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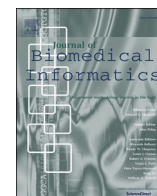
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Discovering prescription patterns in pediatric acute-onset neuropsychiatric syndrome patients

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ABSTRACT

Objective: Pediatric acute-onset neuropsychiatric syndrome (PANS) is a complex neuropsychiatric syndrome characterized by an abrupt onset of obsessive-compulsive symptoms and/or severe eating restrictions, along with at least two concomitant debilitating cognitive, behavioral, or neurological symptoms. A wide range of pharmacological interventions along with behavioral and environmental modifications, and psychotherapies have been adopted to treat symptoms and underlying etiologies. Our goal was to develop a data-driven approach to identify treatment patterns in this cohort.

Materials and methods: In this cohort study, we extracted medical prescription histories from electronic health records. We developed a modified dynamic programming approach to perform global alignment of those medication histories. Our approach is unique since it considers time gaps in prescription patterns as part of the similarity strategy.

Results: This study included 43 consecutive new-onset pre-pubertal patients who had at least 3 clinic visits. Our algorithm identified six clusters with distinct medication usage history which may represent clinician's practice of treating PANS of different severities and etiologies i.e., two most severe groups requiring high dose intravenous steroids; two arthritic or inflammatory groups requiring prolonged nonsteroidal anti-inflammatory drug (NSAID); and two mild relapsing/remitting group treated with a short course of NSAID. The psychometric scores as outcomes in each cluster generally improved within the first two years.

Discussion and conclusion: Our algorithm shows potential to improve our knowledge of treatment patterns in the PANS cohort, while helping clinicians understand how patients respond to a combination of drugs.

1. Introduction

In cohorts of patients with multiple medication usage –polypharmacy– it is important to understand if there are groups of patients that share similar patterns of usage and what are the differences between these groups of patients. Polypharmacy is common in older patients with multimorbidity [1]; and it is associated with adverse

outcomes including mortality and adverse drug reactions [2], increased length of stay in hospital and readmission to hospital soon after discharge [3]. Polypharmacy can also occur in children and adolescent patients with psychiatric diseases [4], and other non-elder adults with complex chronic syndromes such as lupus [5], human immunodeficiency virus (HIV) infection [6], ischemic and respiratory diseases [7], or cancer [8]. These diseases are often multifactorial, with physicians

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treating related, but separate, symptoms and pathologies. One of these syndromes is the pediatric acute-onset neuropsychiatric syndrome (PANS).

The PANS clinical presentation [9] is characterized by abrupt-onset of obsessive-compulsive disorder and/or food restriction, along with at least two other severe neuropsychiatric symptoms from the following categories: anxiety; mood lability or depression; irritability, oppositionality, or rage; behavioral regression; deterioration in school performance/cognitive difficulties; sensory or motor abnormalities; and somatic symptoms like sleep disturbances or enuresis. Patients typically experience a relapsing-remitting course in which disease flares are interspersed with remissions [10]. In some cases, the disease course is chronic, when the patient's neuropsychiatric status does not return to baseline.

Current evidence suggests that PANS has an inflammatory or autoimmune etiology that is associated with an infection [11–16]. A recent MRI study in children with PANS showed an increased median diffusivity in multiple brain structures including basal ganglia, thalamus and amygdala compared to controls, suggesting neuroinflammation in these regions. Multidisciplinary clinics are well-positioned to care for patients with PANS [17]. Although treatment protocols are lacking, interim guidelines suggest using antibiotics to treat or prevent infections, immunomodulatory therapies to manage inflammation, and psychiatric medications supplemented with cognitive behavioral therapy to treat PANS [18]. The heterogeneity and complexity of PANS presentation, clinical course, treatment, insurance status, and irregular follow-up make it difficult to compare treatment courses across patients and patient-groups. The difficulties in documenting an association between streptococcal infection and symptom onset/exacerbations makes it challenging to understand when to use antibiotics such as penicillin [9]. A novel method to cluster patients given their temporal medication prescriptions, is needed to identify potential disease subgroups.

In precision medicine, patient similarity is an emerging concept that aims to help discover groups of patients (clusters) that share similar characteristics estimating a numerical distance between components of patient data [19]; and ultimately, to use those clusters in predictive modeling tasks [20]. The data features commonly used include demographics and population characteristics [21], genetics [22], prescriptions and lab tests [23,24], medical billing codes [25], and even clinical narratives processed with natural language tools [26]. Meanwhile, commonly used algorithms for this task employ distance-based functions that consider geometrical space (e.g. Euclidean, Manhattan, etc.) [23,27]; machine learning models that employ representations of patients in the multivariate space (e.g. decision trees [28] or random forests [29]); and the use of ontologies to find hierarchically related concepts (e.g. patients with closely related diagnosis [30]). However, the temporal dimension of the patient journeys is often not addressed by these algorithms, which requires a broader exploration.

Previous work using temporal information encoded clinical events into streams of information, enabling the use of sequence alignment algorithms in bioinformatics pipelines. Recently, Ledieu et al. [31] used a modified version of the Smith-Waterman sequence local alignment algorithm for pharmacovigilance in electronic medical records, detecting inadequate treatment decisions in patient sequences. Meanwhile, Lee & Das [32] developed a local sequence alignment strategy to find HIV patients with similar treatment histories, leveraging a simple ontology to improve local alignment of antiretroviral regimens. The use of the ontology certainly adds value to the algorithm, but it is also a limitation if the ontology is not well defined or unknown, for example in the case of the PANS patients.

In this study, we developed a modified version of the global alignment Needleman-Wunsch algorithm to the medication prescription patterns of a PANS cohort from Stanford University to elucidate groups of patients with similar treatment patterns. Our medication alignment algorithm *MedAI* retrospectively finds patients with similar prescription patterns, and groups them into clusters to associate their overall

impairment scores. Our goal was to provide a data-driven approach to identify treatment patterns in the PANS cohort.

2. Materials and methods

This is a retrospective cohort study, using patient/parent questionnaires and ledgers collected routinely as part of clinical care, as well as electronic medical records (EMR) data. The objective was to understand patterns of medication usage in patients. Our study involved extracting data from electronic health records, using *MedAI* to create a patient similarity metric, grouping patients into clusters, visualizing them, evaluating the cluster assignment, and validating the clusters with clinical outcomes in the PANS cohort. The study outline is shown in Fig. 1, where our algorithm *MedAI* allows for downstream clustering by defining a distance between the study subjects.

