Research and Applications

Embedding electronic health records onto a knowledge network recognizes prodromal features of multiple sclerosis and predicts diagnosis

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ABSTRACT

Objective: Early identification of chronic diseases is a pillar of precision medicine as it can lead to improved outcomes, reduction of disease burden, and lower healthcare costs. Predictions of a patient’s health trajectory have been improved through the application of machine learning approaches to electronic health records (EHRs). However, these methods have traditionally relied on “black box” algorithms that can process large amounts of data but are unable to incorporate domain knowledge, thus limiting their predictive and explanatory power. Here, we present a method for incorporating domain knowledge into clinical classifications by embedding individual patient data into a biomedical knowledge graph.

Materials and Methods: A modified version of the Page rank algorithm was implemented to embed millions of deidentified EHRs into a biomedical knowledge graph (SPOKE). This resulted in high-dimensional, knowledge-guided patient health signatures (ie, SPOKEsigs) that were subsequently used as features in a random forest environment to classify patients at risk of developing a chronic disease.

Results: Our model predicted disease status of 5752 subjects 3 years before being diagnosed with multiple sclerosis (MS) (AUC = 0.83). SPOKEsigs outperformed predictions using EHRs alone, and the biological drivers of the classifiers provided insight into the underpinnings of prodromal MS.

Conclusion: Using data from EHR as input, SPOKEsigs describe patients at both the clinical and biological levels. We provide a clinical use case for detecting MS up to 5 years prior to their documented diagnosis in the clinic and illustrate the biological features that distinguish the prodromal MS state.

Key words: knowledge graph, electronic health records, multiple sclerosis, preventative medicine

INTRODUCTION

Efforts to move toward precision and preventative medicine have increased in the last decade and are now pervasive in most aspects of biomedicine.1 As a result, there has been a sharp increase in medical research studies that implement machine learning (ML) approaches using electronic health records (EHRs).2,3 ML approaches have been moderately successful and have substantially advanced tasks such as disease diagnosis and specimen classification.4 However, because

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they identify patterns in data without knowledge of the underlying clinical or biological meaning, their overall performance has been limited and interpretability of the results remains a black box.

Most chronic diseases lack a unique sign or symptom at presentation. On the contrary, patients may consult a specialist following a clinical event, but often acknowledge that symptoms presented months or even years prior. Early identification of individuals at risk for chronic diseases who are still healthy or have subclinical manifestations would be beneficial for both patients (to receive early treatment or close monitoring) and the health system as a whole (to help optimize across multiple visits and expensive testing).

In order to systematically assess the earliest symptoms (ie, prodromal period) and the biological changes underlying a chronic disease, clinical record standardization is critical in order to overcome the incompleteness in a patient’s biomedical history. The Observational Medical Outcomes Partnership (OMOP) format helps bridge the incompatibility of disparate EHR systems and facilitates the unification of patient records and timelines. Additionally, projects that incorporate basic science-level data (genomics, proteomics, etc.) into EHR research, such as Electronic Medical Records and Genomics, have furthered our understanding of disease pathogenesis and offered practical applications. A recently recognized need is the consideration of known general biological mechanisms in patient-specific health data analytics. This need can be addressed by knowledge graphs (KGs) which naturally bridge the gap between basic science research and medical practice. KGs connect information from multiple classes of biological and medical concepts, thus allowing to constraint the vast solution space faced by traditional ML methods. SPOKE is a KG that connects information from over 30 databases and contains more than 3 million nodes of 16 types and more than 16 million edges of 32 types. The subset of nodes and edges used here is listed in Tables 1 and 2.

Early detection of chronic diseases such as diabetes or hypertension has enabled their effective management to avoid or delay clinical complications. However, despite current efforts in quantifying genetic and environmental risk factors, accurate methods to predict diagnosis of multiple sclerosis (MS) do not yet exist. MS is a chronic, autoimmune disease of the central nervous system (CNS) with severe and life-long consequences. Early symptoms of MS, such as fatigue or depression, are often nonspecific, which can make it difficult for the general practitioner to identify and refer the patient to a neurologist. However, previous studies suggest that healthcare utilization by some patients increases even 10 years prior to their MS diagnosis. Since early treatment of MS is associated with improved long-term neurological outcomes, early recognition of a (sub)clinical presentation and understanding its biological basis could have a major impact on disease trajectories of individual patients. Here, we present a computational method to identify patients before they are diagnosed with MS using only the structured portion of their medical records and biological knowledge from a KG. This method for incorporating biological knowledge in health data analysis has broad applicability to other chronic conditions.

