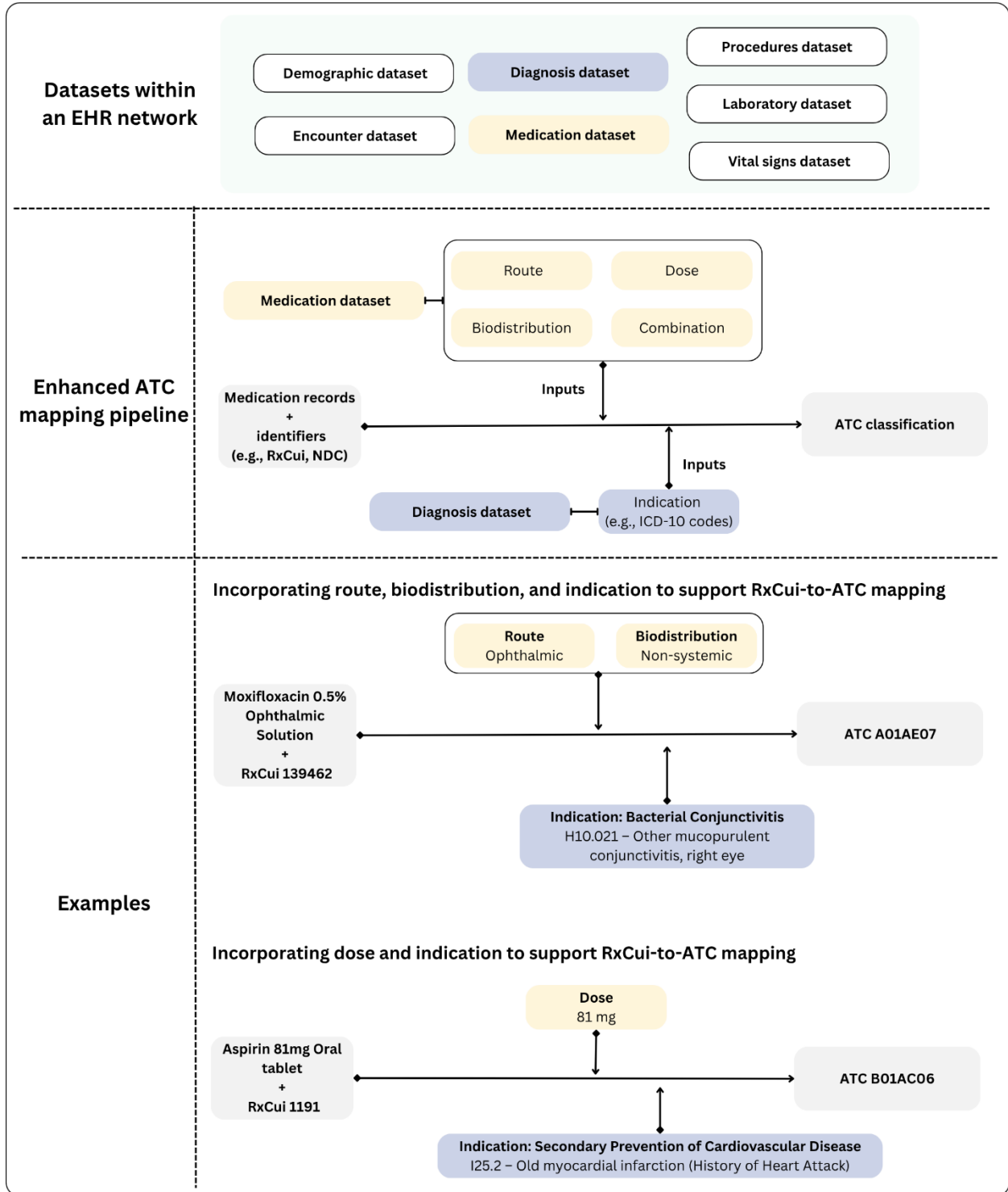


Supplemental figure 1: Integrating medication attributes and clinical context to enhance RxCUI-to-ATC mapping



Supplemental Table 1: Cohort characteristics

	Subjects (N=29,123)
Age	
Mean (SD)	78.24 (7.5)
Median (IQR)	77 (11)
Age group	
65-74	10805 (37.1%)
75-84	11910 (40.9%)
≥85	6408 (22.0%)
Sex	
Male	13083 (44.9%)
Female	14188 (48.7%)
Unknown	1852 (6.4%)
Race	
White	24842 (85.3%)
Black or African American	2549 (8.8%)
Other	614 (2.1%)
Unknown	1118 (3.8%)
Ethnicity	
Hispanic or Latino	502 (1.7)
Not Hispanic or Latino	28310 (97.2)
Unknown	311 (1.1)
Previous hospitalization	0.31 (0.8)
Age-adjusted CCI	5.14 (1.5)

Abbreviations: CCI, Charlson Comorbidity Index; IQR,

Interquartile Range; SD, Standard Deviation.

