impacted medication change orders specifically [13, 22]. One reviewed claims data and compared when PGx tests were ordered, results received, and when patients filled their prescriptions [13]. Of the 1,059 patients, 540 (51%) filled their prescriptions before test results were delivered. The study reported that the clinicians did not rely on PGx results for the first round of prescriptions and used testing to inform future prescribing decisions. Another study investigated medication changes following PGx testing using EHR data [22]. Of the 90 *CYP2D6* tests identified, 34 (38%) involved provider-facilitated medication changes.

Finally, one study associated the type of healthcare provider with the rate of PGx recommendation acceptance [30]. The investigators assessed pharmacists, physicians, and advanced practice providers and found 100% (23/23) of pharmacists, 91% (88/97) of physicians, and 84% (41/49) of advanced practitioners followed PGx recommendations.

Subtheme 2.2: patient sub-groups in retrospective RWD analysis

Patient demographic information varied widely, with many studies missing key demographic details. Of the 25 articles/studies included in our full-text analysis, 19 [13–18, 20, 22, 23, 25–29, 31, 33–36] contained at least some demographic information, which our team considered to include total study size, gender/sex, age, race and ethnicity, and genetic ancestry data. The most consistently reported demographic information across studies were total study size (n = 19), gender/sex (n = 17), and average participant age (n = 14). Study sizes ranged widely, from 30 participants to 2,436,654 [22, 27, 28]. The median participant group size was 985 (IQR = 20,157.5) with study-level sample sizes reported in Supplementary Table S5.

Subtheme 2.2.1

A lack of differentiation for gender and sex (sub-)categories existed within the literature (n = 17) [13–18, 20, 22, 25–29, 31, 33, 35, 36]. Most studies reported gender and sex-based information as a single category, though studies reported sex and gender interchangeably. Studies in general did not discuss possible differences between self-reported gender in EHRs and genetically determined sex. One study discarded biobank samples in the event "genetically defined sex and EHR reported sex" showed "discordance" [36].

Reviewing the gender/sex data, females (58%) were represented more than males (42%) within the literature. The greatest difference between females and males within a study, drawn from a sub-group of 90 *CYP2D6* analyzed participants, was 19 females (18%) and 74 males (82%) [22]. The smallest ratio disparity was 31,781 females (55.7%) and 25,277 males (44.3%) [33].

Subtheme 2.2.2

The second subtheme identifies a lack of racial, ethnic, and genetic ancestry data within RWD sources. The literature categorized racial demographics into the following groups: White or Caucasian, Black or African American, Asian or Asian American, Native Hawaiian/Pacific Islander, Biracial, or Unknown. Ethnic categories, when considered separately from race, were Hispanic/Latinx and Ashkenazi Jews. Thirteen (13) studies reported some form of self-reported racial/ethnic information, both qualitatively and quantitatively [14–18, 22, 25–28, 31, 33, 36]. The categories Native Hawaiian or Pacific Islander, Biracial, and Ashkenazi were only reported once; weighted averages for all other categories are reported below (Table 6). Like metabolizer phenotype calculations, racial data

TABLE 6 Weighted averages per racial and ethnic categories.

Racial or ethnic category	Weighted average
White	74.5%
Black or African American	10.2%
Asian or Asian American	1.8%
Native Hawaiian/Pacific Islander	0.1%
Unknown	13%
Hispanic	4.3%
Non-Hispanic	95.7%

were reported inconsistently across studies and therefore do not equal 100% when added together.

Study participants were most often majority White or Caucasian with the exception of one study [15]. Six studies comprised of 85% or more data from White participants. An average of 13% participants, across 11 studies, had Unknown racial data. Black or African American was the next most represented racial group, although making up an average of only 10.2% of the study population. Notably, this calculation does not include demographic data from one study due to the fact that the study combined, without specific rationale, "Black or African American" with "Biracial" (i.e., only two categories, "White" and 'Black or Biracial', were reported [27]. The last reported racial categories were Asian or Asian American, 1.8% (n = 4) and Native Hawaiian or Pacific Islander, 0.1% (n = 1).

Four studies reported ethnicity data, which largely distinguished between Hispanic/Latinx and non-Hispanic/Latinx [14–16, 36]. An average of 4.3% of participants belonged to the category. One article reported Ashkenazi Jewish ethnic data—0.4% (146/36,511) of participants within the study made up this sub-group [15].

Genetic ancestry data was reported in one study [36]. Of the study's 1,896,012 participants, 69.2% (n = 1,314,800) had European ancestry, 25.7% (n = 488,300) were African, 1.6% (n = 30,400) were East Asian, 1.3% (n = 24,700) were South Asian, 1.3% (n = 24,700) were Mixed American, and 0.9% (n = 17,100) of participants had Unknown genetic ancestry.

Subtheme 2.2.3

The third subtheme describes the relatively greater proportion of participants aged 65 or older and underrepresentation of participants under 18-years-old. While average age was consistently reported within the literature (n = 14), individual studies differed in reporting 'average age' as a mean or median calculation [13, 14, 16–18, 20, 22, 23, 25–27, 29, 31, 35]. The weighted mean age calculated by our team across studies was 49.4; the median was 53.6. Three studies had average ages of 65 or older, and five studies had averages below 50.

Three studies assessed pediatric patient populations in some capacity [12, 24, 32]. One research team expressed being "challenged by the lack of drug/gene evaluations in pediatric patients" and the need to draw conclusions from research based primarily on adults as the motivation for their investigation into pediatric populations [32]. Studies assessing pediatric populations called for addressing "an urgent unmet need in pediatrics to refine and develop precision actionable PGx guidance" [24]. However, because *CYP2D6*'s expression reaches stable "levels equivalent to adults during infancy," one study emphasized focusing on possible impacts of *CYP2D6*-implicated drugs "used in children for different indications than in adults" [12].

Subtheme 2.3: PGx implementation efforts for clinical care, decision-making, and EHRs

Following findings on participant demographic information, our team explored PGx implementation efforts for clinical care, decision-making, and EHRs (Subtheme 2.3). Of the four subthemes, three identify different technological (2.3.1), financial (2.3.2), and knowledge (2.3.3) implementation barriers. Subtheme 2.3.4 outlines diverging strategies for which kind of provider—physicians or pharmacists—led a health system's implementation effort.

Subtheme 2.3.1

When attempting to integrate PGx test results into patients' medical records, data inoperability issues between PGx test results and EHRs commonly occurred. Five studies qualitatively addressed this subtheme [16, 20, 24, 25, 32]. The study discussed that PGx test results are most often returned as unstructured data, like PDFs. EHRs, on the other hand, operate using structured data. Due to mismatched data types, PGx test results often could not be directly nor automatically uploaded to EHR systems. This hurdle, studies reported, prevented providers from easily integrating test results into their clinical decision workflow. One health system contracted with an external software company to develop a program that transformed unstructured PGx data into a structured format to address this issue [24]. The study team developed a structured number system matched to specific metabolism levels and generated pre-alerts based on the severity of possible DGIs.

Subtheme 2.3.2

The second observed implementation challenge were high costs of PGx testing and testing reimbursement barriers. Four studies—all published during or after 2020—discussed this difficulty [14, 24, 25, 32]. These studies found PGx tests, particularly when those tests were pre-emptive, had limited insurance coverage. One study reported reimbursement issues as a barrier to PGx test utilization, but did not "have sufficient data to understand reimbursement based upon patient insurance" differences [24].

Two studies provided quantitative data on how insurance coverage affected patients' willingness to receive PGx testing. One utilized an internal medicine clinic to study PGx clinical adoption [14]. The clinic was grant funded for the first 2 years of the clinic's operation. During this time, 91 patients were seen, 84 of which were recommended for PGx testing. Of these, 77 followed through with testing and seven (8.5%) refused due to costs. In its third year of operation, the clinic began billing insurance and saw 36 patients. For the 33 patients who were recommended testing, eight (23%) declined any kind of testing and two (6%) participants sought external PGx testing. The second study followed 69 patients who were recommended PGx testing [25]. Here, 68 (98.6%) of patients received testing and only one (1.4%) refused. However, that one patient "refused testing due to costs"—the out-of-pocket expenses were generally $300 or less [25].

Subtheme 2.3.3

A general lack of PGx knowledge in clinicians and patients was the final identified implementation barrier, present in eight studies [16, 18, 20, 22–24, 26, 32]. Within healthcare provider study groups, clinicians often felt as if they did not have a deep or satisfactory understanding of pharmacogenomics. Limited provider knowledge resulted in diminished "engagement" with PGx testing from clinicians [26]. Regarding clinicians' responsiveness to clinical decision support tools, providing "education on the scientific basis of pharmacogenetics" was "essential to improve the prescribing physicians' understanding of the clinical significance of PGx alerts" [23]. When that education was integrated into clinical care at the point-of-care, those modules were "well received by clinicians and pharmacists" [21]. Only one study reported on patient understandings of PGx information. In this study, 33% of patients either understood their PGx results a little or not at all [19].

Subtheme 2.3.4

The last subtheme did not focus on challenges with implementing PGx testing into clinical care, but rather general implementation strategies. Out of nine studies, two kinds of methods emerged: centralized, pharmacist-led clinics and decentralized, physician-led prescription decision-making [14, 16, 19, 20, 23–25, 30, 32]. The first method involved establishing a clinic run by a pharmacist with a specialty in pharmacogenomics (n = 4) [14, 16, 25, 32]. Physicians could refer patients who they thought might benefit from PGx testing to the clinic. While individual study sites differed, clinics followed the same general protocol. First, patients would meet with the pharmacist for an initial assessment, where the pharmacist would review their medical history (from both the EHR and patient) to decide whether or not to recommend PGx testing. If recommended, patients would receive testing and meet with the pharmacists when the results were available. Often, both the patient and their original provider would attend this second meeting. The pharmacist would review the test results, discuss its implications on whatever medication(s) a patient was taking or may take in the future, and provide a recommendation. The patient's physician would then decide whether or not to accept the recommendation. Pharmacists effectively provided clinician and patient education about "the applications of PGx in clinical practice" [16].

Despite overarching similarities, individual PGx clinics were structured and operated differently. Some had only one pharmacist on staff, while others had several. Others met with patients only, physicians only, or had both present. The last major difference in clinic structure was who was able to submit clinic referrals. Only one study noted that 46% (32 of 69) of patients referred themselves [25].

Five studies reported a decentralized PGx implementation approach, with physicians individually ordering PGx tests, interpreting the results themselves, and subsequently making treatment decisions [18, 20, 23, 24, 30]. Often, physicians were supported by PGx-based clinical decision-making software, which provided recommendations based on (1) guidance from established clinical frameworks or (2) patients' individual test results.

Discussion

Our study holds several key findings that will be useful and informative for clinicians, epidemiologists, health researchers and economists, and regulators in the field of evaluating RWE to contextualize the value of *CYP2D6* PGx testing. First, of the ten *CYP2D6*-drug pairs with strong and final (CPIC Level A, Final) evidence, nine (90%) were identified in our review; tropisetron, an oncology drug that helps with nausea and vomiting, was not identified [38]. Additionally, only one drug among those nine, atomoxetine (a psychiatric drug), did not have a corresponding FDA PGx Drug label. This demonstrates a strong emphasis on investigating drug-gene pairs with known PGx risks within RWE literature. And, as seen in the range of healthcare provider decisions following PGx testing theme, when presented with PGx recommendations for strong evidence pairs, providers most often incorporate those recommendations into their decision-making. Combined with the six studies that reported clinical outcomes, only nine of 25 studies had findings relevant to clinical settings [14, 16, 22, 23, 29–31, 34, 35]. The remaining studies largely focused on either lessons learned from implementing PGx into clinical systems or reported on phenotype prevalence in different patient cohorts (e.g., managed care, advanced cancer, etc.) [12, 13, 15, 17–21, 24–28, 32, 33, 36].