Clinical setting and population

The pilot study took place at the Stanford PANS clinic located in California, United States of America, which is a multidisciplinary clinic staffed by practitioners of various disciplines (psychiatry, primary care, rheumatology, immunology), as well as a social work psychotherapist and an education specialist.

The data used in this study were generated during clinical care and includes prospectively collected impairment scores (global impairment and caregiver burden inventory), but we also retrospectively collected medication use data abstracted from the clinical charts. Data were collected on those patients seen between the clinic inception on September 3rd, 2012, and the patient cohort identification date for this study, January 31st, 2018. In this period there were 305 patients seen in clinic, out of which we excluded: those whose parents refused consent

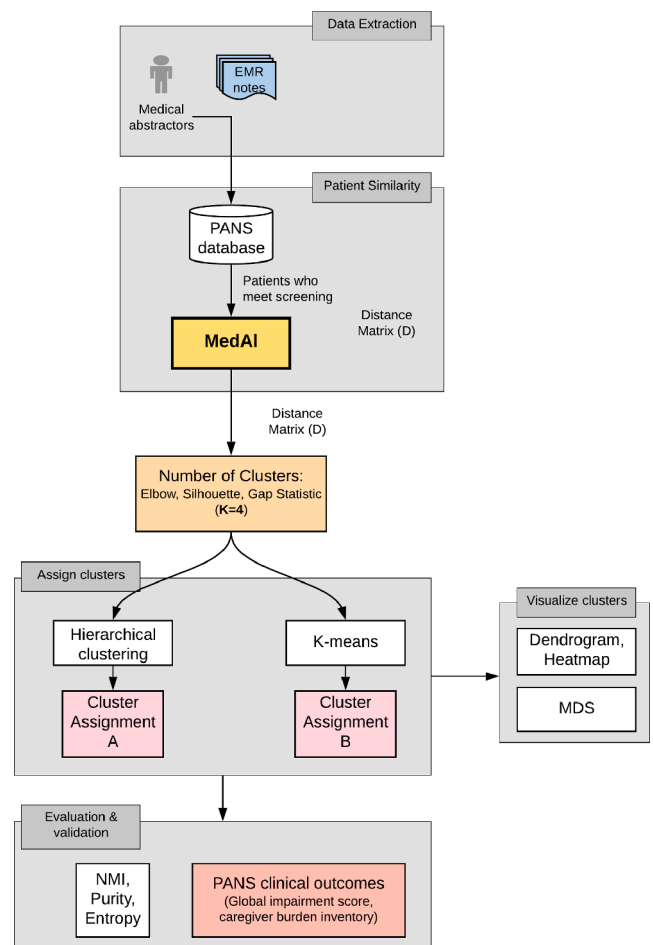


Fig. 1. Study outline.

for the study ($N = 4$), those patients who did not meet the strict PANS criteria [9] ($N = 97$), had fewer than three visits to the PANS clinic ($N = 36$), were older than 12 years at clinic entry ($N = 60$) and presented to the clinic more than 4 months after onset of psychiatric symptoms ($N = 65$). The final cohort includes 43 pre-pubertal new-onset patients, as shown in [Supplementary Material 1](#). One patient was dropped from the primary analysis because the only medication was taken after the first two years at the clinic.

We only included patients with established care with the clinic (at least three visits) because the first few visits aim to understand the history and disease course, to examine patients and to counsel parents about different treatment options. We used a cut-off age of 12 years to include only pre-pubertal children, as hormones might play a role in psychiatric symptoms and behaviors [33]. We restricted patients to those with such a short time difference between PANS onset and first PANS clinic appointment because we wanted to analyze patients with new-onset PANS, for whom we had more complete information close to the beginning of their PANS illness.

Data sources

We collected data on medical treatment from the electronic medical record using a keyword search method [34], and we made a final update of medication history in mid-October 2018. For this patient group, a limited number of medications are offered and were decided upon a priori by the clinical team. We excluded short courses (less than 21 days) of antibiotics for acute infections, NSAID taken as needed by patients, and psychiatric medications as the aim of this analysis was to study the similarity of using medical (non-psychiatric/non-psychological) therapies in this group of patients. Our medication keyword search method is outlined in [Table 1](#).

For medications taken daily, we determined the start and stop dates. For medications with long acting effects (i.e. Rituximab, IV corticosteroids) we determined the start date only. In some cases, determining start and stop dates is challenging. For example, a patient/parent may have decided to discontinue a medication between two clinic visits but

failed to recall the exact stop date. In these cases, we estimated the stop date using one of two methods: a) if the provider estimated a unit of time during which patient stopped taking the medication, we used the midpoint of that unit of time (e.g. “patient stopped NSAIDs March 2017” would be coded as March 15, 2017; early March will be coded as March 1; late March will be coded as March 30; two weeks ago will be 14 days before the encounter date); b) if no estimate was given, we used the clinic visit date on which the provider reported the patient stopped taking the medication as the stop date. All stop dates for active medications were set at the last visit dates. If a patient suspended the drug for less than a week, we would consider it to be a continuous use; otherwise, we would state two separate periods.

Patient outcomes

In the PANS cohort, like in many other psychiatric syndromes, evaluating outcomes is a complex task which requires the use of scales and assessment scores that are subjective in nature. The Stanford PANS clinic utilizes two parent rated impairment scales that have been validated in this patient population:

Global Impairment Scale [35]. A scale ranging from 0 to 100, where the highest value indicates severe challenges for the patient to interact with others and carry on their daily activities, and the lowest value indicates a child without impairment.

Caregiver Burden Inventory [36]. A scale ranging from 0 to 96, where the highest value indicates the greatest caregiver burden. A score greater than 36 indicates respite care [37].

The Stanford PANS clinic collects electronic patient questionnaires that caregivers and patients fill out before each clinic visit. The questionnaire queries symptom-specific scales corresponding to the severity of the patient symptoms. The outcome data (Global Impairment and Caregiver Burden) may be skewed by the fact that the frequency of follow-up clinic visits and corresponding completed questionnaires trends with the severity of the psychiatric symptoms (i.e. when patients

Table 1
Medication list and keywords (underlined> used in the EMR search-box.

