Comparative Analysis of Pharmacotherapy Trajectories in Treatment-Resistant and Non-Resistant Depression

A Case Study

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Abstract. Treatment-resistant depression (TRD), defined as inadequate response to at least two adequate trials of antidepressants, poses major challenges in managing major depressive disorder (MDD). We applied process mining to electronic health records of 31,881 patients (4,630 TRD, 27,251 non-TRD) with 415,641 antidepressant exposures. TRD patients showed extreme heterogeneity, with nearly a one-to-one ratio of trace variants to cases. They also underwent frequent switches across antidepressant categories, whereas 74% of non-TRD patients completed treatment within a single category. Median treatment duration was 1473 days in TRD versus 112 days in non-TRD. These results establish a reproducible baseline for applying process mining in psychiatric pharmacotherapy and highlight the need for advanced comparative techniques and multi-site validation.

Keywords: Major Depressive Disorder · Process Mining · Treatment-Resistant Depression · Care Pathways

1 Introduction

Major depressive disorder (MDD) is a leading cause of disability worldwide, affecting over 280 million people, and is often complicated by treatment failures, including treatment-resistant depression (TRD) [10]. TRD, affecting 20–30% of patients, is typically defined as inadequate response to at least two antidepressant trials [19]. It is marked by poor response to standard therapies and highly heterogeneous treatment pathways. While observational studies have highlighted the burden of TRD, the detailed, real-world treatment trajectories of these patients remain poorly understood [7].

Process mining is a promising approach for uncovering care pathways from large electronic health record (EHR) datasets [14]. Although established in structured domains, its application in psychiatry is still emerging due to incomplete

data and unclear definitions [17]. As a result, the structure of individualized treatment patterns in real-world psychiatric care is not well characterized.

To address this gap, we apply process mining to large-scale EHR data to compare antidepressant treatment trajectories in patients with and without TRD.

The contributions of this paper are as follows:

- A reproducible analytic pipeline for process mining in psychiatric pharmacotherapy.
- Basic comparative analysis of TRD vs. non-TRD pathways, quantifying heterogeneity and timing.
- Discussion of methodological challenges and future directions for psychiatric process mining.

Our research question is: How do antidepressant treatment pathways differ between TRD and non-TRD patients in real-world EHR data, in terms of structure and timing? All analytic code and process models utilized to answer this question are openly available (see Supplementary Materials 6).

2 Related Work

Several strands of research underpin this study, spanning observational analyses of treatment-resistant depression (TRD), methodological developments in healthcare process mining, and recent efforts to reconstruct psychiatric care pathways from real-world data.

Howes et al. [10] reviewed definitions, prevalence, and challenges in treatment resistance, while Ruhe et al. [19] examined staging methods and difficulties in operationalizing TRD. Chan et al. [5] quantified excess mortality and healthcare resource utilization in TRD, showing higher premature death risk and costs.

Process mining is widely adopted for healthcare pathways. Rojas et al. [18] and Muñoz-Gama et al. [14] surveyed the state of process mining in healthcare, emphasizing its utility for reconstructing clinical trajectories from event logs and identifying deviations from best practices. Remy et al. [17] and Dwyer et al. [8] developed frameworks for generating high-quality event logs from electronic health record (EHR) data using ontology-driven mapping and standardized data models, such as OMOP and SNOMED. Klessascheck et al. [11] applied event abstraction techniques to improve the clinical interpretability of psychiatric process mining models.

Comparative process mining has introduced several methods for contrasting cohorts. Bolt et al. [3] proposed statistical testing on annotated transition systems to highlight differences in activity frequencies and timing. Brockhoff et al. [4] used Earth Mover's Distance to quantify differences between subprocesses identified via selection–projection structures. Mazhar et al. [13] extended the process comparison methodology with stochastic awareness (P2CM), incorporating pathway likelihoods and automated cohort analysis. Since our aim here was to obtain an overview of antidepressant trajectories, we report baseline models and defer integration of these advanced comparative techniques to future work.

Focusing on depression and TRD, DiBello et al. [7] conducted a large-scale longitudinal analysis of pharmacological therapy trajectories among TRD patients, finding that treatment lines become increasingly complex over time, with greater use of combination and augmentation strategies. Potts et al. [15] used process mining to uncover patterns of outcomes in psychological therapies.