Second, most studies (21 of 25) focused on two drugs used in pain management, likely reflecting a heightened scrutiny due to the ongoing opioid crisis [12, 14–24, 26–29, 31, 33–36]. Pain management often involves complex medication regimens and PGx testing can identify genetic variations that affect drug metabolism, efficacy, and safety. Additionally, 17 studies explored

five different drugs relevant to psychiatry, demonstrating a considerable interest in how PGx testing might enhance treatment strategies in this field [12–19, 21, 22, 24, 25, 31–33, 35, 36]. Given most drugs identified are within the therapeutic scope of psychiatry, our findings are of particular importance for this field as it struggles with issues like workforce shortages that impact ability to diagnose and treat psychiatric patients in need [39, 40]. Patients in psychiatry often endure extensive trial-and-error phases when prescribed medications, characterized by poorly managed symptoms and adverse drug reactions, until suitable medications and dosages are identified [41]. Hence, there is a demand for strategies that anticipate or mitigate these adverse reactions and streamline treatment processes. This knowledge holds crucial importance for populations currently underrepresented in clinical trials and/or RWE studies with either an ability or potential to guide treatment protocols for managing the mental health of diverse patient populations, including but not limited to early mental illness intervention.

Third, RWD/E can be an important tool to enable inclusion of subgroups traditionally underrepresented in research. US Census data reports 75.3% of the population is White, 13.7% is Black, 1.3% are American Indian and Alaska Native, 6.4% are Asian, and 0.3% are Native Hawaiian and Other Pacific Islander [42]. Compared to demographic data from our review, White participants were researched comparably to the broader population at 74.5%. At 10.2% of research participants, Black patients were researched at a somewhat lower level. Asian patients were researched roughly 3.5 times less than their broader population make up. Native Hawaiian or Pacific Islander patients' research was similarly disproportionate. Native Americans and Alaskan Natives, who compose 1.3% of the population, were not researched in any identified study. Given White and Black patients close to their proportion in the broader U.S., evidence for these *CYP2D6*-drug pairs is likely generalizable. But, for other patient subgroups with limited (or no) representation within this review, evidence may not be generalizable. This can reinforce treatment inequities, perpetuate data bias resulting from overestimations, and further exclude subgroups from benefits of the knowledge and innovation derived from research. However, as mentioned above, key gender/sex and racial/ethnic data were often unavailable in datasets. Furthermore, we found that pediatric populations are underrepresented in PGx research; only 3 of 25 studies reported on this patient population. Effectively utilizing RWD/E in PGx requires mitigating this tension to develop more inclusive/generalizable findings. Further, research should be more inclusive of individuals with varied sex chromosomes regardless of gender. Additionally, genetic ancestry was only investigated once, despite large impacts on population pharmacogenomics findings [43]. Other research programs, like the U.S. All of Us Research Program, have revealed health disparities driven by genetic ancestry [44].

Fourth, researchers largely emphasized implementation outcomes from the clinician's perspective—both in terms of PGx knowledge and response to PGx-based recommendations. This clinician perspective preference may blur the distinction between changes in prescriber behavior and real-world patient outcomes. While it is critical to understand how clinicians adopt and apply PGx test results, it is equally important to understand how patient outcomes may or may not improve. PGx guidelines need to be informed by evidence, and researchers must take those guidelines and see how they measure in real-world based on both clinician and patient experiences with PGx testing. Another way to bridge this gap is for research to focus on patient-centered real-world outcomes, such as changes in pain levels, quality of life, or incidence of adverse drug reactions following the implementation of new practices.

To move the field forward, research subsidies can be helpful to address patient expenses associated with PGx testing. As seen in our review, despite increased coverage of PGx testing, research participants vary in responses to PGx testing costs before and after grant funding ends with rates of commercial and no testing increasing after grant funding runs out [45]. Identified studies were carried out in clinical settings, which already holds cost barriers, rather than strictly research settings. By providing financial support for research into PGx testing, subsidies can help cover these costs, in turn making the testing more affordable for patients. This financial assistance can enable broader implementation of PGx testing in clinical settings, ensuring that more patients benefit from personalized medicine approaches. It also encourages further research and development in the field, potentially leading to innovations that could reduce the cost of testing over time.

Despite the recognized benefits of improving sub-group representation in RWE research, these findings highlight persistent gaps in engaging traditionally underrepresented communities. Future RWE studies on *CYP2D6* and other pharmacogenomic biomarkers should be done in partnership with communities that are engaged in work focused on 1) improving the translation of study results across patient communities, 2) exploring the effect of *CYP2D6* biomarker testing to help address priority health concerns across one or more therapeutic areas described herein, and/or 3) building community-based participatory precision medicine research training or capacity. In fact, meaningful, trustworthy, and sustained community engagement across the RWE study development and implementation process will be critical to help characterize previously unknown *CYP2D6* variants of uncertain or undefined significance, such as those identified within the All of Us Research Program [46].

There are limitations to our study and findings. Given the *CYP2D6* phenotype is reliant on copy-number and structural variation and there are certain CYP2D6 star-alleles that do not define or include structural variation or a gene deletion, our findings do not provide such insight across the therapeutic areas noted herein [36]. Future work should continue to address this limitation by considering published work on this topic [47–49]. The Pharmacogene Variation Consortium, or PharmVar, for example, offers usable nomenclature and summaries describing structural variations of human *CYP2D6*, as well as recommended terms and definitions for clinical and research reporting, which can be useful to

support ongoing work [50]. Additionally, key demographic data were reported inconsistently within the literature, leading to cumulative averages for racial and metabolizer phenotype data not equaling 100%. This represents a broader need for consistency in demographic reporting. A third limitation is that, upon inclusion in the review, the strength of evidence presented in each study (e.g., randomized control trial vs. observational, or small vs. large sample size) was not systematically differentiated or measured. Future studies should explicitly categorize studies based on evidence strength and assess how evidence strength influences author-proposed recommendations. Lastly, future research should employ more comprehensive keyword strategies (e.g., including variations such as "claims database" and "claims dataset") to ensure broader capture of relevant literature.

Our findings can be used to substantiate the need for ongoing policy efforts intended to advance pharmacogenomic research and testing in real-world settings, like the most recent bipartisan legislation in the US called the Right Drug Dose Now Act [51]. The Act intends to accomplish the following key goals: 1) "update the National Action Plan for Adverse Drug Event Prevention by integrating advancements in pharmacogenomic research and testing," and 2) enhance EHRs "with pharmacogenomic information to improve patient care and reduce adverse drug events" [51]. Therefore, such policy efforts hold significant value and serve as critical steps to help drive RWE research focused on *CYP2D6* and other pharmacogenomic biomarkers implicated across a range of therapeutic areas.

Conclusion

Pharmacogenomic testing and research represents a beneficial way to advance precision medicine initiatives and improve patient care. Our work demonstrates that despite challenges with and varied strategies for implementing PGx into routine clinical care, when implemented, PGx testing for *CYP2D6*-drug pairs with high, established evidence can successfully support providers in their decision-making processes. Additionally, EHRs and insurance claims are useful data sources for establishing PGx testing effectiveness in real-world settings. Based on our findings, we recommend expanding patient sub-group analyses in future research to improve generalizability, exploring patient-centered real-world outcomes to better contextualize PGx-informed treatment, and investigating the effectiveness of PGx testing where evidence is limited or conflicting for *CYP2D6* and associated pharmaceuticals.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Author contributions

PR: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Writing – original draft, Writing – review and editing. EK: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Writing – original draft, Writing – review and editing. NE: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Writing – original draft, Writing – review and editing. CL: Investigation, Methodology, Supervision, Writing – review and editing. RH-S: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Validation, Supervision, Writing – original draft, Writing – review and editing. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The author(s) declare that no Generative AI was used in the creation of this manuscript.

Supplementary material

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A review to determine regulatorily and reimbursement successes of studies conducted using data from Canadian patient support programs based on the real-world evidence guidelines published by Canadian drug agency and health Canada

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Introduction: Patient Support Programs (PSPs) are growing globally to support early reimbursement, disease and medication dosing management. In Canada, the lack of public health support has promoted the rapid expansion of company-supported disease-specific or drug-product-specific PSPs. Data collected from these programs generate unique Canadian data serving as a valuable source of real-world data (RWD), generally adopted in EU and US as a source of evidence generation. This review evaluates the suitability of PSP data for regulatory or reimbursement submissions, based on recently published Real World Evidence guidelines by the Canadian Drug Agency (CDA-AMC).

Methods: Peer-reviewed publications evaluating patients with chronic diseases enrolled in a PSP from 1 January 2020, to 31 March 2025, were selected for review. The checklist in the CDA-AMC RWE Guideline was used to measure the quality and suitability of the PSP data.

Results: Nine studies were reviewed against the checklist. Based on the criteria required to inform decision-making, most studies failed to meet key criteria for regulatory submissions. One recently published study, "Therapeutic Drug Monitoring of Infliximab" met most regulatory and reimbursement submission requirements.

Conclusion: Data quality validation, data source transparency, validated methodology to manage study bias, measured or unmeasured confounders, and robust outcome analysis, including sensitivity and quantitative bias analysis, are essential to ensure PSP data analysis results in successful decision-making.

KEYWORDS

regulatory, patient-support-program (PSP), Canada's-drug agency CDA-AMC, RWE-checklist, health Canada

Introduction

Real world evidence (RWE) in medicine is evidence on the use, safety, effectiveness, and cost of health technologies, which is observational data obtained outside the context of randomized controlled trials (RCTs) and generated during routine clinical practice. RWE is generated by analyzing data obtained from patient registries, medical records, or in some cases hybrid trials, pragmatic trials, and late-phase trials [1, 2]. As part of an effort to accelerate medical product development and bring innovations faster and more efficiently to patients who need them, the 21st Century Cures Act was signed into law on December 13, 2016, with the US FDA issuing its "Framework for FDA's Real-World Evidence Program" in December 2018 [3]. Since then, the FDA has updated the guidance multiple times to assist with using RWE to approve a new indication for a drug [4, 5]. Health Canada followed suit and, on April 16, 2019, published the document "Optimizing the Use of Real-World Evidence to Inform Regulatory Decision-Making," acknowledging that the use of RWE in regulatory decisions is increasing globally in the assessment of drug safety, efficacy, and effectiveness [6]. However, upon review of regulatory reports supporting approvals, Health Canada's use of RWE in regulatory decision-making was considerably lower than that of European Medicine (EU) and US FDA [7]. Recently, on April 2023, the Canadian Drug Agency (CDA-AMC) and Health Canada jointly published a submission-ready RWE guidance outlining a step-by-step path to prepare quality documents for submission [8]. The Canadian guidance document, more so than other regulatory guidance, stresses the importance of "Transparency" in every step of the submission preparations. In the United States, the availability of sophisticated databases from electronic health and medical records provides rich platforms for generating RWE based on routine clinical practice outside clinical trials [4, 5]. While the utility of provincial, institutional datasets and registries can provide valuable data sources for RWE, the absence of a unified, pan-Canadian database underscores the importance of PSP capturing nation-wide patient data. Canada and Europe struggle to access large national databases for real-world data to generate RWE. The lack of robust common databases and the strength of patient privacy laws appear to be the most prominent obstacles [9]. In Canada, the arrival of specialty drugs in the past decade has promoted the growth of company-supported, nationwide PSPs. The goal of PSP is to help patients navigate the complex path of the drug reimbursement environment, assist with dosing administrations (including infusions/injections and training), manage side effects, and provide general patient support [10]. Most programs collect patient demographic data, dosing information at initiation and subsequent changes, and critical laboratory data essential to patient management and disease activities. As drug utilization is a key measurement yardstick, most programs collect individual patients' data from the start to the end of treatment, providing essential data for drug adherence and persistence [11]. Moreover, Patient Support Programs (PSPs) offer valuable insights into the early effectiveness and safety profiles of drugs. These programs often provide critical data points, such as optimal treatment duration and potential signals for early withdrawal. This information not only aids in refining treatment protocols but also supports healthcare providers in making evidence-informed decisions that enhance patient outcomes.