### MATERIALS AND METHODS

#### Patient encounter snapshots

The initial cohort consisted of deidentified EHR from 2 180 882 patients who visited UCSF between 2011 and 2018. Available “snapshots” from the medical history of 5752 patients with a confirmed diagnosis of MS were taken using only past encounters 1–7 years prior to their first MS diagnosis code (Fig. 1A). These snapshots represent everything a doctor knows about a patient (through their EHRs), up to a given point in time (ie, snapshot at year $-1$ contains data up to 1 year before MS diagnosis). These snapshots represent the de facto prodromal period of MS.

A control group (non-MS, $n = 2 175 130$) was selected among individuals who never received an MS diagnosis during the observational period. For the non-MS group, $t_0$ was set at 6 months prior to their most recent visit to UCSF. This aligned MS and non-MS snapshots and ensured that the control population had a follow-up period without MS equal to the minimum amount of observation time available for MS patients after diagnosis.

Parallel analyses were conducted to simulate 2 possible scenarios: patients who visited multiple specialists all visit type (All-Visits) and patients with only primary or emergency care providers (PCP-Only) visits. A patient could potentially be in both simulations if they received both primary and specialist care at UCSF, but only data collected during primary care type visits were used for the PCP-Only analysis. Figure 1B depicts the number of MS and non-MS patients included in the All-Visits (left) and PCP-Only (right) groups for each snapshot (years $-1$ to $-7$).

#### Embedding EHRs into SPOKE

The EHRs used for this analysis were translated into the OMOP Common Data Model. We first created Propagated SPOKE Entry Vectors (PSEVs), machine-readable embeddings that quantify the significance of each node in SPOKE for a given cohort of patients. To create PSEVs, SPOKE Entry Points (SEPs) were first identified by finding all concepts that are present in both the EHRs and SPOKE. For this work, we identified 7535 SEPs, defined as the EHR concepts from the primary tables “condition_occurrence,” “drug_exposure,” and “measurement” that directly corresponded to nodes in SPOKE. Then, for a given concept (eg, carbamazepine), a connection was made between a patient’s SEPs in the EHRs and SPOKE. A modified version of topic-sensitive Page Rank was then used to generate PSEVs for each SEP (Fig. 2A and B). Specifically, a random walker was placed onto a node in SPOKE and allowed it to randomly traverse edges within the network until the walker is forced to restart ($P = .1$) at one of the input patients (that was prescribed carbamazepine in this example). This process continues until the amount of time (importance) the walker spends on each node becomes stable. The resulting PSEV holds weights for each node in SPOKE based on how important a node is for the corresponding patient population.

Once population-level embeddings (PSEVs) were created for all matching EHR concepts, they were aggregated to create vectors for

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**Table 1. SPOKE node statistics**

| Node type          | Count |
|--------------------|-------|
| Compound           | 286 790 |
| Protein            | 33 857 |
| Gene               | 19 567 |
| Anatomy            | 13 257 |
| Biological process | 13 136 |
| Disease            | 9128  |
| Side effect        | 3865  |
| Molecular function | 3407  |
| Pathway            | 2428  |
| Pharmacologic class| 1748  |
| Cellular component | 1725  |
| Symptom            | 369   |
Building a classifier for early detection of MS

Random forest classifiers were used to determine if SPOKEsigs could predict prodromal MS. Random forest was chosen based on its combination of interpretability and performance.27 To measure the importance of the knowledge network in the prediction, we also created a classifier using only the binary vector corresponding to the patient’s SEP. Since SEPs are simply the EHR input variables used to derive the SPOKEsigs, comparing the performance between the 2 classifiers allowed us to gauge the predictive performance gained by using SPOKE.