Class	Generic name	Brand name	Common use	Freq*	Admin.
Antibiotic (<u>Penicillin</u>)	Penicillin G	Various	Streptococcal infection and prophylaxis against strep	Once every 3–4 weeks	IM
	Penicillin V	Various	<i>Idem</i>	Daily	Oral
	<u>Amoxicillin</u>	Amoxil	<i>Commonly used to treat otitis media, sinusitis, and streptococcal infections</i>	Daily	Oral
Antibiotic (<u>Cephalosporin</u>)	Amoxicillin + Clavulanate potassium	<u>Augmentin</u>	<i>idem</i>	Daily	Oral
	<u>Cefalexin</u>	Keflex	Gram-positive infections	Daily	Oral
	<u>Cefadroxil</u>	Duricef	<i>Idem</i>	Daily	Oral
Antibiotic with Anti-inflammatory Effect (Macrolide)	<u>Azithromycin</u>	<u>Zithromax</u>	Streptococcal and Mycoplasma infections, syphilis, respiratory infections, etc. Also used as an anti-inflammatory in some diseases.	Daily	Oral
Non-steroidal Anti-inflammatory Drugs (<u>NSAID</u>)	<u>Ibuprofen</u>	Advil	Anti-inflammatory	Daily	Oral
	<u>Naproxen</u>	Aleve			
	<u>Indomethacin</u>	Indocin			
	<u>Sulindac</u>	Clinoril			
	<u>Aspirin</u>	Aspirin			
Corticosteroids (oral)	<u>Prednisone</u>	Prednisone	Anti-inflammatory	Daily	Oral
	<u>Dexamethasone</u>	Decadron	Anti-inflammatory	Daily	Oral
Corticosteroids (IV)	<u>Methylprednisolone</u>	<u>Solumedrol</u>	Anti-inflammatory	Short course over 1–3 days	IV
Immunoglobulins	Intravenous Immunoglobulin (<u>IVIG</u>)	Various	Inflammatory diseases and immunodeficiencies	Short course over 1–3 days	IV
Disease-modifying anti-rheumatic drug (DMARD)	<u>Rituximab</u>	Rituxan	<i>Autoimmune disease</i>	One round over a day	IV
	<u>Methotrexate</u>	Various	Anti-rheumatic	Daily	Oral or SC
	Mycophenolate mofetil	<u>Cellcept</u>	Anti-rheumatic	Daily	Oral

After keywords were highlighted, clinical records were reviewed in detail to ensure that the patient was taking the medication as listed. Abbreviations: Freq: Frequency of administration; Admin: Route of administration; IM: intramuscular; IV: intravenous; SC: subcutaneous.

*Daily dose can be divided into several doses.

are highly symptomatic, they come to the clinic weekly for psychiatric medication titration and therapy, but when the child improves/resolves their psychiatric symptoms, it is difficult to get the family to return to clinic). An example of the medication journey and outcome for a selected PANS patient in this cohort is shown in Fig. 2.

A modified sequence alignment algorithm

In this manuscript, we propose medication alignment for patient similarity (*MedAI*) algorithm, that adapts a protein sequence alignment paradigm [38,39] to medication usage history. The alignment edit distance is used to estimate medication usage similarity, in order to construct a clustering strategy. The algorithm is as follows: a) encode the medication history in a sequence representation; b) perform alignment of pairs of medication sequences; and c) compute a weighted patient pairwise edit distance.

Encode the medication history. Medication usage was encoded into a binary vector representing daily intake. We considered missing values to be not missing at random (NMAR), and therefore assigned an explicit missing value (represented by the character 'Ø'). For example, consider a patient taking two 3-day rounds of a corticosteroid burst (represented by the character 'C'), followed by two resting days. The encoded version for this would be a "CCCØØCCC".

Sequence alignment. We used a dynamic programming approach to align the medication history encoded vectors. There are two steps: (1) matrix fill, and (2) traceback. First, we create a data matrix between two patient's histories, and initialize it with zeros in the first column and row. The remaining elements of the matrix are filled from left to right and top to bottom. For each cell the substitution is evaluated using the pattern table shown in Fig. 3 (Panel A). By the end of this step the matrix contains all the alignments between the two sequences. The second step finds the best alignment by tracing back the path from the bottom right corner (end of two patient records) to the top left corner (start of patient records) based on the alignment that leads to the score. For a step by step annotated example, please refer to [Supplementary Material 2](#).

It is important to clarify that MedAI is different from other sequence alignment algorithms because of the use of its pattern table, corresponding to four medication usage patterns: start of medication,

continuing medication, end of medication, and continuing gap. For any pair of patients there are 16 possible combinations for how the medication is being administered to both patients, and four penalty calculations, represented under each tile of Fig. 3 (Panel A): (1) if both patients have the same medication usage pattern, then the minimum neighboring value is assigned; (2) if one of the patients has switching pattern (e.g. the first patient starting medication, and second patient continuing medication), then the maximum neighboring value is assigned; (3) if both patients have complete opposing patterns (e.g. first patient is starting medication while the second patient is ending medication), then the maximum neighboring value plus one is assigned; and (4) lastly, if one of the patients has a pattern involving missing values (e.g. first patient is starting medication, while the second patient is not taking anything), then the minimum neighboring value plus one is assigned.

Weighted edit distance. The edit distance is a metric of the minimum number of operations needed to align two sequences. Traditionally in genome sequences, these operations could be insertion of a gap, deletion of a position, or substitution for an equivalent letter. However, for medication alignment, we only allow insertions, since we do not want to delete medication histories, and a substitution for an equivalent letter is difficult to assess. In Fig. 3, the minimum distance, for a toy example, is shown as the green path.

Cluster assignment and evaluation

Assigning patient similarity can be important for diagnostic and treatment purposes particularly in hard to diagnose or complex diseases. An experienced physician can often provide a measure of this similarity, but an automatic score is needed for large databases to evaluate the physician prior knowledge (e.g. the cost associated for stopping a drug or switching to a new drug can be determined by the physician). If the cost is properly assigned, various clustering algorithms should provide similar answers. For illustration purposes, we used two well-known clustering algorithms: hierarchical clustering and k-means.

Hierarchical clustering (hclust). This is a popular technique that creates clusters with an ordering (hierarchy). We selected an