With the lack of national and, in some cases, even provincial databases, will pan-Canadian PSP databases be able to fill the gap for the generation of RWE? Several recent publications advocate using PSP data as a source of RWD and assess whether the RWE generated meets regulatory/reimbursement requirements [10, 11]. This publication reviewed peer-reviewed studies from 1 January 2020, to 28 February 2025, based on data from PSPs enrolling patients with chronic diseases. The recently published CDA RWE guidance was used to evaluate the appropriateness of the data source and subsequent analysis for submission purposes.

Methods

Selection of published studies using PSP data

This review focused on peer-reviewed articles published between 1 January 2020, and 28 February 2025. Only company-sponsored PSPs for chronic diseases (non-oncology) were selected to ensure adequate size of the program and sufficiently long follow-up time. As most RWE guidelines were published initially around 2016–2019, peer-reviewed articles published from January 2020 onwards were selected to ensure authors would be familiar with various guidelines published by regulatory or reimbursement agencies. Several search engines were used, including Google, Google Scholar, Pubmed, and Microsoft Academia, to search for peer-reviewed articles. In addition, the websites of Disease- Associations in Canada which list company-sponsored PSPs were reviewed, and the drugs listed were used to search for articles on Google Scholar. Links to Canadian disease associations with PSPs and medications included in PSPs are shown in Supplementary Table S1. A Google Scholar search was performed on all medicines listed in Supplementary Table S1 to capture PSP publications from Jan 1, 2020, to Feb 28, 2025. Nine publications were identified for further analysis (Table 1) [12–20]. The selection was confirmed with another comprehensive database of the Canadian PSP websites listed up to August 2023 [21].

Analysis of the peer-reviewed articles using PSP data

CDA RWE checklist

The nine selected articles and their Supplementary Material were reviewed for regulatory or reimbursement assessment, using the CDA RWE guidance checklist for suitability (Supplementary

TABLE 1 Studies Selected for Evaluations using CDA RWE Submission Guidelines.

Name of the drug (date of publication)	PSP program	Disease indicated	Size of patient population (N)	Effectiveness measured
[a]Infliximab (Remicade) [12] Feb 2025	BioAdvance	Inflammatory Bowel Diseases	13203	Persistence after Therapeutic Drug Monitoring and dose optimization
[a]Videolizumab (Entyvio) [13] March 2024	OnePath	Inflammatory Bowel Diseases	436	Relation between drug concentration and symptoms
[a]Mepolizuman (Nucala) [14] Feb 2024	MYNUCALA	Asthma	275	Treatment outcomes compared between beginning to end of treatment
[a]Brodalumab (Siliq) [14] April 2023	SILIQ patient support program	Plaque Psoriasis	864	Clinical symptoms improvement and persistence
Ustekinumab (Stelara) [16] July 2023	BioAdvance	Inflammatory Bowel Disease	8724	Treatment Persistence
Ixekizumab (Taltz) [17] July 2023	LillyPlus Support Services	Plaque Psoriasis	1891	Treatment persistence
Tofacitinib (Xeljanz) [18] Feb 2023	eXel	Rheumatoid Arthritis	4276	Treatment pattern and persistence
Dimenthyl Fumarate (Tecfidera) [19], April 2022	Biogen ONE	Multiple Sclerosis	12608	Treatment adherence and persistence
Erenumab (Aimovig) [20] August 2021	Go Program	Migraine	14,282	Treatment persistence

[a]Studies grouped under Interventional (outcome based).

Tables S2–S10). The checklist has 12 sections: 1. Study design and research questions, 2. Setting and content, 3. Data specifications, access, cleaning methods and linkage, 4. Data sources, data dictionary and variables, 5. Participants, 6. Exposure definitions and comparators, 7. Outcomes, 8. Bias, confounding, effect modifiers or subgroup effects, 9. Statistical methods, 10. Study findings, 11. Interpretation and generalizability, 12. Limitations. Each item has 2–12 points for consideration. All publications were graded individually against each point with the page number(s) (section numbers if available) from the publication entered under the column "Reported on page" if reported. Under the column "If not reported or applicable, justify why," the entries were NR (not reported) or NA (not applicable) (Supplementary Tables S2–S10).

Three sections have sub-bullets, 2.1 (2), 2.4 (4), 5.6 (3) and 9.3 (7). Sections 2.1, 2.4, and 5.6 could be grouped with one score, whereas, for section 9.3 on statistical methods, the 7 points must be addressed separately as studies vary in statistical stringency. The total score for the checklist is 103. Meanwhile, the score for NA should stay relatively consistent with the articles reviewed as the settings are based on company/drug-oriented PSPs. The lower score on NR represents better compliance with the RWE checklist. Each article was scored separately and unbiasedly (Tables 2, 4).

Articles selected for analysis

Following FDA guidance [3, 4], the nine articles can be grouped under the Interventional and non-interventional categories (Table 1).

Interventional (Outcome based): According to the study protocol, study participants are assigned to one or more interventions to evaluate their value for studying outcomes.

1. Infliximab (Remicade) in Inflammatory Bowel Disease (IBD): Patients' serum levels were measured after induction dosing to determine whether a dose increase was required for longer persistence [12] (Supplementary Table S2).
2. Vedolizumab (Entyvio) in IBD: Patients' serum levels were measured 4–6 weeks after dose induction to evaluate correlation to study effectiveness [13] (Supplementary Table S3).
3. Brodalumab (Siliq) in Plaque Psoriasis: Efficacy outcomes were compared between baseline and end of the study with the drug being the intervention [15] (Supplementary Table S4).
4. Mepolizuman (Nucala) for the treatment of severe eosinophilic asthma symptoms with treatment as the intervention [14] (Supplementary Table S5).

Noninterventional: Participants are identified as belonging to a study group according to the drug or drugs received following routine medical practice and subsequent study outcomes evaluated.

1. Ustekinumab (Stelara) in IBD: A cohort study measuring patient persistence to the study drug [16] (Supplementary Table S6).
2. Ixekizumab (Taltz) in Plaque Psoriasis: A cohort study to assess treatment persistence [17] (Supplementary Table S7).

TABLE 2 Interventional studies selected for evaluations.

CDA guidelines sections (items)	Infliximab in IBD[a]		Vedolizumab in IBD[a]		Mepolizumab in asthma		Brodalumab in PsA	
Reporting Scores	NR	NA	NR	NA	NR	NA	NR	NA
1. Study design and research questions [11]	0	0	1	0	0	0	4	0
2. Setting and content [4]	0	1	1	1	0	1	1	1
3. Data specifications, access, cleaning methods and linkage [10]	0	8	1	8	1	1#	2	8
4. Data Sources, data dictionary and variables [12]	2	2	2	2	1	0#	5	2
5. Participants [3]	1	1	3	1	1	1	3	1
6. Exposure definitions and comparators [8]	0	5	0	5	0	5	0	5
7. Outcomes [7]	1	1	2	1	0	1	1	1
8. Bias, confounding, and effect modifiers or subgroup effects [11]	2	1	11	1	11	0	11	0
9. Statistical Methods [5]	1	1	3	1	3	1	3	1
10. Study findings [8]	2	0	3	0	3	0	6	0
11. Interpretation and generalizability [7]	1	0	2	0	2	0	2	0
12. Limitations [2]	0	0	0	0	0	0	0	0
Total	10	20	29	20	22	10#	38	19

NR, Not Reported; NA, Not Applicable.
[a]With Supplementary Data published. # Sections 3 and 4 applied to this study as multiple data sources and vendor databases were used.

3. Tofacitinib in Rheumatoid Arthritis (RA): A cohort study to study treatment pattern [18] (Supplementary Table S8).
4. Dimethyl Fumarate (Tecfidera) in Multiple Sclerosis (MS): A cohort study to measure adherence and treatment persistence [19] (Supplementary Table S9).
5. Erenumab (Aimovig) A cohort study to measure persistence in patients with chronic and episodic migraine [20] (Supplementary Table S10).

Analysis performed to evaluate submission suitability

The two groups of published articles (interventional and noninterventional) were compared separately based on total scores from the CDA-AMC RWE Checklist. Each article was semi-quantitatively analyzed with the checklist score and descriptively commented on using additional 5 critical factors which summarize the 12 items on the CDA-AMC checklist: 1, Transparency in Data Collection and Reporting (items 1, 3,12); 2, RWD data sources and data validations (item 4); 3, study settings and Study population (items 2, 5, 6); 4, Study Monitoring; and (items 7,10) 5, Robust statistical analysis (items 8, 9,11).

Additional analysis conducted on interventional studies

The four interventional studies were further analyzed to determine suitability for submission purposes. Issues commonly arise in observational research that lead to erroneous interpretations and conclusions, and these issues were examined for the four studies according to "Common Issues with Biostatistics" for cohort studies [21]. These include the adequacy of study design, data quality handling, misunderstanding of confounders, and bias from group membership being attributed to future exposure in a retrospective study, such as immortal time and selection bias (Table 3).

Results

The group under interventional studies had the highest potential for regulatory or reimbursement submissions as they evaluated interventions that could support claims of efficacy or cost-effectiveness [4]. In addition to assessment using the CDA-AMC checklist, the validity of the studies was further examined under "Common Mistakes in Biostatistics" for cohort studies. The non-interventional studies focused on longitudinal follow-up of patients remaining on the drug or the program, and these patient persistence data are generally not candidates for regulatory submissions.

Table 1 lists the nine studies selected for evaluation. The first four studies were grouped under interventional and the last five as noninterventional.

TABLE 3 Evaluations of the design and statistical issues with interventional studies using PSP data [21].

	Subgroups prospectively designed to avoid bias	Adequate handling of databases, patient disposition	Applying sensitivity analysis	Adjusting for confounders and mediators	Account for immortal time bias	Account for selection bias
Infliximab in IBD	No	yes	yes	yes	yes	yes
Vedolizumab in IBD	No	no	yes	no	no	no
Mepolizumab in Asthma	No	yes	no	no	no	no
Brodalumab in Psoriasis	no	no	no	no	no	no

Interventional studies

Table 2 lists CDA-AMC checklist results for the four interventional studies based on PSP databases. The not applicable (NA) scores were the same for the infliximab, vedolizumab, and one point higher for the brodalumab study, as no sensitivity analysis was conducted (Section 8, point 8). The Mepolizumab study merged the PSP database with the ICES (Institute for Clinical Sciences) database, and many items in sections 3 and 4 apply to the study, resulting in an NA score of 10. The Mepolizumab study met all but one of the points for consideration of sections 3 and 4 so the NR score was not impacted compared to the other three products. The infliximab study, scored 10 for not reported (NR) and was the lowest among the four studies, followed by the mepolizumab study 22, the vedolizumab study 29, and the brodalumab study 38. In section 1, the brodalumab study had a higher NR of 4 due to a lack of study protocol, patient disposition chart, study committee, and formal ethics approval. All four studies scored well against Sections 2 and 3 with few NRs. The higher score of Brodalumab than the other three in Section 4 was mainly due to a lack of data transparency. The most significant differences in NR scores between the infliximab study and the other three studies were in Section 8, where selection bias, confounders, effect modifiers, or subgroup effects were discussed. The infliximab study adopted the Cox proportional hazards model with the intervention (therapeutic drug monitoring) as the time covariant to avoid immortal time bias, which was not used by other studies. Quantitative models (Quantitative Bias Analysis) were developed to evaluate the potential impact of measured and unmeasured confounders. None of the other studies mentioned bias or measured or unmeasured confounders. Each patient's outcome in a specific subset in the infliximab study was artificially increased or decreased to determine the magnitude of adjustment required to contradict the observed result on comparisons between patient subsets. Such validation was not conducted in the other studies. Only two studies, the infliximab and the vedolizumab mentioned protocols were designed *a priori* for the analysis, and only two studies, infliximab and mepolzumab, provided patient disposition tables. The brodalumab study scored worse than the others in Section 10 regarding Study Findings as the study did not control for variables during the follow-up period, did not account for patient attrition during follow-up, comparing outcomes of patients that remained in the program to all patients at program initiation was selection bias, leading to erroneous interpretations.