These studies form the clinical foundation for process mining in TRD, but most prior work examined TRD in isolation or only aggregate metrics. Few studies have systematically compared antidepressant treatment pathways between TRD and non-TRD patients using large-scale EHR data and process mining techniques. This study addresses this gap by quantifying and benchmarking real-world pharmacological trajectories in both cohorts, extending the literature on the complexity and diversity of depression care.

3 Methodology

This study applies a reproducible pipeline to analyze antidepressant treatment trajectories in major depressive disorder (MDD), structured into three phases—*cohort selection, event log generation*, and *process discovery and analysis*. The transparent design follows best practices in healthcare process mining [14,17,6].

Data were drawn from the Mount Sinai Data Warehouse (MSDW), structured under the OMOP Common Data Model (CDM), and processed on high-performance computing resources at Minerva [12].

OMOP CDM is a widely adopted data model that standardizes the format and relational structure of electronic health records (EHRs) for consistent analysis across diverse healthcare systems [20]. In the United States—the source of data for this study—diagnoses are typically coded using ICD-9/10 (International Classification of Diseases) in hospital settings, while OMOP provides mappings to standardized terminologies such as SNOMED CT (Systematized Nomenclature of Medicine—Clinical Terms) for comprehensive clinical concept representation. This harmonization ensures interoperability across multiple clinical sites and supports accurate cohort identification and event extraction. Our analytic workflow integrates key OMOP tables for diagnostic and prescription history, including `condition_occurrence`, `drug_exposure`, `concept`, `concept_ancestor`, and `visit_occurrence`. To identify the relevant patient cohort, we mapped MDD-related diagnoses from ICD-9/10 to SNOMED CT, and linked antidepressant exposures (using RxNorm ingredient codes) recorded in the OMOP tables. This standardized approach enabled accurate extraction of patients and events of interest, following established methods for healthcare event log construction and ontology-based data integration [17,8,6]. Clinical collaborators (I. Landi) reviewed definitions to ensure plausibility.

While patient-level data cannot be shared due to privacy regulations, full SQL queries, Python code, BPMN models, and figures are openly available in the repository and Supplementary Materials 6.

3.1 Cohort Selection

The analysis began by defining a set of relevant antidepressant ingredients, each mapped to its OMOP standard concept identifier and assigned to a pharmacological category. To ensure comprehensive coverage, this set was expanded to include all descendant concepts using the OMOP `concept_ancestor` table. In parallel, a set of SNOMED concept IDs representing major depressive disorder (MDD) diagnoses was curated by manually mapping relevant ICD-9/10 codes to SNOMED, and this set was similarly expanded to include all descendant codes, following best practices for robust case identification adviced by Diba et al. [6].

For each patient, we determined the date of first available record, t_{record}, defined as the minimum of the first visit or condition occurrence. The date of first MDD diagnosis, t_{MDD}, was then identified for each individual. Inclusion required at least one year of history prior to MDD diagnosis,

$$t_{\text{MDD}} - t_{\text{record}} \geq 365 \text{ days},$$

minimizing misclassification of prevalent or chronic cases as incident. Patients with any antidepressant exposure prior to diagnosis, specifically in the interval $[t_{\text{record}}, t_{\text{MDD}} - 30]$, were excluded to avoid confounding by prior treatment.

The final analytic cohort thus comprised individuals with a first-time MDD diagnosis, at least one year of prior clinical observation, and no antidepressant exposure before diagnosis (with a 30-day buffer). This approach—grounded in ontology-driven concept expansion and transparent, SQL-based implementation—ensures clinical relevance and reproducibility, and is consistent with current methodological guidance [8,17,6]. Full technical details, including code and concept mappings, are provided in the supplement and project repository 6.

3.2 Event Log Generation

After selecting the cohort, we excluded patients without any antidepressant exposure to antidepressants on the predefined descendant list, ensuring that every individual in the subsequent analysis had at least one relevant antidepressant prescription. The resulting dataset, extracted from `drug_exposure` table, comprised prescription records, with each entry denoting a unique instance of drug exposure annotated by patient identifier, drug concept, and exposure period.

First, prescription records were systematically de-duplicated to retain only the first occurrence of each unique combination of patient, drug, and exposure interval, reducing redundancy from 436,476 to 415,835 records while preserving the unique patient count (31,941).