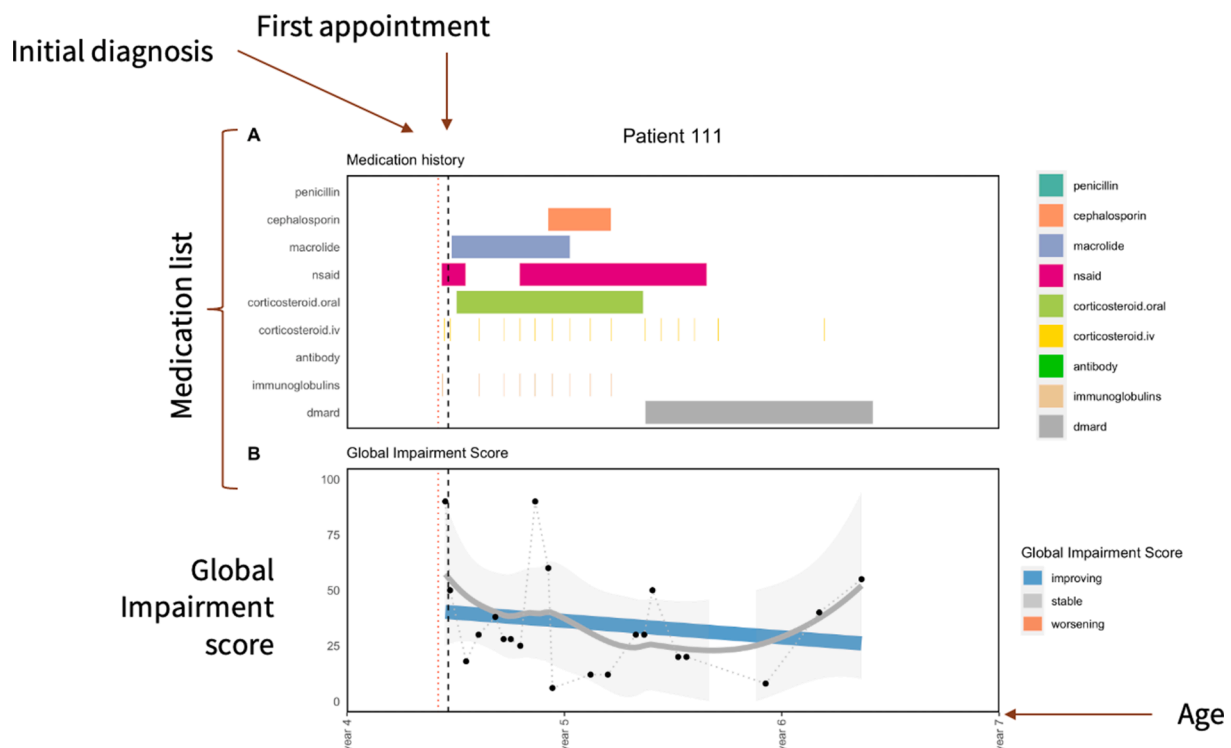


Fig. 2. Medication journey for a selected PANS patient in the cohort.

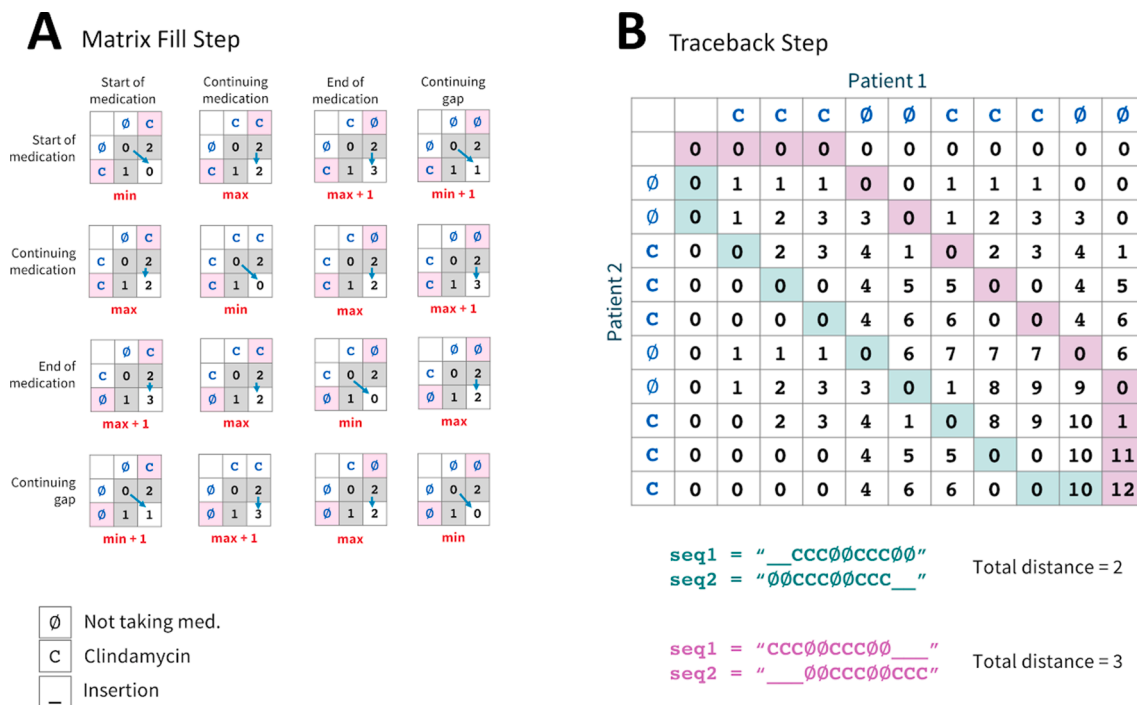


Fig. 3. Dynamic programming approach to medication alignment. (A) Matrix fill step; (B) Traceback step. The path starts from the bottom-right cell and ends at the top-left cell of the matrix. Only two insertions were needed to align the sequences. The purple path is an alternative sub-optimal alignment that requires three insertions, but this distance is not selected.

agglomerative (bottom-up) algorithm with complete linkage. This method starts by assigning each sample to its own cluster. Then, to join the two most similar patients into a larger cluster, we used the *MedAl* distance. The algorithm continues to recursively aggregate clusters until all samples have been added to a single cluster.

K-means. This clustering method is also a popular clustering method which has been previously used in psychiatric disorders [40]. This technique aims to partition observations of patients into k clusters in which each observation belongs to the cluster with the nearest mean. The metric to estimate distance is typically a geometrical distance (e. g. Euclidean distance). This metric was not feasible with the medication history data, therefore *MedAl* was used.

We used three metrics to compute external criteria that evaluates how well the clustering matches the gold standard classes (normalized mutual information (NMI), cluster purity, and cluster entropy). For the PANS cohort, the ground truth of cluster assignment is unknown, and therefore these metrics only serve to provide confidence on the equivalence of clustering assignment between two methods (hclust and k-means). All three methods range from 0, being the worst evaluation, to 1, being the best evaluation.

Four quantitative methods were used to estimate the optimal number of clusters (k) in the PANS cohort: (a) elbow method, which measures the compactness of clusters by summing the within-cluster sum of squares; (b) Silhouette method [41], which measures the cohesion of clusters, through averaging the distance between each element and the rest of the elements in that cluster, and comparing to the average distance of neighboring clusters; (c) Gap statistic [42], which estimates the statistical comparison between the total intra-cluster variation and the null hypothesis without cluster assignment; and (d) Clest method [43], which is a variation on the gap statistic, selecting the number of clusters within a range from the maximum global standard error.