In order to build a classifier that could be used to compute risk of MS in the general population, the classifier was tested using the prevalence of MS at UCSF, which approached 1:1000 for all groups (comparable to the prevalence of MS in the United States).28,29 The classifiers (using either SPOKEsigs or SEPs) were run from snapshots at years −5, −3, and −1 from diagnosis for both the All-Visits and PCP-Only groups.

RESULTS

MS-related nodes increase in significance as time of diagnosis approaches

In order to measure the flow of information from thousands of subjects through the “MS” node in SPOKE before diagnosis, we generated SPOKEsigs without using the PSEV corresponding to the concept MS (as MS is naturally the top-ranked node within the MS PSEV).23 Of interest, nodes related to the physiopathology of MS were found to be highly ranked likely due to the biologically meaningful connections within SPOKE. To investigate the importance of the MS node in our subject population, the rank distribution of MS was compared for years −7 to −1 relative to MS diagnosis in the index group. Figure 3A shows that MS increases in significance as time to diagnosis approaches for both the All-Visits and PCP-Only groups ($r^2 = 0.93; P < .037$ PCP-Only and $r^2 = 0.96; P < .018$ All-Visits). Furthermore, when compared with all other diseases in SPOKE, MS remains within the top 1% in the All-Visits group and (and within 2% for PCP-Only visits), during years −7 to −1. Further, the importance of MS is statistically significant ($t$ test) for both groups between years −5 (5.5e-6 PCP-Only; 1.6e-26 All-Visits) to
-1 (6.4e-62 PCP-Only; 3.4e-147 All-Visits). Note that this cannot be explained by prescriptions of MS-specific disease-modifying medications (DMTs), as these individuals have not been yet diagnosed with MS. There is a noticeable gap between the $P$-values for the All-Visits and the PCP-Only groups, suggesting a substantial increase in information related to MS being recorded during specialist visits. Though this increase in significance (overtime as well as the difference between PCP-Only and All-Visits groups) can partially be attributed to the increased sample size, the average $P$-value at any time point is not significant. Further, the slope for the MS node compared with the slope of the average $P$-value over time is 215/2 and 127/2 higher (All-Visits and PCP-Only, respectively), suggesting that only a small portion of the increase in significance can be attributed to increased sample size.

To ensure that these results were MS-specific and not simply the outcome of visiting a neurologist (in the All-Visits group), a similar analysis was conducted using snapshots from patients diagnosed with amyotrophic lateral sclerosis (ALS). Similarly, ALS was the most important disease ($P < 3.17e-9$) in the ALS snapshots at year $-1$. In contrast, the MS node was not differentially ranked compared with the control population ($P > .9$). This indicates that although both MS and ALS patients can see neurologists during the prodromal period, each prodromal disease has a distinct signal in SPOKE.

Considering that a first demyelinating event must occur prior to the diagnosis of MS,30,31 we speculated that SPOKE nodes related to myelin might also increase in significance as time to diagnosis approached. Figure 3B illustrates the increased significance of the concept Myelin sheath adaxonal region (GO:0035749). Furthermore, the same trend is observed for any node with “myelin” in its name (Figure 3C). These results suggest that the biological underpinnings of the disease might be detectable during the prodromal period using only information from the EHR.

### Predicting prodromal MS

After confirming that SPOKEsigs contained meaningful information related to MS, a predictive model was built using patient-specific SPOKEsigs as inputs to a random forest classifier. The average area under the receiver operating characteristic (ROC) curve (AUC) for

![Figure 1. Patient timeline aligning and filtering.](image-url)
the SPOKEsig All-Visit (AV) classifier was 0.76 at \(-7\) years, and progressively increased to 0.84 for year \(-1\). This same trend was observed for all 4 classifier types (AUC\textsubscript{SPOKE AV}: 0.76–0.84, AUC\textsubscript{SPOKE PCP}: 0.6–0.78, AUC\textsubscript{SEP AV}: 0.7–0.83, and AUC\textsubscript{SEP PCP}: 0.53–0.75; Figure 4). As expected, the classifier that used all encounters outperformed the classifier that used PCP-Only encounters (Avg. ΔAUC\textsubscript{SPOKE Years \(-7\) to \(-1\)}: 0.11 and Avg. ΔAUC\textsubscript{SEP Years \(-7\) to \(-1\)}: 0.15; Avg. ΔAUC = Avg. AUC All-Visits—Avg. AUC PCP-Only). In all cases of information loss, either from smaller time windows (time from diagnosis) or missing specialist visits (PCP-Only), the enhancement of EHRs with SPOKE drove classifier performance. The greatest improvement was seen at 3 years prior to diag-
nosis using PCP-Only encounters (ΔAUC_SPOKE-SEP: 0.12). Altogether, these results demonstrate that embeddings of patients’ clinical data from the structured portion of the EHR onto a KG contain relevant information about their health status. Furthermore, adding structured knowledge to EHR data through SPOKE can compensate for missing and incomplete EHR data.