Next, a quality control step excluded patients with implausible prescription histories—specifically, those with zero-day case duration (i.e., the interval between their earliest and latest start of recorded antidepressant exposure) and more than two unique prescriptions—resulting in a final analytic cohort of 31,881 patients and 415,641 records. This exclusion criterion was adopted to remove likely data entry errors or records reflecting batch imports of historical prescriptions, as it is clinically implausible for a patient to initiate multiple distinct

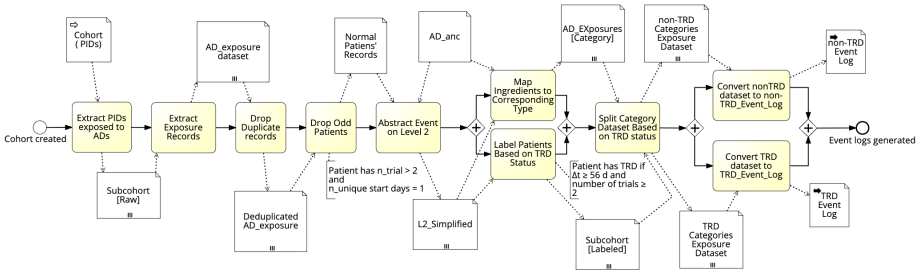

Fig. 1. BPMN process model illustrating the event log generation (ELG) phase of the analytic pipeline. Key abbreviations: AD = antidepressant, PID = patient identifier, TRD = treatment-resistant depression, non-TRD = non-treatment-resistant depression, AD_anc = antidepressant ancestor (standardized parent ingredient and mapping to therapeutic category), Δt = time interval (days), L2 = Level 2 abstraction (ingredient level). Complete BPMN models for all analytic phases with high resolution are available in the project GitHub repository 6.

antidepressant therapies on the same day. Retaining such cases could bias downstream analyses of treatment trajectories and process patterns.

Prescription events were semantically enriched by mapping each OMOP drug concept identifier to its canonical ancestor (active ingredient), supporting consistent abstraction and clinical interpretation as recommended by prior studies [17,6,8]. This reduces heterogeneity due to differences in drug brand names, formulations, or coding practices, allowing for more meaningful aggregation and analysis of pharmacological treatment patterns across the cohort.

Furthermore, TRD status was operationalized following the STAR*D definition of ≥ 2 failed adequate antidepressant trials, a widely used but not universally accepted standard [9]. Specifically, for each patient, consecutive exposures to the same ancestor drug were merged into continuous intervals, with intervals of at least 56 days considered adequate trials. Thus, dosage changes within the same drug were not considered switches. Patients with more than two such trials were classified as TRD, while all others were labeled non-TRD.

To facilitate interpretable process mining and manage model complexity, each ancestor drug was abstracted to a therapeutic class (SSRI, SNRI, atypical antidepressants, tricyclic antidepressants, MAOIs, augmentation agents, or others), as recommended for process simplification and interpretability [6,17,11]. For each exposure event, only the patient identifier, drug category, and prescription start and end date were retained, consistent with the XES event log standard [1].

Having extracted such datasets, separate event logs were generated for TRD and non-TRD patients by filtering on computed TRD status. Data integrity was validated by confirming the absence of missing values in the essential event attributes [6]. Finally, the formatted event logs were exported to XES files using the PM4Py framework [2] for further analysis.

3.3 Process Discovery and Analysis

Process discovery was performed on the TRD and non-TRD event logs generated in Section 3.2 using the Directly-Follows Graph (DFG) algorithm in the PM4Py framework [2]. To enforce a single-entry, single-exit structure, each trace was prepended with a synthetic `Start` event and appended with a synthetic `End` event—both time-stamped to the first and last original events, respectively—facilitating consistent visualization and comparison. To improve readability, we applied a 50-occurrence threshold to filter low-frequency edges, retaining any edge involving `Start` or `End`—in accordance with clinical modeling best practices. Both unfiltered (available in Supplementary Materials 6) and filtered graphs were rendered using PM4Py's frequency-based visualizer.

In the resulting DFGs (see Figure 3 and Figure 4), nodes correspond to drug-category activities, and directed edges are weighted by the frequency of consecutive transitions.

We further computed process-complexity and variability metrics via PM4Py's variant-analysis module (e.g., number of unique trace variants, case-length distribution) and temporal metrics (case-arrival, case-dispersion, and case-duration) to quantitatively characterize each cohort's treatment pathways.

4 Results

The analytic samples included 4,630 TRD cases (184,979 antidepressant exposures) and 27,251 non-TRD cases (230,662 exposures), with 73,947 and 40,954 category switches, respectively. Case-level statistics are summarized in Table 1. The median case duration was 1,473 days for TRD and 112 days for non-TRD, while the median number of events per case was 23 and 4, respectively.