Evaluation and validation of the assigned clusters was done by comparing the aggregated outcomes in two questionnaires the Global Impairment score and Caregiver Burden Inventory, where we conducted an analysis of variance (ANOVA) accounting for longitudinal sampling

from each individual. Slopes were fit stratified by cluster using a linear mixed-effects model to determine trends within clusters for both scores. The null hypothesis was that there is no difference between groups, therefore having a p-value smaller than 0.05 would reject this hypothesis, and show that *MedAl* distance was successful in finding significant clusters.

3. Results

Clinical characteristics

Patient characteristics in this study were evenly distributed by sex, and heavily skewed by self-reported race and ethnicity (mostly non-Hispanic white) in patients. The age at first neuropsychiatric deterioration occurred on average between 7 and 8 years old, with a rapid intake by the PANS clinic (patients seen >4 months after psychiatric symptom onset were excluded). Table 2 shows a detailed description of the clinical characteristics of this cohort.

Number of clusters

A graphical inspection of the methods in Fig. 4 shows disagreement between them. The elbow method does not clearly show an elbow, suggesting that any number of clusters would show some effect. In the Silhouette method, the maximum value was at $k = 9$ (the highest rated), however, there are two good candidates at $k = 2$ and $k = 4$. The gap statistic method shows the best value at $k = 2$. The Clest method suggests a number of clusters of $k = 6$. On the other hand, when comparing cluster purity, NMI and Entropy, these metrics seem to converge around $k = 6$.

Cluster assignment

A critical point in the selection of a cluster assignment is to select an appropriate number of clusters. From the metric evaluation shown in Fig. 4, there were some good candidates (Gap: $k = 2$; Clest: $k = 6$; Silhouette $k = 9$). From Panel E in Fig. 4, we also observed that $k = 2$ and $k = 6$ had the most similar cluster assignments (lowest entropy, and highest NMI and Purity). However, since there was no clear selection of the best number of clusters, we used a heatmap with the *MedAl* score, showing how the different patients would cluster together using

Table 2

Clinical characteristics of 43 consecutive pre-pubertal patients with new-onset PANS.

Characteristic	PANS
Overall	N = 43
Sex	
Female	23 (53.49%)
Male	20 (46.51%)
Age at first neuropsychiatric symptom onset (years)	mean = 7.77 SD = 2.35
Age at first clinic visit (years)	mean = 7.93 SD = 2.39
Race/ethnicity*	
Non-Hispanic White	39 (90.7%)
Non-Hispanic Asian	4 (9.3%)
Hispanic/Latino	4 (9.3%)
Other/unknown	4 (4.65%)
PANS symptoms at first presentation to the clinic	
Obsessive compulsive symptoms	36 (83.72%)
Food intake problems	18 (41.86%)
Anxiety/phobia	37 (86.05%)
Emotional lability/depression/suicidal ideation	33 (76.74%)
Aggression/irritability/opposition	33 (76.74%)
Cognitive problems	9 (20.93%)
Inattention/deterioration in school	24 (55.81%)
Behavioral regression	27 (62.79%)
Sensory amplification	19 (44.19%)
Sleep disturbances	26 (60.47%)
Urinary problems	14 (32.56%)
Motor/vocal tics	24 (55.81%)

SD = standard deviation. *Race/ethnicity is a self-reported item on the patient questionnaire and more than one category could be selected. The medication list included seven categories of drugs: (1) penicillin, (2) cephalosporins, (3) macrolides, (4) non-steroidal anti-inflammatory drugs (NSAIDs), (5) corticosteroids (oral and intravenous), (6) antibodies, and (7) disease-modifying anti-rheumatic drugs (DMARDs). For each patient, a detailed medication history was collected and included initiation date and intake duration. This input was then used by MedAI to create an edit distance matrix, from which a hierarchical cluster was built.

dendrograms, as shown in Fig. 5, panel A. The heatmap visually grouped patients with similar medication journeys (blue isles). We tried out all candidates from Fig. 4 ($k = 2, 6, 9$), finally choosing $k = 6$ as the most appropriate. For the remainder of the analysis we used $k = 6$, given that it was the number of clusters that most clearly differentiated between the groups.

Cluster characteristics

We also assessed the qualitative value of the clustering assignment, based on the patient similarity metric calculated using MedAI. The medication usage by cluster and medication class is shown in Fig. 6. The patients were censored at two years of follow-up, and the index date used to align all medication histories is the first visit to the PANS clinic. Each medication class varies from none of the patients taking that drug to all of the patients taking the drug. Clusters 4 and 6, composed by patients with the most severe groups requiring high dose IV steroids; Clusters 1 and 2, composed by patients requiring prolonged NSAID which are used frequently by arthritic or inflammatory diseases; Cluster 2 was also a group of patients with likely underlying Streptococcal infections treated with penicillin; Clusters 3 and 5, composed by patients taking a short course of NSAID for their relapsing/remitting courses of PANS illness. The psychometric scores as outcomes in each cluster generally improved within the first two years except the group of patients using prolonged NSAID and likely suffering from arthritic or inflammatory diseases that ultimately required more aggressive immunomodulation.

Upon performing an analysis of variance (ANOVA), we found in Table 3 that there is significant heterogeneity in trend of scores over time within an individual and between clusters for both Global Impairment ($P_{ANOVA} = 0.005$) and Caregiver Burden ($P_{ANOVA} = 0.0004$).

We note that all clusters, with the exception of cluster 2, demonstrate on average a decreased Caregiver Burden Inventory and decreased Global Impairment Scale over time. This is a sign of general improvement on the patient's condition.

4. Discussion

Here we present a method to align patient history to identify distinct clusters of medication usage, and we apply the method to a PANS cohort. Our approach relies on constructing a symmetric matrix of the pairwise distances between patients. The dynamic programming approach used for constructing the distance between each pair scales quadratically. Therefore, construction of the distance matrix for N patients taking D drugs over a period of length T takes $O(DN^2T^2)$ time and uses $O(N^2 + T^2)$ memory. In cases where the exact intervals and number of days that the drug is administered is not crucial the time periods can be collapsed (e.g. from days to weeks) in order to increase computational and memory efficiency.

Our strategy identifies clusters to characterize the PANS patient population, but cluster assignment should not be considered an association without further investigation. This approach is merely a way to generate new hypotheses that could be further investigated by the clinical and research teams. In a polypharmacy context, this approach could further be used to better understand treatment patterns and potentially disease clusters. These patterns may represent clinician's preference of treatments for certain clinical characteristics and severity levels, or effectiveness of a treatment such that it is continuously prescribed.