More SEPs will likely improve classifier performance
We recognize SEPs themselves are incomplete because they currently do not map every EHR concept to SPOKE (88% of conditions, 79% of medications, and 47% of measurements for All-Visits at year −1). To estimate how much SPOKEsigs could improve if each EHR concept was mapped to SPOKE, the same classifiers were run using the full set of EHR concepts. Interestingly, the average difference in AUC between full OMOP and SPOKEsigs was the same as that between SPOKEsigs and SEPs (ΔAUC: 0.053). The majority of OMOP concepts that drove the full OMOP classifiers were measurements that were not mapped to SPOKE (Supplementary Tables S1 and S2). These results suggest that if more EHR concepts were mapped to SPOKE, a significant improvement in the classifier could be achieved.

Biological drivers of the classifier
Our previous results suggest that the improved performance of classifiers using SPOKEsigs over those using only SEPs (ie, straight from the EHR) is due to biologically relevant information from SPOKE being utilized in the computation (ie, because the network connects these variables). To understand how the incorporation of biological knowledge increased the AUC, we extracted the scores of each biological node using the average feature value across all years for both the All-Visits and PCP-Only groups. Next, the top 20 nodes from each biological node type (Gene, Protein, Biological Process, Molecular Function, Cellular Component, and Pathway) were selected and split into MS or non-MS significant groups according to the sign of the t-statistic (Figure 5A and B, respectively). To further interpret how each group of top nodes was connected to one another, additional SPOKE nodes were added if they had direct edges to at least 2 top biological nodes (Figure 5A and B). Remarkably, the highest-ranked nodes in the MS groups corresponded to myelin biology (myelin sheath adaxonal region, MAG, glial cell differentiation, etc.), neurophysiological functions (axonogenesis, ceramide binding, etc.), and adaptive immunity (CD4+ T cells and B cell-specific pathways, CCR5, etc.; Figure 5A and Supplementary Table S3). Also significant were nodes related to the CNS, muscle behavior, the extracellular matrix (eg, matrix metalloproteinases, collagen, NCAM, Basigin interactions, etc.), and genes associated with other neurological diseases such as spastic paraplegia (MPV17L2), ataxia (RNF170) Alzheimer’s disease (APBA3), and lysosomal storage disease (NAGLU). Together, these nodes illustrate how the classifier detected the importance of neurological and immunological processes in MS patients several years before their diagnoses. In contrast, the highest-ranked nodes within the non-MS group were related to Th2 cell differentiation (eosinophil migration, prostaglandins, CCR3 chemokine receptor binding, etc.), an immune subset associated with protection against inflammatory diseases like MS (Figure 5B).

Medications and common laboratory tests drive information flow to neurological nodes
The difficulty in identifying MS at an early stage is due to the combination of the EHRs being sparse and MS symptoms being vague and common in the general population. Often this results in OMOP codes only being associated with one or a small number of MS patients (Supplementary Figure S2) which does not contribute to the classifier. However, after mapping an OMOP concept to a SEP it is transformed into a multidimensional SPOKEsig that represents the importance of each node in SPOKE for that OMOP concept/SEP. Therefore, 2 distinct OMOP concepts could “push” information to the same downstream nodes.
To identify which OMOP concepts were responsible for "pushing" information downstream to each of the MS-significant biological nodes, network paths were traced back to the originating SEPs (see Materials and Methods). For most of the top MS nodes, the SEPs that were essential for the high rank of the MS-significant nodes were mapped from medication orders and common laboratory tests (note that MS DMTs are not SEPs, as none of these individuals had been diagnosed with MS at the time of analysis).