Comparison of initial treatment strategies showed no major differences in the distribution of starting drug categories between TRD and non-TRD patients (see Supplementary Materials 6).

The unfiltered directly-follows graph (DFG) models comprised nine activity nodes, with 61 of 72 possible edges (see Supplementary Materials 6). After filtering for transitions occurring at least 50 times (retaining all `Start`/`End`), the final DFGs for both cohorts contained 49 edges (see Figures 3 and 4), highlighting the most prevalent treatment transitions.

Trace variant analysis demonstrated pronounced heterogeneity in TRD: 4,332 unique variants were identified among 4,630 TRD cases (almost one variant per case), with the most common variant in only 16 cases and single-category pathways in 4.9% (228/4,630). In contrast, non-TRD was more homogeneous, with 4,698 variants across 27,251 cases; the most frequent variant appeared in 2,943 cases and 74% (20,141/27,251) followed a single-category trajectory. Figure 2 depicts this stark difference in variant prevalence.

Switch delay analysis showed that 58.9% of TRD and 55.7% of non-TRD switches were zero-day (i.e., same-day transitions). In TRD, 17.4% occurred after one day; in non-TRD, 36.2% did. The majority of switches occurred within

Table 1. (a) Cohort and event log statistics for TRD and non-TRD groups; (b) Distribution of delays (in days) between antidepressant category switches.

	TRD	**non-TRD**
Number of cases	4,630	27,251
Number of events	184,979	230,662
Number of category switches	73,947	40,954
Median case duration (days)	1,473	112
Median events per case	23	4
Mean events per case	40.0	8.5
Max events per case	1,064	1,174
Unique trace variants	4,332	4,698
Single-category cases (%)	4.9	74

(a)

	TRD	(%)	**non-TRD**	(%)
Total switches	73,947		40,954	
0-day delay	43,542	58.9	22,793	55.7
1-day delay	12,889	17.4	14,820	36.2
≤7-day delay	58,343	78.9	38,427	93.8
≤28-day delay	65,811	89.0	39,901	97.4

(b)

seven days (TRD: 78.9%, non-TRD: 93.8%), and within 28 days (TRD: 89.0%, non-TRD: 97.4%)—see Table 1(b). Delays from the end of failed trials to new category initiation were typically brief (median 1 day in both groups), though outliers were observed.

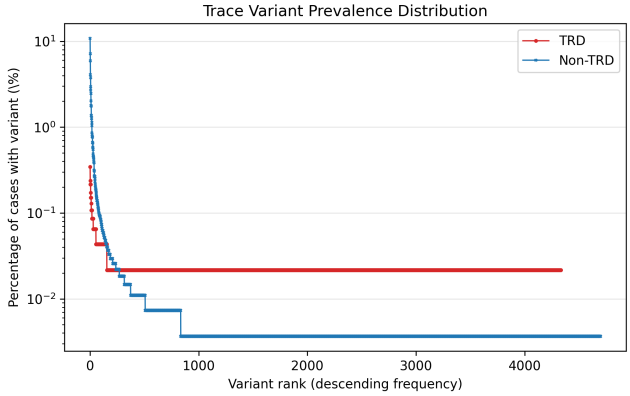

Fig. 2. Trace variant prevalence distribution for TRD and non-TRD cohorts. Each point denotes the percentage of cases exhibiting a given trace variant, ranked by descending frequency (logarithmic y-axis).

5 Discussion

This process mining study provides detailed insight into real-world antidepressant treatment trajectories for both TRD and non-TRD patients. The noted differences in trace diversity, sequence structure, and temporal patterns between the two cohorts have important methodological and clinical implications.

The trace variant distribution (Figure 2) vividly demonstrates the extreme heterogeneity that characterizes TRD; nearly every TRD case followed a unique sequence of antidepressant switches. By contrast, non-TRD pathways were simpler and more homogeneous, with most patients following a single-category trajectory. Such heterogeneity, absence of standard pathways, and limited effective-