The infliximab study is accompanied by a 200-page Supplementary Material, transparently displaying all the tables used for quantitative bias analysis, subgroup interactions, and sensitivity analysis. The study also completed a STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) checklist, like the CDA-AMC RWE checklist, with satisfactory results. When evaluated against a recent publication on "Common mistakes in Biostatistics" for cohort studies [22], the infliximab study, which did not have a prospective subgroup design, included robust statistical models to address immortal time-bias, potential issues due to confounders and selection bias which were not considered by the other publications (Table 3).

Noninterventional studies

Table 4 shows five noninterventional study scores using the CDA RWE checklist. Due to analogous study designs, the NA (not applicable) scores were similar for the five studies except for Dimethyl Fumarate and Tofacitinib, which showed a higher NA as both did not have study protocols. All studies used persistence as the study outcome, except dimethyl fumarate, which also included adherence as an additional endpoint. The Ustekinumab study in IBD patients [16] exhibited the highest compliance rate of 33 (lowest score in the not reported (NR) category), followed by three studies with the same score, erenumab for migraine treatment [20], tofacitinib for RA [18] and dimethyl Fumarate for MS [19], with the same NR score of 39. Ixekizumab in Plaque psoriasis [17] had the highest score of NR = 48.

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TABLE 4 Noninterventional studies selected for evaluations.

CDA guidelines sections (items)	Ustekinumab in IBD[a]		Ixekizumab in PsA		Dimethyl fumarate in MS[a]		Tofacitinib in RA[a]		Erenumab in migraine	
Reporting scores	NR	NA	NR	NA	NR	NA	NR	NA	NR	NA
1. Study design and research questions [11]	0	1	2	1	3	1	3	1	3	1
2. Setting and content [4]	1	1	1	1	1	1	1	1	0	1
3. Data specifications, access, cleaning methods and linkage [10]	1	8	2	8	2	8	2	8	0	8
4. Data Sources, data dictionary and variables [12]	1	2	6	2	4	3	4	3	2	2
5. Participants [3]	3	2	6	2	2	2	3	2	4	2
6. Exposure definitions and comparators [8]	0	5	0	5	0	5	2	5	0	5
7. Outcomes [7]	2	1	1	1	0	1	1	1	1	1
8. Bias, confounding, and effect modifiers or subgroup effects [11]	9	0	11	0	11	0	11	0	10	0
9. Statistical Methods [5]	7	0	10	0	8	0	6	0	9	0
10. Study findings [8]	5	0	6	0	5	0	3	0	6	0
11. Interpretation and generalizability [7]	2	0	2	0	2	0	2	0	3	0
12. Limitations [2]	0	0	1	0	1	0	1	0	1	0
Total	31	19	48	19	39	20	39	20	39	19

NR, Not Reported; NA, Not Applicable.
[a]With Supplementary Data published.

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The Ustekinumab study [16] showed better compliance, illustrated by the lower scores in Sections 4 and 5, followed by 8, 9, and 11. Compared to the other three studies. Compliance with Section 4 was marked by the transparency of data sources, the availability of the database (Yale Open Data Access), data assessment on key variables before study initiation, and time-varying and continuous variables, which were reported with means and standard deviations. Compliance with section 5 was illustrated by a detailed description of the recruitment process and patients under study over time, a distinct protocol design diagram, details of exposure groups, discontinuation rules, and a definition of the study gap. All five studies had high NR scores in section 8 as confounders impacting assessment were not analyzed, and variables selected for regression analysis were controlled but not for confounders or missing data in section 9. Potential bias and confounders not evaluated in the study, limit the interpretation of the study findings.

Three studies, dimethyl fumarate, tofacitinib, and erenumab showed identical NR scores of 39. Erenumab scored higher in NR than Ustekinumab, mainly due to no study protocol *a priori*, lack of study governance, and no disclosure of a funding source. It was the only study that discussed the impact of bias on study results. Tofacitinib in RA lacked compliance, mainly in section 4, marked by inadequate data sources. The tofacitinib study also listed statistical packages and controlled variables under the statistical methods, which were not reported by the other two. None of the three studies mentioned data validity in terms of completeness or reliability, protocol design, or patient disposition. Confounders and biases were not mentioned in the study results or discussion. Ixekizumab had the lowest compliance mainly due to a lack of information on data sources, participants' exposure details, and the issues mentioned for the other three products.

Discussion

In the past few decades, the rise of specialty drugs, often requiring complex drug administrations such as infusions/injections or patient-safety monitoring, necessitated specialized patient assistance [10, 23]. In Canada, Patient Support programs (PSP) grew quickly in terms of numbers and level of service offered. In addition to drug administration and safety follow-up, staff from PSPs also help patients access reimbursement, provide education regarding the disease and the drug, and collect patient-level data to facilitate better patient management. An early report suggests that there are over 400 PSPs in Canada, each with the infrastructure to administer specialty drugs, provide patient care, and collect patient-level data [21]. A more in-depth analysis [24] at the drug level indicates that up to Aug 2023, of the 2556 prescription drugs marketed by 89 companies in Canada, 256 (10.0%) had a patient support program. Some drugs had multiple PSPs, and they were mostly managed by outside vendors.

The large and growing number of PSPs in Canada should serve as a gold mine for the generation of pan-Canadian RWE. Regulatory and HTA agencies consider data generated as part of a PSP to be a low level of evidence [8]. Most of these programs are tied to special drugs or companies, and the lack of public transparency in their operations is of high concern [10, 11]. Data quality remains obscure, including how missing data were handled, data completeness, data governance, and patient privacy. Databases used in PSPs are designed to collect information for patient management and not prospectively address scientific questions. How can that be used retrospectively to generate new effectiveness and safety information? Grundy et al., after analyzing a comprehensive database of PSPs in Canada up to August 2023, saw a strong correlation between drug prices and availability of PSPs, suggesting a commercial motive in the setting up of these PSPs besides patient care [24]. Due to these limitations, most PSP data publications focus on patients' persistence and adherence to the drug tied to the specific PSP. For RWE from PSP data to be acceptable to regulatory agencies, additional rigor in transparency in design, data validation, and analysis are critical parameters.

With RWE gaining momentum in decision-making globally, manufacturers are interested in capturing and utilizing data from PSPs to gain additional insight into their products post-launch, such as effectiveness studies for reimbursement or supporting new indications. They are also aware that the databases currently structured are inadequate, and the data collection methodology would have to be revamped to meet the quality and transparency requirements matching those of clinical trials.

In collaboration with academic partners, regulatory agencies recently published checklists and templates to guide the generation of fit-for-purpose RWE intended for decision-making. The HARPER template [25], the STROBE checklist [26], and the CDA-AMC RWE checklist [8] were among the most recent ones. The HARPER template provides a set of core recommendations for clear and RWE protocols, whereas the STROBE checklist includes a list of high-level items that should be included in reports of cohort studies. The RWE checklist guide published by CDA-AMC is more prescriptive, specifying in detail the specific information required for each section. The CDA-AMC checklist has 12 sections, each with 2–12 items plus some with subitems. This publication evaluated nine peer-reviewed publications based on Canadian PSP databases using the CDA-AMC RWE checklist of 103 items (see Methods). The nine publications of cohort studies were divided into two groups, interventional and non-interventional, according to FDA RWE guidance [27]. The scores of NR (not reported) and NA (not applicable) were compared across studies. The NA scores serve as an indicator of the type of study design, highlighting that similarly designed studies will exhibit the same NA. On the other hand, NR scores

measure the lack of compliance to critical parameters, which are deemed essential for a robust RWE study according to the CDA.

The infliximab study in IBD patients demonstrated the highest compliance with the lowest NR score among the interventional studies. The study was based on a protocol prospectively designed before the analysis (after data collection), with quality data checked and validated by a third party, a formal governance committee, ethics board approval, and justifications for missing data management. The study population and variables were well-defined and controlled, and study windows and gaps were specified. The Cox Proportional Hazards Model with the intervention time as the covariant was used to avoid immortal time bias. To account for measured and unmeasured confounders, quantitative bias analysis was used to evaluate critical endpoints. The study also completed a STROBE checklist and is in good standing. The study might still be inadequate in meeting all Health Canada and CDA-AMC requirements due to the lack of data transparency, as data extraction methods, code, algorithm, and data dictionary were not provided in the publication. The company probably considers the data information proprietary and would not disclose it in a publication, but would submit confidentially to the regulatory agencies. The rest of the interventional studies (vedolizumab in IBD, mepolizumab in asthma, and brodalumab in psoriasis) failed stringent data quality requirements, lacked statistical vigor, did not account for bias or confounders, and scored inadequately against the checklist. As for the non-interventional studies Ustekinumab in IBD, ixekiuzmab in psoriasis, dimethyl fumarate in MS, tofacitinib in RA, and erenumab in migraine, drug persistence was the objective of the studies, and endpoints were descriptive. The lack of control for bias and confounders might have skewed the data to be more favorable for the study drug; there was insufficient information for concluding, and these publications did not score favorably against the CDA-AMC checklist.

Limitations of the study: The most significant limitation was that the evaluations were performed on publications rather than study reports. These publications often omits details deemed confidential to manufacturers, restricting an assessment based on the checklist. The current paper attempts to perform the most precise evaluations based on publicly available information. The author believes that peer-reviewed publications serve as a good proxy for the quality of the study. Despite the need to protect confidential information, data quality validation, considerations of bias and confounders, and measures to control all key variables should be transparent in the publications. Without these details, the information cannot be used for decision-making. It is also acknowledged that most of the publications were written before the issuance of the CDA RWE guidance; however, the guidance was developed to align with established global standards, key principles for generating RWE were available for reference at the time these studies were conducted and should not have major impact on the quality of the studies.

Conclusion

Nine published studies using PSP databases were analyzed using the CDA-AMC checklist. Only one study scored adequately to be a potential submission candidate for decision-making. For successful regulatory considerations, data quality validation, data source transparency, validated methodology to manage study bias, measured or unmeasured confounders, and robust outcome analysis, including sensitivity and quantitative bias analysis are critical factors to consider.

Data availability statement

Publicly available datasets were analyzed in this study.

Author contributions

CL conceived the original research idea, and all information used in the article was collected from publicly available websites or publications. Analysis of the data collected, discussion, and conclusion were all written by CL.

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The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontierspartnerships.org/articles/10.3389/jpps.2025.14587/full#supplementary-material

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Expanding the eligibility criteria for drugs in Canada's time-limited health technology assessment and temporary drug access processes will further accelerate access to new medicines

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Background

Canada's Drug Agency (CDA-AMC) conducts health technology assessments (HTA) for Canada's federal, provincial, and territorial public drug programs (except Quebec's) to guide their drug reimbursement decisions [1, 2]. The pan-Canadian Pharmaceutical Alliance (pCPA) conducts joint negotiations for Canada's public drug plans [3]. It takes more than 1.5 years after regulatory approval for a new drug to be listed on the public plans in Canada – one of the slowest timelines among OECD20 countries [4, 5], many of which have established novel reimbursement decision pathways that enable publicly funded early access [6, 7]. Until recently, the CDA-AMC and pCPA processes did not include a pathway to help balance timely patient access with decision-making for drugs with high levels of uncertainty but promising early data [6, 7].