We identified six apparent clusters in the PANS cohort based on their medication history, including initiation and cessation dates. Traversing the dendrogram structure in Fig. 5, one level up results in three groups of two sub-clusters: (a) those patients requiring high dose IV steroids (clusters 4 and 6); (b) patients with higher arthritic or inflammatory burden requiring prolonged NSAID (clusters 1 and 2), where one was also treated with penicillins presumably due to concerns for Streptococcal infections (cluster 3); and (c) patients with mild relapsing/remitting syndrome treated with a short course of NSAID (clusters 3 and 5).

The peak of IV corticosteroid use in Clusters 2, 4 and 6, was followed by a steady increase in use of several other medications (steroid sparing agents including DMARDs and IVIG). This pattern is consistent with a more severe phenotype since the clinicians in the PANS clinic reserve IV corticosteroids for the most severe cases, who tend to also have comorbid arthritis and other autoimmune diseases. This is supported by the outcomes data (Fig. 6, last two rows). At clinic entry, the patients in these clusters had a starting Global Impairment score above 40 (in a scale up to 100). However, the outcomes for these clusters were very different. Cluster 2 generally worsened throughout the two years of study except perhaps after the peak use of IV corticosteroids; meanwhile Clusters 4 and 6 generally improved overall. This differentiation on outcomes shows that our clustering strategy accurately captured the decision making process by the clinician when prescribing other drugs to account for the patient's health status at the time of prescription.

Constant heavy use of NSAIDs in Clusters 1, 2 may represent a subgroup of patients who respond to NSAIDs but rely on the constant use of NSAIDs to suppress symptoms. This continued long term usage may reflect those patients who had recrudescence of symptoms when the NSAID dose was lowered. However, this group seemed to worsen over time which appeared to be associated with the eventual addition of more aggressive immunomodulation. The low Global Impairment score at clinic entry of Cluster 1 may have led to the decision not to use corticosteroids in the initial treatment. In contrast, short courses of NSAID in Clusters 3 and 5, were associated with improved psychometric scores significantly during the first half year. This pattern is compatible with the relapsing/remitting course of PANS illness. When the patients

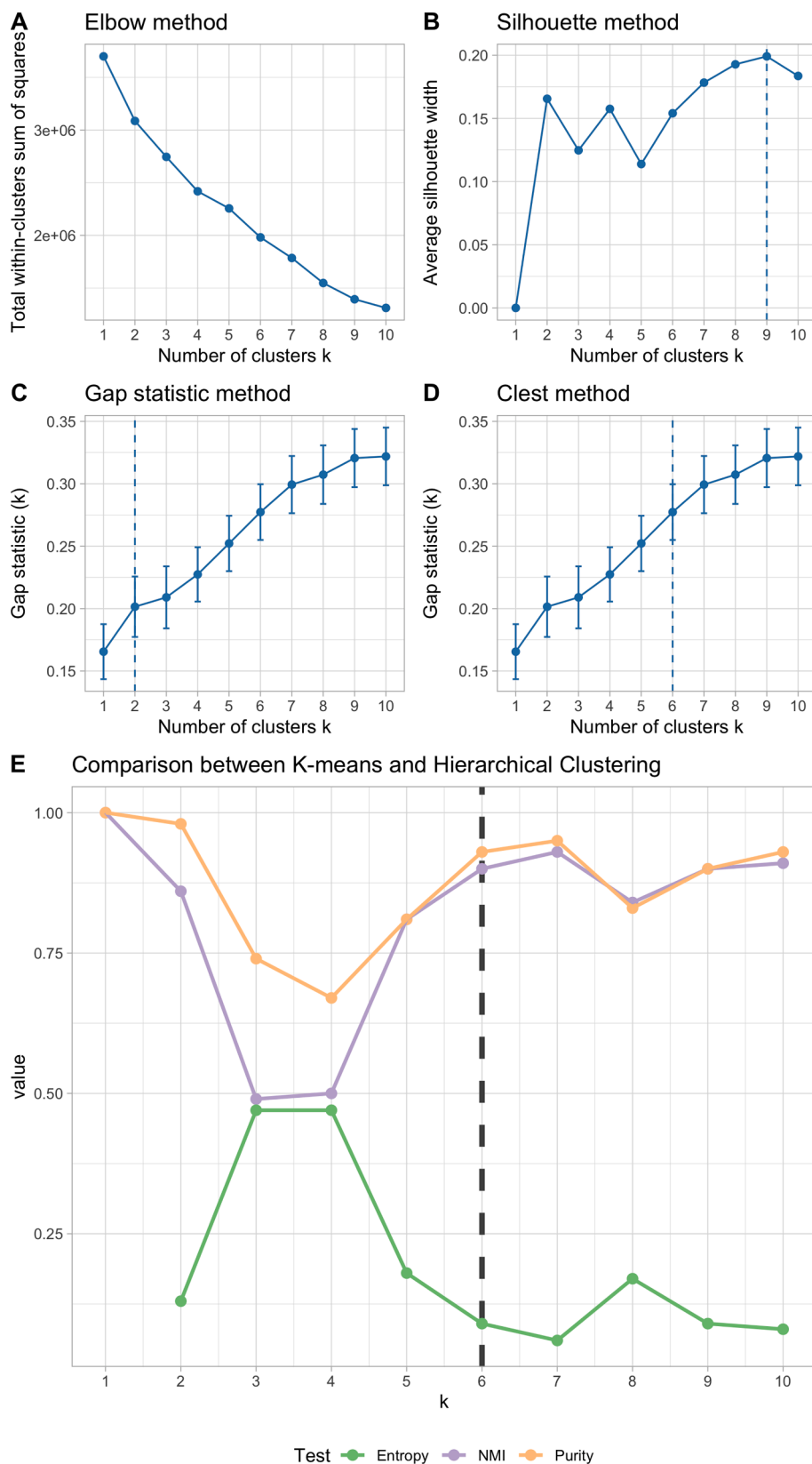


Fig. 4. Analysis of optimal number of clusters. (A) Elbow method, (B) Silhouette method, (C) Gap statistic method, (D) Clest method, (E) Evaluation of normalized mutual information (NMI), Purity and Entropy. The horizontal axis shows our variation of number of expected clusters (k), and the vertical axis shows the score obtained in each metric.