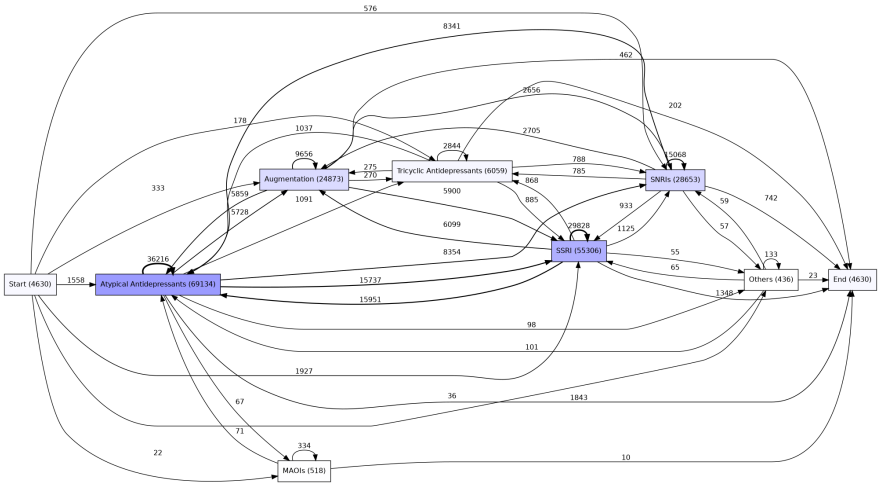

Fig. 3. Filtered directly-follows graph (DFG) for TRD cohort: only transitions with at least 50 occurrences are shown, except transitions involving synthetic `Start` or `End` events, which were retained regardless of frequency.

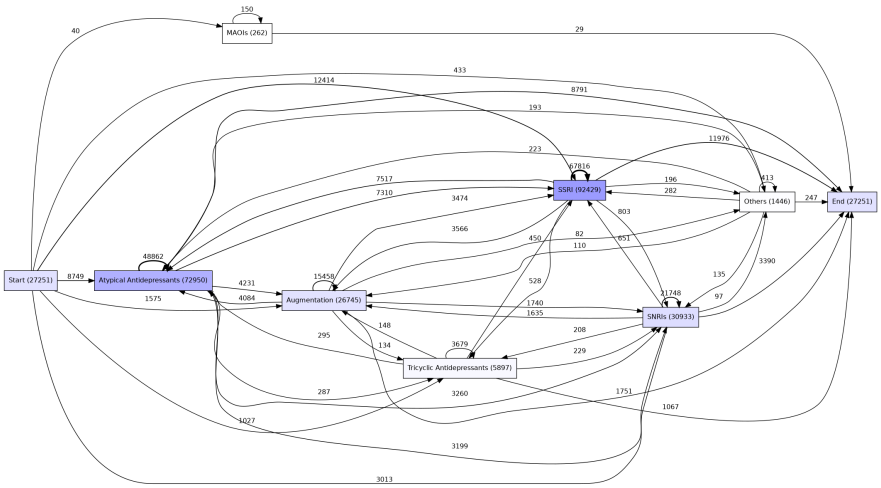

Fig. 4. Filtered directly-follows graph (DFG) for non-TRD cohort: only transitions with at least 50 occurrences are shown, except transitions involving synthetic `Start` or `End` events, which were retained regardless of frequency.

ness of existing TRD options are well-documented in the literature [7,5,10,19], with our findings reinforcing these observations through process mining. The low prevalence of any single variant in TRD (most common: 16 cases) versus the dominant variant in non-TRD (2,943) highlights the reality of highly individualized and flexible care pathways in TRD, which informs future clinical guidelines and research. Initial treatment strategies were similar—including some use of non-standard first-line agents—so TRD heterogeneity emerges later in care.

Pathway completion patterns further emphasized this difference. About three-quarters of non-TRD patients completed treatment with a single antidepressant category, compared to only 4.9% of TRD cases. This observation aligns with prior reports of high rates of switching and combination therapy among patients with TRD [7,5], and highlights the dynamic, often protracted, nature of TRD [10,19].

Filtering process models by edge-frequency thresholding was essential for interpretability. Reducing DFG edge coverage from 85% to 68% focused attention on prevalent transitions, suppressing noise and rare events. This abstraction has been reported as valuable in complex healthcare process mining [17,14,11], especially in psychiatry with highly variable pathways [15].

Temporal characteristics further differentiated the cohorts. Median case duration in TRD exceeded four years, compared to roughly three and a half months in non-TRD, with correspondingly higher event counts per patient. Quantitatively, the average event count per TRD case was 40, versus 8.5 in non-TRD, with extreme outliers in maximum pathway length in the TRD group (as documented in Table 1). These findings quantitatively illustrate the extended and often protracted treatment journeys typical of TRD, a phenomenon repeatedly documented in the literature [9,5,19]. Prior studies have shown that TRD is not only associated with longer treatment episodes, but also presents significant clinical management challenges due to its persistence, greater morbidity, and higher healthcare resource utilization [5].