New Canadian time-limited HTA and temporary drug access processes

In September 2023, the CDA-AMC announced a new time-limited drug reimbursement recommendation category that aims to "help provide earlier access to

Abbreviations: AIFA, Agenzia Italiana del Farmaco; CDA-AMC, Canada's Drug Agency – L'agence des médicaments du Canada; HAS, Haute Autorité de Santé; HTA, Health technology assessment; INESSS, L'Institut national d'excellence en santé et en services sociaux; NOC/C, Notice of Compliance with Conditions; NICE, National Institute for Health Care and Excellence; OECD, Organisation for Economic Co-operation and Development; pCPA, pan-Canadian Pharmaceutical Alliance; pTAP, pan-Canadian Pharmaceutical Alliance Temporary Access Process; RWE, Real-world evidence; TLR, Time-limited recommendation.

promising new treatments that target the unmet needs of people in Canada living with severe, rare, or debilitating illnesses." [8] [CIT] In parallel, the pCPA developed a set of principles and conditions for a Temporary Access Process (pTAP) to "inform the negotiation process and potential product listing agreements for any drug products that follow" the CDA-AMC's time-limited recommendation (TLR) pathway [9]. Together, these processes represent a significant development in addressing timely patient access as they form the first Canadian early access pathway.

Current eligibility for TLR and pTAP

The drug eligibility criteria for TLR include a Notice of Compliance with Conditions (NOC/c) from Health Canada, plans to generate evidence for a phase III clinical trial in the same patient population as the original submission, and study completion within 3 years [8]. The same criteria apply to pTAP [9].

The CDA-AMC noted that the initial TLR eligibility is a "first step," and plans to evaluate and refine the criteria based on experiences using the processes "after the first 3 to 5 recommendations have been issued or after 18 months, whichever is soonest." [CIT] [8] pTAP is a "pilot project and will be subject to regular monitoring and assessment." [9].

First use of TLR and pTAP significantly reduces the time to listing

To date, one drug has leveraged these new processes [10]. On 28 November 2023, the CDA-AMC accepted the drug epcoritamab, for relapsed or refractory diffuse large B-cell lymphoma, as eligible for consideration of a TLR, and granted it a TLR on 18 June 2024 [11]. Negotiations between the manufacturer and the pCPA were concluded with a signed letter of intent on 19 July 2024 [12, 13]. First provincial listings were achieved on 14 August 2024, in Quebec and Ontario [14, 15] – 306 days after epcoritamab's regulatory approval, a significantly earlier time-to-listing than the historical average, which is closer to 600 days for oncology therapies [4].

Early observations: current eligibility criteria may limit pathway uptake

Almost 12 months after the launch of TLR and pTAP, it is encouraging to see that the first drug has successfully navigated these new processes, leading to timelier patient access. At the same time, this is the only drug to have leveraged this pathway to date – and it is uncertain whether other drugs will follow suit anytime soon. Of the estimated 2 NOC/c drug files that will receive approval by the end of 2024, one is currently going through the HTA process without leveraging TLR and the other file is pending at the time of writing [16–19].

Given the CDA-AMC's goal of using TLR to expedite access for patients to promising new treatments, the current eligibility criteria may be too restrictive. If few drugs meet the eligibility criteria and even fewer apply, the TLR and pTAP processes will have a minimal impact.

Considerations for the future evolution of TLR and pTAP drug eligibility criteria

Fortunately, there are many jurisdictions to learn from when considering adaptations of eligibility criteria for drugs that could increase TLR and pTAP use and impact. Examples abound in established early access pathways in OCED countries – for example, those at NICE, AIFA and HAS [6]; in emerging pathways, such as Taiwan's conditional listing policy introduced in July 2023 [20] and, closer to home, in Quebec's HTA agency INESSS's "promise of value" recommendation option, which has been in place since 2018 and facilitates conditional listings that may include requirements for clinical monitoring and real-world data generation to support a subsequent re-evaluation [21]. Specifically for TLR and pTAP, stakeholders may consider the following:

1. NOC/c expansion to allow for other drug files. As previously noted, there will only be an estimated total of two NOC/c drug files approved by the end of 2024 [17]. Furthermore, a recent CDA-AMC analysis found that from 2018 to 2021, 94% of NOC/c authorisations issued were for oncology drugs [22]. Expanding eligibility beyond drugs that receive NOC/c would allow for a greater number of therapies that meet a high unmet patient need – including those for rare diseases and conditions – to leverage this pathway.
2. Incorporating greater flexibility into the Phase III clinical trial requirements by allowing the use of phase III data where the patient population, line of therapy, and/or indication do not fully align with the phase II trial data provided in the original HTA submission. This change alone could make up to 50% more files eligible for TLR [23].
3. Accepting real-world evidence (RWE) as a supplement to clinical trial data. As recent examples of RWE use in a timely access process in Canada, in the May 2024 INESSS reassessments of two therapies with initial recommendations based on the promise of value, the confirmatory data included both clinical trial data and eight real-world studies – three of which included RWE from Canadian patients [24, 25].

Encouraging progress – but is it enough to meaningfully improve timely access for patients?

The current TLR and pTAP processes represent an encouraging step forward towards modernising Canada's approach to HTA and drug reimbursement – a priority noted recently by Ontario premier Doug Ford [26].

It is hoped that TLR and pTAP will continue to evolve through the integration of learnings from early experiences, the study of other jurisdictions' early access pathways, and input from and transparent collaboration of Canadian stakeholders – key to achieving a "made-in-Canada solution" [27] that supports evidence-based decision making and timely patient access to promising medicines. To ensure that TLR and pTAP can fulfil their potential and reach the greatest number of patients in need, the expansion of drug eligibility criteria would be a logical next step.

Author contributions

The author confirms being the sole contributor of this work and has approved it for publication.

Conflict of interest

The author is a shareholder and employee of 20Sense, a pharmaceutical research and consulting agency. 20Sense has provided consulting services to CDA-AMC (formerly CADTH) and AbbVie. The author is a co-chair of the Real-World Evidence and Outcomes-Based Agreements Working Group, which receives research funding from its members. At the time of writing this article, members include AbbVie, Amgen, AstraZeneca, Janssen, Novartis, Pfizer and Roche.

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Real-world data: a comprehensive literature review on the barriers, challenges, and opportunities associated with their inclusion in the health technology assessment process

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Objective: This review aimed to assess the current use and acceptance of real-world data (RWD) and real-world evidence (RWE) in health technology assessment (HTA) process. It additionally aimed to discern stakeholders' viewpoints concerning RWD and RWE in HTA and illuminate the obstacles, difficulties, prospects, and consequences associated with the incorporation of RWD and RWE into the realm of HTA.

Methods: A comprehensive PRISMA-based systematic review was performed in July 2022 in PubMed/Medline, Scopus, IDEAS-RePEc, International HTA database, and Centre for Reviews and Dissemination with *ad hoc* supplementary search in Google Scholar and international organization websites. The review included pre-determined inclusion criteria while the selection of eligible studies, the data extraction process and quality assessment were carried out using standardized and transparent methods.

Results: Twenty-nine (n = 29) studies were included in the review out of 2,115 studies identified by the search strategy. In various global contexts, disparities in RWD utilization were evident, with randomized controlled trials (RCTs) serving as the primary evidence source. RWD and RWE played pivotal roles, surpassing relative effectiveness assessments (REAs) and significantly influencing decision-making and cost-effectiveness analyses. Identified challenges impeding RWD integration into HTA encompassed limited local data access, complexities in non-randomized trial design, data quality, privacy, and fragmentation. Addressing these is imperative for optimal RWD utilization. Incorporating RWD/RWE in HTA yields multifaceted advantages, enhancing understanding of treatment efficacy, resource utilization, and cost analysis, particularly via patient registries. RWE complements assessments of advanced therapy medicinal products (ATMPs) and rare diseases. Local data utilization strengthens HTA, bridging gaps when RCT data is lacking. RWD aids medical device decision-making, cancer drug reassessment, and indirect treatment

comparisons. Challenges include data availability, stakeholder acceptance, expertise, and privacy. However, standardization, training, collaboration, and guidance can surmount these barriers, fostering enhanced RWD utilization in HTA.

Conclusion: This study highlights the intricate global landscape of RWD and RWE acceptance in HTA. Recognizing regional nuances, addressing methodological challenges, and promoting collaboration are pivotal, among others, for leveraging RWD and RWE effectively in healthcare decision-making.

KEYWORDS

real-world data, real-world evidence, health technology assessment, acceptance, barriers, challenges

Introduction

RWE and RWD are increasingly used for evaluating health technologies to inform decision-making in the healthcare sector. RWD refers to data related to patient health status and/or the delivery of healthcare that are routinely collected from various sources outside of traditional clinical trial settings. RWE refers to data generated from RWD and it's actually the clinical evidence about the usage, benefits, and risks of medical products, which is derived from the analysis of RWD. The evidence derives from sources such as electronic health records, claims data, product or disease registries, pragmatic trials, and data generated by patients (patient-reported outcomes) as well as digital health technologies, among others [1, 2]. RWE can provide a more comprehensive and representative picture of how treatments and interventions work in real-world conditions, beyond the controlled environment of clinical trials. The role of RWE is undergoing continuous development and broadening while has gained prominence in healthcare decision-making, particularly during the COVID-19 pandemic [3]. While RCTs are still considered the benchmark for assessing the effectiveness of treatments including new cancer treatments, there is a growing consensus that relying solely on RCTs may not provide comprehensive solutions to all pertinent clinical or research inquiries and RWE can contribute in advancing decisions by providing complementary evidence [4].

In a general context, the advantages of using RWD in patient care are to:

- Evaluate the effectiveness and safety of treatments and interventions in real-world populations and environments provides a more holistic view of patient health and care outcomes, as data is derived from routine clinical care rather than controlled settings.
- generate data on subpopulations that may be underrepresented in clinical trials by capturing a wider range of patient populations and health conditions, including underrepresented groups, and identify rare or long-term adverse events that may not be captured in clinical trials.
- monitor the safety and efficacy of new treatments or interventions in real-world settings, beyond the limited scope of clinical trials [5].

The utilization of RWD and the generation of RWE hold immense promise for transforming healthcare decision-making. However, there are also challenges associated with the use of RWD, including issues related to inconsistent data quality, comparability and bias (subject to bias and measurement errors, both random and non-random) [6], as well as the need for appropriate statistical methods and analytical frameworks. Such challenges among others, are the following:

- Data Quality and Consistency: RWD originates from various sources in the real-world healthcare ecosystem, including electronic health records, claims databases, and patient registries. Consequently, data quality can be inconsistent due to differences in data collection methodologies and standards across healthcare institutions. Incomplete, inaccurate, or missing data can lead to flawed analyses and unreliable conclusions. Furthermore, the diverse nature of RWD sources means that data may vary in terms of completeness, timeliness, and relevance.
- Bias and Measurement Errors: RWD is inherently subject to bias and measurement errors, which can emanate from several sources. Selection bias can occur when certain patient populations are overrepresented or underrepresented in the data due to factors such as healthcare seeking behavior or data collection practices. Information bias may arise from discrepancies in the way data is recorded or measured, leading to inaccuracies. Additionally, non-random error can be introduced through factors like data entry mistakes, misclassification of variables, or systematic differences in data collection across institutions. These biases and errors can skew RWE findings, potentially leading to misleading conclusions about the safety and effectiveness of medical interventions [7].

Considering the formidable challenges inherent in the field, it is noteworthy that the prominence of RWE in shaping healthcare

decision-making continues to ascend and the importance of RWE in healthcare decision-making is growing. Regulatory agencies such as the U.S. Food and Drug Administration (FDA) recognize its potential and have issued guidance on its use in regulatory decision-making. These guidelines provide a structured framework for how RWE can be employed to support various stages of drug development and post-market surveillance. For example, the FDA has issued guidance on the use of RWE in regulatory decision-making [8], while the Institute for Clinical and Economic Review (ICER) has developed a framework [9] for integrating RWE into coverage decisions and acknowledges the value of RWE in evaluating the real-world effectiveness and cost-effectiveness of medical interventions, particularly in comparison to traditional clinical trial evidence. While RWD is progressively attaining prominence in influencing healthcare decision-making, it remains a subject of discernible complexity and resistance within the healthcare milieu.