Supplemental Table 2: Taxonomic Ambiguities and Structural Considerations in RxCui-to-ATC Mapping

Considerations	Explanations	Examples
<p>Route</p>	<p>The ATC classification system often assigns different codes to the same active ingredient based on its route of administration because the route determines the organ system targeted. An RxCUI ingredient code represents the chemical substance regardless of its delivery method, leading to ambiguity when mapped directly without accounting for the route.</p>	<p>Moxifloxacin: When administered as ophthalmic drops, it maps to the sensory organ class (S01AE07) for treating eye infections, whereas oral or injectable forms map to antibacterials for systemic use (J01MA14).</p>
		<p>Timolol: When administered as ophthalmic drops, it maps to the sensory organ class (S01ED01) for treating glaucoma, whereas the oral tablet form maps to the cardiovascular class (C07AA06) for managing high blood pressure.</p>
<p>Dose</p>	<p>The therapeutic intent of a drug can change entirely based on its dosage strength. High-dose and low-dose versions of the same ingredient may be approved for treating completely different conditions, resulting in classification under different ATC anatomical groups or therapeutic subgroups.</p>	<p>Aspirin: low-dose regimens (81 mg) are mapped to antithrombotic agents (B01AC06) for heart attack and stroke prevention, whereas higher doses (325 mg) are categorized as analgesics (N02BA01) for pain and fever relief.</p>
		<p>Finasteride: Based on its dosage strength, the 1 mg dose is classified as a dermatological (D11AX10) for treating hair loss, while the 5 mg dose is classified as a urological (G04CB01) for treating benign prostatic hyperplasia.</p>
<p>Combination</p>	<p>RxNorm assigns a unique identifier to the combination itself. However, the ATC system handles combinations inconsistently: sometimes assigning a dedicated code for the specific mix, and other times requiring the product to be mapped to the primary ingredient's code or split into multiple codes. Direct ingredient mapping fails to capture this structural difference.</p>	<p>Lisinopril + Hydrochlorothiazide: Lisinopril (C09AA03) and Hydrochlorothiazide (C03AA03) each have separate codes as an individual agent, but their combination product maps to a specific "ACE inhibitors and diuretics" code (C09BA03).</p>
		<p>Metformin + Sitagliptin: The combination of Metformin (A10BA02) and Sitagliptin (A10BH01) is assigned to a dedicated class for blood glucose-lowering</p>

		combinations (A10BD07), rather than simply listing the two original codes.
Indications	A single ingredient may be indicated for multiple pathologies. Since ATC is a therapeutic classification system, it assigns codes based on the disease or problem being treated. Without knowing the indication, an ingredient code alone cannot verify which therapeutic class is appropriate.	Bupropion: It is classified as an antidepressant (N06AX12), but as a nervous system agent for smoking cessation (N07BA02).
		Methotrexate: When used for cancer treatment, it maps to antineoplastic agents (L01BA01), but when used for rheumatoid arthritis or psoriasis, it maps to immunosuppressants (L04AX03).
Biodistribution	ATC strictly separates therapeutic classes based on this mechanism of action. An ingredient might be classified as an anti-infective (systemic) in one form but as a dermatological or intestinal agent (local) in another, even though the chemical identity remains identical. This may be collectively assessed from the route of administration and indication.	Vancomycin: The intravenous form for severe systemic infections maps to systemic antibacterials (J01XA01). The oral capsule to treat <i>C. difficile is</i> specific to the intestinal system, classifying it as an intestinal anti-infective (A07AA09).
		Diclofenac: The oral tablet is a systemic anti-inflammatory (M01AB05), while the topical gel is classified as a separate topical product for joint pain (M02AA15).

Abbreviations: ATC, Anatomical Therapeutic Chemical; ACE, Angiotensin-Converting Enzyme.