The high prevalence of zero-day switch delays in both groups indicates that changes in antidepressant category are frequently implemented on the same day, either via simultaneous prescribing (polypharmacy) or immediate transitions during a single clinical encounter. Such rapid or concurrent switching is common in real-world practice, particularly in more refractory cases, and reflects guidelines emphasizing prompt adjustment for nonresponse [9,10,7]. The difference in short delays—TRD patients having more same-day switches, non-TRD more one-day switches—may reflect differences in clinical urgency, workflow, or prescribing habits, but in both cases is consistent with clinical guidance advocating timely medication adjustment in depression management [10,21]. As summarized in Table 1(b), the distributions of switch delays differ between TRD and non-TRD cohorts: non-TRD patients exhibit a higher proportion of rapid switches (especially at 1-day delays), while TRD patients display a relatively greater frequency of extended delays between treatment changes. This pattern underscores periods of clinical uncertainty or monitoring in TRD and further illustrates the complexity of TRD care and the challenges clinicians face in establishing effec-

tive, standardized strategies reflected by Howes et al [10]. A visualization of the full delay distribution is provided in the Supplementary Materials 6.

Delays following failed antidepressant trials were also brief in most cases, with a median of just one day in both groups. Occasional long delays indicate that, while timely adjustment is typical, substantial waits still occur for a minority of patients—potentially due to system-level, clinical, or patient-level barriers, as described in recent large-scale and review studies [5,10,16]. Negative delay values, although rare, reflect overlapping prescription intervals, a phenomenon previously described in process mining studies of antidepressant therapy and psychological care, suggesting either intentional cross-tapering, augmentation strategies, or limitations in data granularity [7,15].

Our analysis intentionally reports a reproducible baseline (DFGs, variants) for psychiatric pharmacotherapy. We tested trace clustering at ingredient and drug levels, but the resulting DFGs were not interpretable at cohort scale. Future work will incorporate comparative techniques (e.g., Earth Mover's Distance, overlay-based model comparison, cluster-based contrasts) to systematically validate cohort differences.

Limitations of this approach include the inability to assess within-category dose changes, possible misclassification due to prescription data incompleteness, and reliance on duration-based TRD definitions, which might miss some nuanced, clinically important aspects of TRD, and this type of limitation has also been noted in prior studies of antidepressant management and EHR-based TRD research [9,10,19]. We did not conduct formal clinical validation of the extracted cohorts or process models; dedicated feedback sessions with domain experts are planned as essential future work. Also, we did not model contextual covariates (e.g., comorbidities, age, sex), which likely shape switching behavior and pathway complexity. Additionally, the requirement for at least one year of history and the exclusion of patients with antidepressant exposure preceding their first recorded MDD diagnosis may introduce selection bias, restricting the cohort to incident cases with comprehensive longitudinal data. While this enhances temporal clarity, it may underrepresent chronic, relapsing, or recently transferred patients, thereby limiting generalizability to the broader MDD population. Furthermore, our analysis was restricted to pharmacological treatment and did not capture complete care pathways, like psychotherapy or other interventions.

6 Conclusions

This study systematically applied process mining to real-world antidepressant prescription data, revealing marked differences in treatment trajectories between patients with treatment-resistant depression (TRD) and non-TRD patients. TRD was characterized by substantially greater pathway complexity, a near one-to-one ratio of unique trace variants to cases, more frequent and rapid medication changes, and prolonged treatment durations. These process-level insights quantify the clinical and operational challenges inherent to TRD care and

highlight the strengths of process mining for benchmarking, comparison, and quality assessment in psychiatric treatment pathways.

Future work should extend this analytic pipeline with advanced comparative techniques to better characterize latent care patterns and deviations from guidelines. Multi-site replication will be essential to assess generalizability across health systems, and structured clinical validation of model outputs is needed to ensure interpretability. Moreover, integrating additional EHR modalities such as psychotherapy, neuromodulation therapies, comorbidity profiles, and sociodemographic information will enrich our understanding of treatment resistance and support the development of more adaptive, patient-centered care pathways.

Supplementary Materials

All SQL scripts, Python code, BPMN process models, and corresponding screenshots used in this study are available in the project's GitHub repository[3]. Supplementary Materials also include detailed cohort definitions, full concept mappings, and additional methodological documentation. The underlying patient-level data are not publicly available due to institutional and ethical restrictions.

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Disclosure of Interests.

The authors declare no competing interests relevant to this article.

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