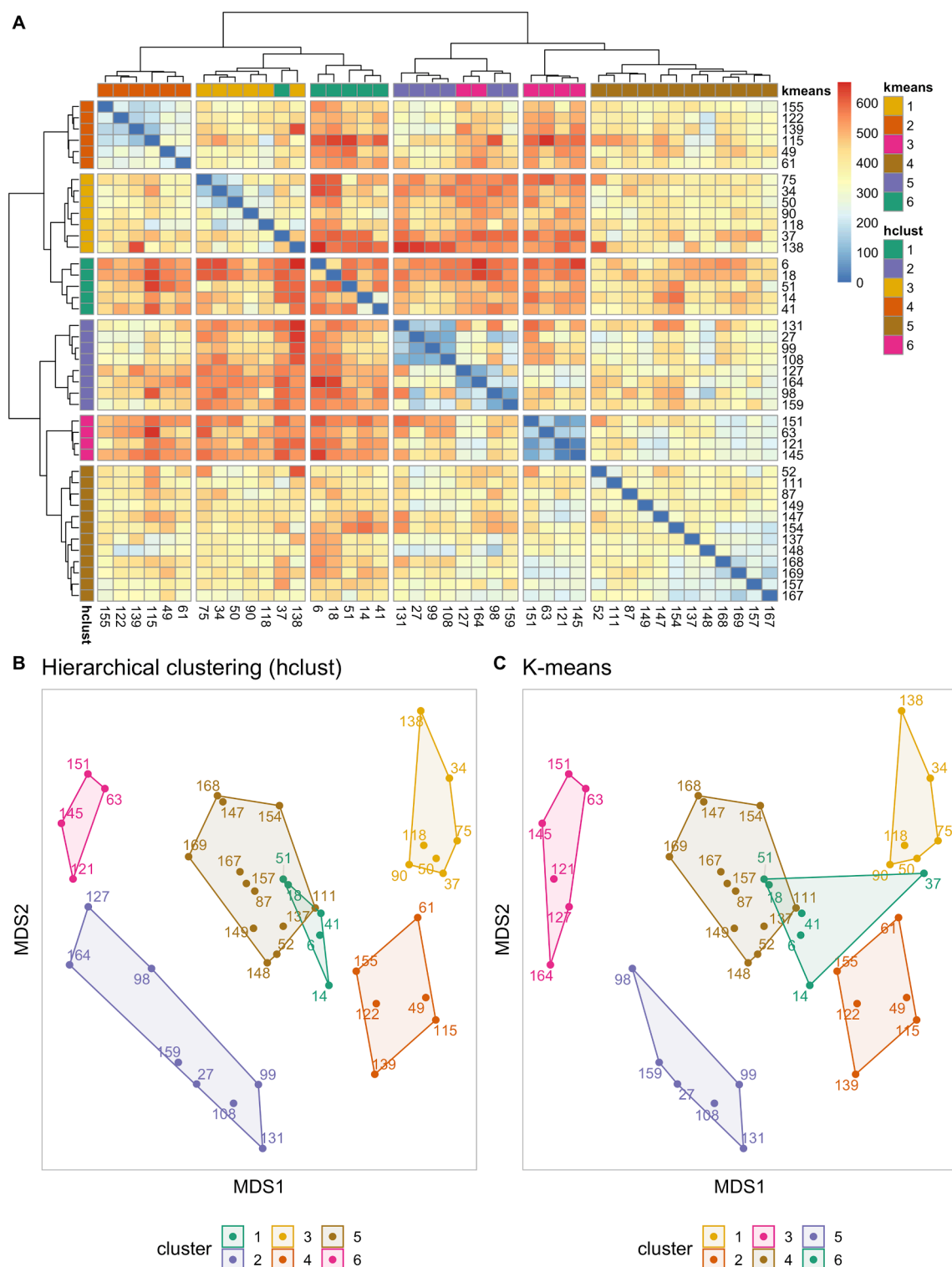


Fig. 5. Cluster assignment for hierarchical clustering using $k = 6$. (A) Heatmap of the MedAI score, clustering dendrogram in rows (hierarchical clustering, hclust) and columns (k-means); (B) MDS components 1 and 2 with hierarchical clustering assignment; (C) MDS components 1 and 2 with k-means assignment.

returned to near baseline, clinicians stopped most pharmacological treatments.

Heavy penicillin use was observed in Clusters 2 and 5 (also moderate use in Cluster 3) which may indicate that the clinician had suspicion or evidence for a streptococcal infection, coincident with the onset of the psychiatric illness (an association seen in epidemiological studies [9]) and likely reflects the clinicians attempt to use penicillin as prophylaxis against streptococcus.

The most important finding from the clinical standpoint is that there is a subgroup of patients who presented with relatively low GI scores and they slowly get better over time with minimal antibiotics and immunomodulation (primarily penicillin and NSAIDs)(cluster 3 and 5). This appears to be a distinct group from cluster 2 (for example) where GI is high at clinic entry and continues to remain high and despite penicillin and NSAIDs (among other interventions). This data may be instructive in designing a clinical trial to test the effectiveness of penicillin and/or