Based on the above, the objective of the study is to investigate the integration of real-world data and real-world evidence in health technology assessment process around the world. In particular, the aim of this systematic review was to: a) assess the current utilization and level of acceptance of RWD and RWE in the HTA process, shedding light on their prevalence and applications; b) systematically prioritize and examine the barriers, challenges, opportunities, and potential implications that arise from the integration of evidence derived from RWD and RWE within the HTA process. This includes a comprehensive analysis of factors influencing successful integration; c) explore and synthesize stakeholders' perspectives, regarding the incorporation of RWD and RWE in the HTA process.

Materials and methods

Considering the above objective, the research questions defined for this review were the following:

- ➢ Is the utilization and acceptance of RWD and RWE prevalent in the HTA process?
- ➢ What are the barriers, challenges, potential benefits and feasibilities, as well as opportunities presented by the integration of RWD into the HTA process?
- ➢ What are the viewpoints and declarations of stakeholders concerning to RWD and RWE in the HTA process?

No formal protocol was established or registered for this systematic review.

Study design, inclusion and exclusion criteria

A PRISMA-based systematic review [10, 11] was conducted to identify articles assessed by the researchers, employing inclusion criteria to ascertain study eligibility aligned with the review's objectives. The search strategy, as detailed in *Search strategy* section and Supplementary Appendix S1, was utilized to encompass these criteria.

Inclusion criteria were as follows:

- ➢ Population: No restrictions were imposed on populations, and studies from diverse populations worldwide, including sub-populations, were considered eligible for inclusion.
- ➢ Intervention: RWD and evidence derived from the use and analysis of RWD.
- ➢ Comparator: No comparator.
- ➢ Outcomes: Data on the current use of RWD/RWE in HTA, barriers, challenges, weaknesses in their integration in the process, opportunities and stakeholders' regarding the use of RWD/RWE in the HTA process were included. To systematically conduct the above outcome criteria search, a meticulous process was employed for the formulation of search terms. This involved a thorough review of current and relevant literature, ensuring alignment with the latest advancements and key concepts within the field to inform the selection of search terms. The carefully chosen search terms, detailed in brief within *Search strategy* section and provided in detail within Supplementary Appendix S1, were derived from this comprehensive review.
- ➢ Types of studies: All types of studies, such as reviews, policy texts, primary research, RCTs and qualitative research studies. This approach was adopted to ensure a thorough exploration of the subject matter, capturing both empirical data from primary studies and synthesized knowledge from reviews.
- ➢ Language: Studies written in English.
- ➢ Timeline: No time restrictions were specified for the publication of studies and policy reports.

The exclusion criteria for studies in this analysis were as follows:

- ➢ Study Types: Abstracts (oral and posters) that did not include at least one of the above outcome criteria.
- ➢ Language: Studies in languages other than English.

Search strategy

The search strategy was meticulously designed to ensure both breadth and inclusivity. Key terms such as "accept," "use," "barriers," "health technology assessment," "real-world data," "real-world evidence," "opportunities," and "stakeholders" were central to our search strategy, aiming to cast a wide net and capture a diverse range of perspectives.

The detailed search strategy, which was performed on July 2022, is provided in Supplementary Appendix S1.

Search strategy was implemented to multiple databases and particularly: PubMed/Medline, Scopus, IDEAS-RePEc, International HTA database, Centre for Reviews and Dissemination. In addition, supplementary *ad hoc* searches for relevant information were performed on Google Scholar, as well as various international organizations such as the World Health Organization (WHO) and Organisation for Economic Co-operation and Development (OECD), and specific health technology assessment organizations such as National Institute for Health and Care Excellence (NICE), Haute Autorité de santé (HAS), and Institute for Clinical & Economic Review (ICER) to identify relevant texts and references related to the study objectives.

Study selection methods

The literature discovered through the search was archived in a bibliographic database (EndNote), with duplicate entries subsequently removed. A pilot training check process was conducted initially to ensure consistency in selection and identify areas for modifications in the inclusion criteria to provide a more comprehensive and explicit list of study types that would be considered eligible for this review. Two researchers independently checked a random sample of approximately fifty (50) titles and abstracts for eligibility, and a high level of agreement was achieved which indicates that the two researchers largely agreed on whether each of these documents met the inclusion criteria established for the study. After this, a single researcher checked the remaining titles and abstracts for eligibility. Later, the studies resulting from the removal of duplicate entries were uploaded into Abstrackr [12], a specialized software developed by Brown University and the Center for Evidence Synthesis in Health. All abstracts were examined, and full-text documents were retrieved for the files that were flagged for inclusion. The retrieved articles were then analyzed in detail based on the full text. Quality control measures, including periodic checks and inter-rater reliability assessments, were implemented to ensure the accuracy and consistency of the study selection process. This methodological approach, encompassing both manual assessment and the use of specialized software, was designed to enhance the accuracy, consistency, and transparency of the study selection process.

Data extraction and synthesis methods

The study data was meticulously extracted and organized into four tables, a process undertaken to streamline and enhance the subsequent analysis and synthesis of the information. The design of these tables was thoughtfully structured to systematically capture pertinent information derived from the selected studies. Supplementary Table S1 contained details relevant to the characteristics including author, year of study, country, study type, objectives, health technology studied, population and therapeutic category, and subcategory of real-world data. Supplementary Table S2 was dedicated to encompassing data concerning the contemporary utilization and reception of RWD and RWE. In contrast, Supplementary Table S3 comprehensively addressed the hurdles, challenges, and complexities encountered when integrating RWD-RWE into HTA. Meanwhile, Supplementary Table S4 was designed to encompass the potential advantages, opportunities, and viability associated with the adoption of RWD-RWE within the realm of HTA. To ensure consistency and pinpoint any potential adjustments required for the data extraction model, two researchers initially conducted an independent pilot test on a random sample of ten (10) studies. During this process, an appropriate level of agreement was observed, denoting that there was a satisfactory degree of consensus or concurrence among the researchers involved in the extraction of data from the selected studies. The extraction of the remaining studies was conducted by a primary researcher, supported by a secondary researcher who remained readily available to offer assistance in clarifying information or in situations where the primary researcher encountered challenges or uncertainties during the extraction process.

Appraisal of methodological quality

The methodological quality of the studies included in this review was assessed using several critical appraisal tools, namely, the Critical Appraisal Skills Programme (CASP) tool for qualitative research [13], the Joanna Briggs Institute (JBI) checklist for systematic reviews and evidence syntheses [14], and Joanna Briggs Institute (JBI) checklist for text and opinions [15]. Each tool evaluated different aspects of study quality by one reviewer, including the study design, data collection methods, data analysis, and reporting of results. For the assessment of each study done using the CASP tool, the reviewer assessed the quality of the study design, data collection methods, data analysis, and interpretation of findings. The Critical Appraisal Skills Programme (CASP) tool is the most used tool for quality appraisal in health-related qualitative evidence syntheses [16]. Meanwhile, the JBI checklist was used to evaluate the relevance of the studies to the review question, study design, sample size, data collection methods, data analysis, and reporting of results.

Quality appraisal, in detail, of eligible studies can be found in the Supplementary Appendix S2. In the overarching context, it is pertinent to elucidate that the quality of the incorporated studies exhibits a discernible spectrum, wherein, a number of studies may be aptly delineated as demonstrating a standard of moderate

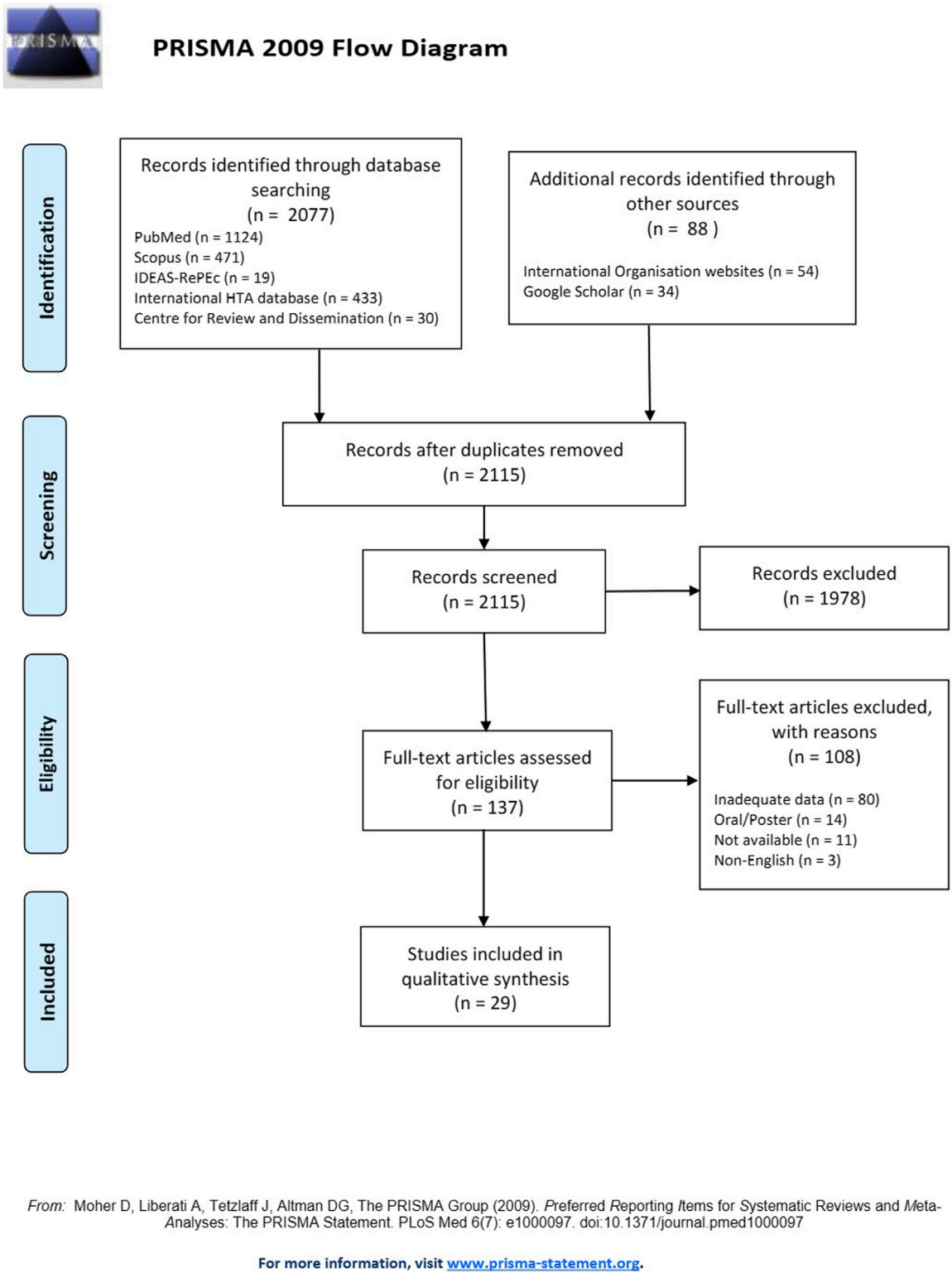

FIGURE 1
PRISMA flow chart of the search strategy.

quality, while the preponderance of the corpus can be distinguished as manifesting a commendable standard of good quality.

Results

During the search process, a total of 2,115 studies were identified based on the pre-specified selection criteria after removing duplicates (n = 50). Among these, 137 studies were selected for inclusion after title and abstract review. Full-text versions of all studies were obtained, with the exception of eleven studies whose authors did not respond to the request of their manuscript since were also not available in the literature. Following a thorough examination of the complete texts, 108 studies were excluded due inadequate data (n = 80), oral/poster presentations without much data (n = 14), non-availability of full-text (n = 11) and non-English manuscripts (n = 3). Eventually, 29 studies (Supplementary Table S1) out of the 137 met the inclusion criteria and were considered eligible for analysis.

Figure 1 illustrates the study selection process in accordance with the PRISMA flow diagram.

Description of study characteristics

Overall, 29 studies (Supplementary Table S1) were included in this review, among which, most of them were referring to European countries. Most of these 29 studies were referring to multiple countries within their analyses while few of them assessed information related to RWD/RWE for HTA in continents. In particular, England (n = 6), Germany (n = 5), United Kingdom (n = 4), Sweden (n = 4), Netherlands (n = 3), Scotland (n = 3), France (n = 3), Norway (n = 2), Italy (n = 2), Spain (n = 1), Austria (n = 1), Denmark (n = 1), and Belgium (n = 1). In addition, Europe was referred in three studies, while one study included European Union countries and another one study included Central and Eastern Europe. Several included studies referred to North America, and particularly United States (n = 2) and Canada (n = 2) and one study referred to South America countries and particularly to Argentina, Brazil, Colombia, and Chile. The review also included one study referring to Asian countries (Bhutan, China, India, Indonesia, Japan, Malaysia, Philippines, Singapore, South Korea, Taiwan, Thailand). Middle East and North Africa [MENA] (n = 1) as well as Saudi Arabia (n = 1) were part of the final studies while international scope was referred in five studies.

Current use and acceptance of real-world data/real-world evidence in HTA

The acceptance and utilization of RWD and RWE vary across HTA organizations and countries. Prevailing preferences for RCTs and systematic reviews were evident in various studies, with RWD from observational studies considered when RCTs are unavailable [17, 18]. Stakeholders generally prioritize RCTs [19, 20], including in the context of Next-Generation Sequencing technologies [21]. Notable discrepancies are observed in Saudi Arabia, with some stakeholders expressing skepticism about the reliability of RWE compared to outcomes derived from RCTs [22]. However, Austrian, French, and English HTA organizations recognize the value of observational studies, especially for biomarker assessments, diagnostic testing accuracy data, and situations where RCTs are non-feasible [23]. They also consider data from all non-randomized controlled trials (non-RCTs), particularly for medical devices assessment [24]. In Asian countries, there is a widespread positive inclination toward embracing and utilizing RWD and RWE by HTAs for assessing clinical effectiveness and reimbursing technologies [25].

Multiple additional studies highlight the crucial role of RWD and RWE in the HTA process. RWD significantly influences HTA submissions, particularly in Latin America, where Argentina and Brazil lead the way, and a rising trend is observed in Chile and Colombia [26]. In Europe and Canada, RWD contributes to HTA submissions for anticancer medications, providing comparative arms in Germany and supplementary evidence in Sweden and Canada [27]. Various European HTA organizations prioritize diverse clinical evidence, emphasizing the importance of RWD, especially in the initial reimbursement discussions, particularly for rare diseases. AIFA, ZIN, and HAS express a preference for RWD in conditional reimbursement schemes, acknowledging its positive impact on decision-making and effectiveness assessments [28]. European HTA representatives generally embrace registry data, with positive feedback on observational studies [29]. England shows a significant increase in RWD utilization in HTA submissions, with NICE leading in acceptance, and pragmatic trials and primary care databases recognized as valid sources [30–32]. Another study underscores extensive RWD use in evaluating the effectiveness and safety of Direct Oral Anticoagulants (DOACs) compared to warfarin in real-world clinical settings [33].

On the flip side, the impact of external control arms (ECAs) on the decision-making processes of drugs within well-known HTA organizations remains unclear and is likely minimal [34]. While concerns persist regarding the general collection of RWD, it is anticipated that the enactment of Germany's new GSAV law will enhance the thoroughness of RWD collection [35]. RWD sources generally furnish relevant health outcomes data for the HTA process, but noticeable gaps exist in economic and comparator data, particularly in studies related to hip and knee arthroplasty [36].

In the realm of cost-effectiveness analyses (CEA), RWE from registries and statistical databases, especially for utility,

cost, resource use, and quality of life data, proves crucial [37, 38]. Numerous European HTA organizations prioritize evidence from RWD for pharmacoeconomic analyses, giving emphasis to local RWD for costs, resource use, epidemiology, and quality of life [28]. Positive contributions to drug approval are noted with cost-effectiveness data from local registries [39]. However, a MENA-based study indicates opposition to the positive acceptance of RWD within the HTA framework [40].

Barriers, challenges, and difficulties encountered in incorporating RWD/RWE within HTA

The challenges and barriers in utilizing RWD and RWE within HTA are diverse and multifaceted, spanning from issues in trial design, data quality, and methodological challenges to barriers related to stakeholder acceptance, industry engagement, and global harmonization efforts.

Methodological challenges associated with RWD and RWE include selection bias within international context [34], lower data quality compared to RCTs in various countries including several European countries and Canada [20, 33, 36, 41]. Standardization issues as well as design and reporting issues of non-RCT studies were also key concerns in European countries [18, 23] and limited infrastructure for collecting RWD with data collection issues in Canada for decision-making pertaining to drug pricing and reimbursement in Canada as well as in South American countries [26, 41], and concerns about the representativeness of RWD data [20].

The obstacles in utilizing RWE encompass bias and confounding factors, incomplete data availability and data accessibility challenges [24, 33, 35], study design and analysis when integrating into HTA [31], the absence of consensus on methodologies, and a shortage of qualified researchers [26]. Issues related to RWE include lack of reliability and bias as shown by stakeholders in Canada [42]. Internationally, there's a scarcity of RWD for advanced therapies [43] and local RWD transferability challenges arizing in MENA countries [40]. An extra challenge in Norway is the exclusion of oncology data from the Norwegian Prescription Database, hindering the reassessment potential of registries [17].

Conversely, in the United Kingdom, there is a notable concern regarding the integration of primary care RWD into CEA models to support clinical inputs within the country's HTA [30]. Simultaneously, the impracticality of conducting indirect comparisons among observational studies has been identified as a significant challenge [32]. In addition, barriers to increasing the use of RWD were the lack of experts/staff to analyze these data in South American countries as well as within international setting [19, 26].

Potential benefits, opportunities, and feasibility of utilizing RWD/RWE in the HTA process

The role of registries in offering comprehensive documentation of disease progression and real-world treatment patterns as well as important data for HTA are highlighted within Norway, and international setting [17, 43], and post-marketing process through observational studies including registries are increasingly vital access strategies for certain technologies within UK's health system [32]. Modeling limitations within CEA can be addressed through better guidance on registries data utilization [39]. The investment and reinforcement of patient registries that derive local data and payer databases within MENA countries [40] or primary care databases within UK are among the potential opportunities to enhance utilization of RWD. On the other hand, initiatives and advancements to address challenges in RWD and non-RCTs for HTA within Europe and Canada include standardized data elements, analytical methods with bias management, and data exchange platforms [23, 42]. Standardization for reliable RWD was also a key advancement reported in other studies for Europe [33, 36].

In regards to the utilization of evidence from non-RCTs in assessing treatment effects within the HTA process, stakeholders from several European countries recommended the enhancement of non-RCTs quality by justifying, designing, and managing rigorously, the improvement of HTA processes, skills, guidelines, and support of research for high-quality data [18]. European HTA organizations could strengthen the RWD but harmonization and alignment incentives are the main contributing factors [28]. Furthermore, evaluating evidence from single-arm trials is challenging and the need for guidelines and best practices is emphasized and it seems that RWD boosts acceptance, especially in oncology [31].

Additional potential benefits and opportunities of using RWD/RWE in HTA include enhancing understanding, complementing trials, careful data selection and rigorous study designs as well as the need for additional guidance on study design and adherence to best practice guidelines and integration of RWD into HTA for oncology medicines [19, 27, 34, 37]. The need for balancing the use of local and international RWE without delaying assessments shown by studies focusing in South American and Central and Eastern European countries (CEEC) [26, 44]. For South America, improved RWD data recording reported as crucial advancement. Within CEEC, collaboration and stability are crucial for successful RWE transferability and implementation.

The complementary role of RWE to strengthen evidence as another opportunity was reported within several studies focusing in United Kingdom, Asian countries and several European countries [20, 24, 25] while can also serve practical for outcome-based contracting [21]. The collaboration and

stakeholder engagement need for RWD utilization improvement is an important aspect [19, 20, 24, 25, 36, 41, 45]. Last, but not least, vital components include implementing effective governance for RWE, establishing comprehensive registries and repositories, and demonstrating commitment to pragmatic trials, ensuring the robustness and reliability of RWE [35], potential usage of RWD and RWE for innovative technologies lacking ample evidence [29].

Discussion

In this study, we conducted a review to comprehensively evaluate the available evidence on RWD and RWE for HTA process. The findings presented reveal a complex landscape in the current use and acceptance of RWD and RWE in HTA across various organizations and countries and illustrate the diversity in attitudes and preferences toward RWD and RWE among HTA organizations across different countries and regions. Several key observations and trends emerge from the diverse set of studies conducted. The acceptance and utilization of RWD and RWE display significant variations among HTA organizations globally. Prevailing preferences for RCTs and systematic reviews are evident in multiple studies, emphasizing a traditional approach to evidence. However, these preferences shift when RCTs are unavailable, leading to considerations of RWD from observational studies. This highlights a pragmatic approach, acknowledging the limitations of RCT availability. Notable disparities surface in different regions, exemplified by the skepticism in Saudi Arabia regarding the reliability of RWE compared to RCT outcomes. This skepticism suggests a cautious approach to embracing RWE in certain contexts. Conversely, Austrian, French, and English HTA organizations recognize the value of observational studies, particularly in situations where RCTs are impractical. This indicates a more open stance towards diverse forms of evidence. The influence of RWD on HTA submissions is pronounced, especially in Latin America, where Argentina and Brazil lead in adopting RWE and RWD significantly influences HTA submissions. This trend suggests a growing acknowledgment of the relevance and impact of RWD in decision-making processes. Similarly, in Europe and Canada, RWD contributes significantly to HTA submissions, providing additional evidence for medications, particularly in the context of anticancer treatments as presented within results. European HTA representatives generally embrace registry data, with positive feedback on observational studies while England shows a significant increase in RWD utilization in HTA submissions, with NICE leading in acceptance. Also, based on one study, it seems that Asian countries show a widespread positive inclination toward embracing and utilizing RWD and RWE by HTAs for assessing clinical effectiveness and reimbursing technologies and another study focusing in MENA indicates resistance to accepting RWD in HTA framework.

In contrast, this review concluded important findings in regards to the barriers and issues arize with the use and acceptance of RWD and RWE for HTA. These findings highlight the challenges faced in leveraging real-world data for informed decision-making in healthcare. One of the prominent barriers identified is the limited availability and transferability of local RWD. This limitation poses a challenge in accessing comprehensive and relevant data sources, particularly in specific regions or healthcare contexts. The lack of local data hinders the ability to generate evidence that is tailored to the specific needs and characteristics of the population under assessment. Accessing high-quality data is crucial for reliable and credible evidence generation. However, several studies revealed difficulties in accessing reliable and high-quality RWD. The challenges can arise from issues such as data privacy and confidentiality concerns, limited data standardization, and variations in data collection and reporting practices. These barriers undermine the reliability and credibility of the evidence derived from real-world data sources. Methodological challenges were also identified as a significant barrier to utilizing real-world data and evidence in HTA. Studies pointed out challenges in study design, analysis, and reporting when relying on non-randomized clinical evidence. Addressing these methodological challenges is crucial to ensure the validity and robustness of findings derived from real-world data sources. Insufficient expertise among stakeholders in utilizing RWE emerged as a common barrier. This lack of expertise can hinder the effective use and interpretation of RWD. Stakeholders, including policymakers, payers, and clinicians, need to possess the necessary skills and knowledge to critically evaluate and utilize RWE in decision-making processes. Fragmentation and lack of collaboration among stakeholders were found to hinder the utilization of real-world data. The absence of harmonized approaches, data sources, methodologies, and decision-making processes limit the consistent and efficient use of RWE. Enhancing collaboration and promoting standardization among stakeholders are essential for maximizing the potential of RWD in HTA. Data quality and reliability were highlighted as significant concerns. Studies identified issues related to low data quality, confounding biases, incomplete data, and challenges in data protection and confidentiality. These limitations can undermine the validity and generalizability of findings derived from RWD sources. Overall, the studies underscore the need to address these barriers and challenges to effectively utilize RWD and RWE in HTA. Improving data availability, ensuring data quality and standardization, addressing methodological challenges, promoting collaboration, and enhancing expertise among stakeholders are key considerations for advancing the use and acceptance of RWD in healthcare decision-making processes. The results of this review concerning to opportunities related to

the RWD inclusion in HTA are in line with the literature and particularly with published manuscript of Crane G, et al. (2022) [46] whom results were similar and highlighted the importance of recommending approaches and initiatives for improving RWE utilization in healthcare decision-making in East Asia and beyond and Encouraging large-scale collaborations among government agencies, hospitals, research organizations, patient groups, and the pharmaceutical industry to ensure access to robust real-world data and alignment on addressing evidence needs.