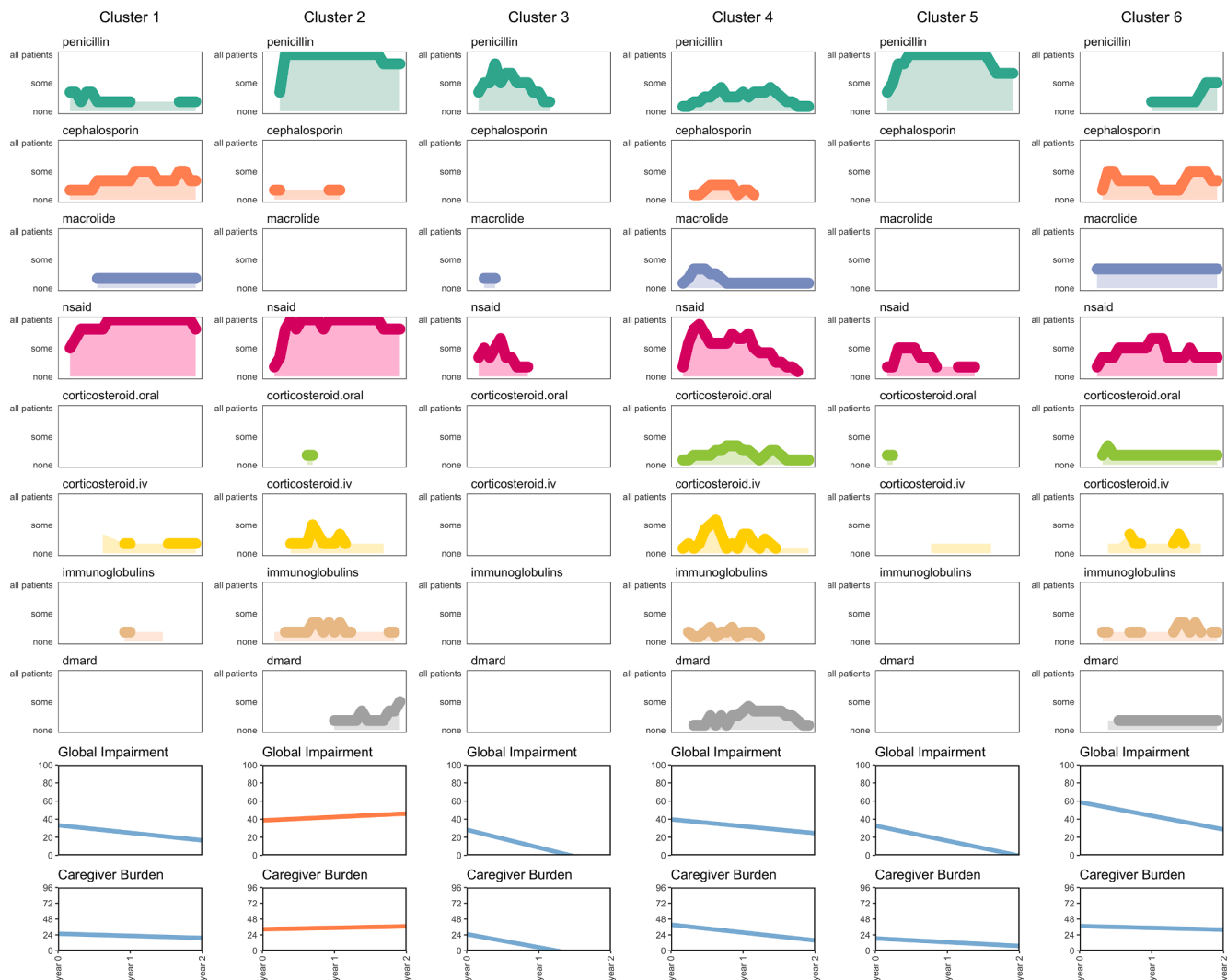


Fig. 6. Drug usage of patients in clusters and overall impairment scales. Abbreviations: dmard: disease-modifying antirheumatic drug; nsaid: Nonsteroidal anti-inflammatory drug. For a full list of drug categories, please refer to Table 1. The last two rows show the Global Impairment Scale and Caregiver Burden Inventory, where linear model fitting for all patients in that cluster, and the color corresponds to a positive slope (red) meaning worsening of the patient; and a negative slope (blue), meaning an improvement on the patient's impairment or caregiver burden. The cluster assignment was obtained from k-means. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 3

Slopes for caregiver burden inventory and global impairment scores over time by cluster.

	Global impairment score				Caregiver burden			
	Intercept	Slope	Std. Error	P-value	Intercept	Slope	Std. Error	P-value
Cluster 1	33.20	−8.32	5.88	0.2234	25.78	−3.20	4.17	0.4595
Cluster 2	38.58	3.80	2.65	0.1562	32.60	2.17	5.05	0.6845
Cluster 3	28.24	−19.75	4.31	0.0002	25.05	−20.10	5.55	0.0029
Cluster 4	40.46	−8.89	5.13	0.1140	39.42	−11.90	3.13	0.0005
Cluster 5	32.72	−16.67	8.52	0.1060	18.69	−5.80	3.56	0.1135
Cluster 6	58.80	−15.14	3.25	0.0006	37.33	−2.70	1.94	0.1734
ANOVA P-value = 0.0054					ANOVA P-value = 0.0004			

NSAID, but this data suggests that the initial study should probably select patients with relatively low GI at study entry.

5. Limitations

Our study was limited by a small number of patients selected for this study. The selection of patients was reduced from an initial cohort of 305 patients seen in the Stanford PANS clinic to 43 pre-pubescent patients

who met strict PANS criteria and who were new-onset at the time of clinic entry, such that their medication history was fully revealed in the charts to avoid recall bias and unclear history. Furthermore, we limited the timespan of medication history to only the first two years of treatment, to make the patient comparisons possible. It is possible that some patients received additional prescriptions outside of the Stanford PANS clinic, and that medication would not be recorded in the EMR. Additionally, we grouped medications of similar effects into clinically

relevant categories instead of treating each drug independently to increase power and applicability to the clinical practice. The stricter study criteria and limited time frame increased comparability between patients to find patterns related to medication usage immediately after diagnosis and treatment initiation. In future research, selecting an appropriate censoring strategy and time zero should be individualized to research questions, as complexity of patients' medical and drug history often exist in real-world data studies.

6. Conclusion

The field of patient similarity is expanding with the inclusion of novel sources of data in electronic format. In this study, we have shown that *MedAI* is capable of providing a reliable similarity metric that can generate new hypotheses for further investigation in a complex syndrome like PANS. The medication histories of other cohorts with a high pharmacological burden will play an important role in our understanding of their treatment patterns.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: ALP declares to be the founder and CEO of Amphora Health at the time of publication. The remaining authors declare that there is no conflict of interest regarding the publication of this article.

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Contributions

ALP designed the study. JF designed the patient inclusion/exclusion criteria, designed the medication categories and medication search strategy, designed the prospective clinical questionnaires and outcome scores and supervised the clinical database and medication abstraction and entry. CMCL, AC, and JF reviewed medical notes and drafted part of the manuscript. GLW, AP, AI, and ALP performed analysis of data. CDB, GLW, and JF provided interpretation of the results. ALP drafted the manuscript, and all authors contributed critically, read, revised and approved the final version.

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Ethics approval

This study was approved by Stanford University's Institutional Review Board (IRB). Written informed consents were obtained from parents of minors, and assents were obtained from subjects aged 7 to 17 (all patients in this cohort) who were able to understand it (IRB protocol #26922). We did not have the opportunity to re-consent two patients at the time of data abstraction and analysis. The inclusion of their data is covered by a retrospective chart review protocol (IRB protocol #28533). Authors CMCL, AC, and JF served as honest brokers securing identifiable information. The remaining authors only had access to de-identified information. Non-human subject determination was provided (IRB protocol #46979).

Data availability

The data that supports the findings of this study is available for research purposes upon written request, which will be reviewed on a

case-by-case basis by Dr. Jennifer Frankovich, director of the Stanford PANS clinic (<http://med.stanford.edu/pans/>), and Stanford's Institutional Review Board (IRB).

Code availability

The MedAI and PyMedAI implementation can be accessed through the public repository: <https://github.com/bustamante-lab/medal>.

Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jbi.2020.103664>.

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