The systematic review methodology employed in this study offers several strengths, enhancing the reliability and credibility of our findings. One of the key strengths of a systematic review is its comprehensive and rigorous approach. By adhering to a predefined and transparent methodology, we ensured that all relevant studies on the research question were identified, appraised, and synthesized. This minimizes bias and increases the validity of our results. An additional notable strength inherent to the systematic review methodology is its innate capacity to mitigate selection bias. This was achieved through the meticulous application of explicit inclusion and exclusion criteria, thereby effectively diminishing the prospect of selectively favoring studies that align with a particular perspective. Such an approach significantly bolsters the objectivity and neutrality of our review. Moreover, our systematic review facilitated the amalgamation of a diverse body of evidence. We thoughtfully incorporated studies employing a spectrum of methodologies, spanning various populations and settings. This comprehensive and inclusive approach underscores the robustness of our findings, fostering a more holistic perspective on the research question at hand. Despite these strengths, it is important to acknowledge the limitations of our systematic review. Firstly, although we aimed to conduct a comprehensive search, it is possible that some relevant studies may have been inadvertently missed, mainly due to the strict inclusion criteria of English-written manuscripts. This linguistic restriction may introduce a potential source of bias, as relevant studies or data published in languages other than English were not incorporated into our analysis, which could impact the comprehensiveness and generalizability of our findings. While conscientiously implementing strategies to mitigate bias within this systematic review, it is imperative to acknowledge that the specter of publication bias persists as a potential limitation. Despite our diligence in data collection and analysis, it is challenging to wholly obviate this concern, as it hinges upon the selective dissemination of research findings, rendering an absolute negation of its influence unattainable. Furthermore, while we have made every effort to conduct a comprehensive review, we recognize certain limitations that may impact the generalizability of our findings. The search strategy, while aiming for breadth and inclusivity, may exhibit some imbalance due to specific limitations in the selection of keywords. This imbalance could influence the identification and inclusion of relevant studies, potentially leading to an underrepresentation of certain perspectives. An additional limitation pertains to the specificity of the keywords used in our search strategy, which may have inadvertently led to the exclusion of relevant articles, particularly from the United States. We recognize that certain terms, such as "economic assessment of pharmaceutical" [47] may not have been adequately accounted for. In particular, the dataset under consideration primarily encompasses experiences from European Union (EU) countries, with limited representation from the United States. It is crucial to acknowledge that the selected studies included only a few instances reflecting the U.S. context. The scarcity of information from the US poses a challenge to the generalizability of our findings. This limitation is noteworthy as the United States, with its unique healthcare landscape and regulatory framework, plays a significant role in the global utilization of real-world evidence (RWE) for regulatory and reimbursement decisions. The dearth of comprehensive representation from the U.S. may restrict the broader applicability of our study outcomes.

The incorporation of RWE within submissions for HTAs has experienced a noticeable surge in recent times worldwide. In particular, based on an IQVIA analysis of 16,515 HTA reports from 83 HTA bodies in 33 countries, the percentage of records integrating RWE within submissions has increased significantly, from a mere 6% in 2011 to 39% in 2021. This indicates a substantial upward trend in the integration of RWE within submissions for HTA reports while several organizations publishing guidelines on how RWD can be used for HTA [48]. The notable increase, from 6% in 2011 to 39% in 2021, suggests a growing recognition and utilization of RWE as a valuable component in informing HTA processes across various countries and health organizations. The dynamic landscape revealed in this study emphasizes the evolving utilization of RWD and RWE within HTA, offering valuable insights for policymakers, healthcare professionals, and stakeholders grappling with the challenges and opportunities in today's HTA assessments. By elucidating the current landscape of RWD/RWE acceptance and challenges across various HTA organizations and countries, these findings contribute valuable insights that can guide policy-makers, healthcare professionals, and stakeholders. This study outlines a spectrum of challenges associated with RWD/RWE, from methodological issues to stakeholder acceptance and infrastructure limitations with up-to-date data. By delineating these barriers, your research serves as a foundation for developing targeted interventions, guidelines, and capacity-building initiatives to enhance the integration of RWE into HTA processes. The study's exploration of potential benefits, opportunities, and feasibility of RWD/RWE usage in HTA provides a forward-looking perspective. This can guide future research endeavors, policy developments, and collaborative efforts aimed at optimizing RWD/RWE contributions to HTA assessments. It is essential to underscore that the efficacy of

systematic reviews is intrinsically tied to the caliber and lucidity of the underlying studies. Regrettably, any deficiencies or methodological shortcomings present within the primary studies inherently permeate our review, thereby potentially undermining the veracity of our collective findings. It is imperative to note that, by and large, the studies incorporated into our review demonstrated commendable quality, although a minority exhibited a moderate level of quality, signaling the importance of interpreting our findings within this context.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Author contributions

KZ played a pivotal role in the project's conceptualization and design, overseeing the comprehensive data gathering and meticulous data analysis, taking charge of all methodological aspects of the manuscript. Furthermore, KZ meticulously crafted the initial sections of the manuscript, carried out a rigorous process of critical revisions, authored the revised manuscript, conducted meticulous editorial work, and finally, provided his full approval for the publication of the complete document. EP, MG, and KA, assumed a central role in the project's conception, design and formulation, and contributed to the design and implementation of the research, provided invaluable project supervision and direction, authored the revised manuscript, conducted meticulous editorial work, and granted their endorsement for the publication of the complete manuscript for which they agreed with all aspects; KA contributed also to several parts of study selection methods as well as data extraction and synthesis. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Manuscript has been uploaded and published into MedRxiv as a preprint [49].

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontierspartnerships.org/articles/10.3389/jpps.2024.12302/full#supplementary-material

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A big leap in prescription drug promotion in Canada

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KEYWORDS

pharmaceutical advertising advisory board (PAAB), real-world evidence (RWE), Canada, patient support program (PSP), PAAB code

Introduction

The Canadian Food and Drugs Act and Food and Drug Regulations regulate the advertising of prescription drugs in Canada. The independent not-for-profit Pharmaceutical Advertising Advisory Board (PAAB) is the preclearance agency for all promotional material distributed to healthcare professionals (HCPs) [1]. Until now, PAAB reviews have strictly complied with Health Canada-approved Product Monographs (PMs), which do not include real-world evidence (RWE) or open-label studies. For that reason, RWE and open-label studies have generally not been included in communications with HCPs [2].

In November of 2022, PAAB struck a committee to generate a framework for the acceptance of RWE in HCP advertising. The framework would focus on evidentiary standards, disclosure criteria around RWE, and other forms of evidence that do not meet gold standards but have value in clinical practice. The guidance was approved on 1 December 2023, to be launched on 1 February 2024 [3]. This announcement represents an astounding development in Canada for communicating medically important information to HCPs.

The draft RWE guidance [4] now allows pre-planned/sub-analyses of patient data matching the Canadian-approved patient population from RWE/open-label studies. This represents a big step forward in providing the timeliest information to HCPs. Inclusion of drug persistence/comparative data from patient support programs (PSPs) and market research that reflects real-life usage in Canada should provide invaluable information to HCPs.

While the PAAB guidance [4] covers important data sources, disease registries and claims databases are not mentioned. In addition, prohibiting the promotion of RWE for conditional approvals could potentially limit the communication of crucial information to HCPs. This editorial recommends additional discussion points in an attempt to improve clarity and to prepare for challenges facing the preparation and reviewing of Advertising/Promotion Systems (APS).

Patient population and patient selection

Following the original PAAB Code, all information not consistent with a PM is considered misleading and rejected. Since it takes over 12 months to update new product claims in Canadian PMs, information in APS is generally outdated, prompting pharmaceutical companies to hire contingents of clinical liaisons to provide HCPs with updated clinical data.

The proposed RWE guidance document [4] states that "In instances where an overall study population exceeds the product's indication, it may be possible to present data from a pre-planned patient subset that reflects the indicated patient population or relevant subset thereof." Similarly, when preplanned, a subset of patients within an approved dose can be carved out within a bigger study consisting of patients receiving not-yet-approved dosing regimens. Information not available in PMs, such as longer-term outcomes (e.g., overall survivals for oncology, longer-term disease remission and quality of life data), can now be legitimately advertised provided that RWE used has been published in reputable peer-reviewed scientific journals (with some exceptions discussed below).

Patient support program (PSP) and market research data

The guidance proposes that the use of RWD/RWE from PSP or market research would in certain specific cases not need to be published in peer-reviewed journals. The exception includes retention/persistence data or adherence data from the sponsor's PSP, together with robust data capture, reporting, and analysis to validate the submission. This allowance of including unpublished PSP data in advertising has both pros and cons. Rapid communication of the most recent data to HCPs is a positive, as patients would benefit from the latest information, especially patients with cancer or chronic illness. The cons are that methodologies for the analysis of PSP data are still in rudimentary stages and a lack of peer-reviewed scrutiny will impact data validity. The burden of proof could be challenging for PAAB staff. Similarly, methodologies are needed for minimizing potential bias in retention/comparative data from market research.

Data transparency

The guidance indicates that published RWE information must contain sufficient content for PAAB to evaluate the methodologies. As most publications have page and word limits, the best way to demonstrate complete transparency with data sources and methodologies is through the supplementals. Sponsors are advised to take advantage of supplemental sections by uploading raw data and analysis methodologies.

Clinician assessment/acceptance

The best way to gain physician acceptance of RWE information will be to involve them throughout, from the inception of the research through the review of the analysis. Clinicians should be invited to study committees to give input, assist in monitoring, and advise data analysis in the most unbiased manner.

Pre-planned analysis

Most real-world information would be derived from data collected retrospectively (electronic health records, PSPs, patient chart reviews, disease registries). To avoid bias, all pre-planned analyses and amendments should be pre-defined without any knowledge of databases. The use of robust analytical methods such as quantitative bias analysis (QBA) to manage confounders is recommended.

Conflicting data

The proposed PAAB guidance also discusses publication of contradictory data from competitors. While this might be a fair and balanced way to present the information, tracking/identification of pre/post superiority data could be burdensome. PAAB might want to consider another pathway for presenting competitor data.

Canada has been considered a slow adopter of RWE for regulatory or health technology assessment [5]. On 18 December 2023, while announcing the creation of the Canadian Drug Agency (CDA) [6] to coordinate a sustainable drug system for Canadians, Minister of Health, the Honourable Mark Holland, also mentioned the creation of specific workstreams to collect pan-Canadian RWE data to support patients, inform healthcare decisions, and enable robust system analytics. This announcement coincides well with PAAB's endorsement of the value of RWE in the upcoming guidance.

Author contributions

The author confirms being the sole contributor of this work and has approved it for publication.

Conflict of interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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