Though these SEPs may not have been significant in the MS population as a whole, their propagation through SPOKE led to increased information flow to the MS top nodes. For example, while Carbamazepine and Lithium are not significant as distinct SEPs, they both direct information flow to the GO concept “Myelin sheath adaxonal region” (GO:0035749, a highly ranked MS-relevant node) in a representative patient shown in Figure 5C. For this patient, information flows from Carbamazepine to a set of Disease nodes (either through “treated by” or “contraindicated for” edges) and then (either directly or through an additional Disease or Gene node) to the genes CNP, MAG, or PTEN which are all components of “Myelin sheath adaxonal region.” Interestingly, Carbamazepine or Lithium can be used to treat symptoms and comorbidities of MS such as trigeminal and glossopharyngeal neuralgia or depression, respectively, which are common symptoms experienced by MS patients. This further demonstrates that distinct clinical presentations can lead to similar SPOKE representations of MS patients.

Similarly, the paths between the laboratory test for Aspartate aminotransferase travel through aspartic acid (Compound) and then traverse 1–2 edge(s) before reaching MAG and PTEN (Genes) (Supplementary Figure S3). Despite the different paths of entry into SPOKE, data are repetitively sent through nodes such as MAG and PTEN, which then converge at the “Myelin sheath adaxonal region” node. Similar patterns were observed for multiple other neurological nodes.

**DISCUSSION**

The purported prodromal period of MS is often described in terms of healthcare utilization.36,37 MS patients in the prodromal stage are, by definition, months or even years away from a recorded diagnosis code for MS. During this period, however, they are not just standing idly—in fact, their healthcare use both within and beyond the primary care setting, steadily increases until time to diagnosis.36 Previous research revealed that MS patients have more encounters with psychiatrists and urologists, as well as higher proportions of musculoskeletal, genito-urinary, or hormonal-related prescriptions.38 These findings hint that underlying biological signals must be present months or even years before diagnosis and the information from these specialist visits could be pivotal in uncovering those differences.

Although patients often pay multiple visits to a specialist before receiving an MS diagnosis, the process of obtaining an appointment with a specialist can itself be prolonged, usually requiring a referral and insurance coverage. As a result, a patient’s initial interface with a health system is often through primary or emergency care. Appreciating the different roles primary care and specialist clinicians play in the diagnosis process, we ran 2 analyses in parallel using data from either PCP-Only or All-Visits. Though it is possible for symptoms to be recorded in the structured portion of EHRs, this typically only occurs if it is necessary for billing. Additional patient data can...
Figure 5. Th1/Th2 balance and neurological nodes drive biological increase in AUC. (A, B) Networks of significant biological nodes for random forest classifier. Red nodes were higher ranked in the MS population (A), whereas blue nodes were higher ranked higher in the non-multiple sclerosis (MS) population (B) (color gradient based on t-statistic). The shape (diamond or oval) of the node denotes whether or not the node is in the top 20 of a given node type. If it is an oval, it must connect to ≥2 nodes in the top 20. Highlighted in the network are some of the nodes that correspond to Th1/Th2 balance or neurology. (C) Illustration of how a prescription for carbamazepine can send information to the Myelin sheath adaxonal region node (GO:0007404, GO:0043360; replaced by: GO:0010001). (D) Depiction of how asthma (a Th2-mediated disease that is more prevalent in the non-MS UCSF population) pushes information downstream to the Eicosanoid ligand-binding receptors node (Reactome R-HSA-391903).
be extracted from the patient notes using natural language processing (NLP). However, NLP methods to date generate rather sparse data, and need further validation in healthcare settings; thus their incorporation is out of scope for this work.

The generation of PSEVs is comparable with word2vec, another machine-learning vector embedding method. Similar to how word2vec learns the embedding of a word by using the words around it as context, PSEVs utilize patient cohorts to give context to the nodes in SPEOKE. PSEVs are then added together to produce the Patient-Specific SPOKE Profile Vectors (SPOKEsigs) that describe a patient in terms of node weights in SPOKE. The main difference between these 2 embedding techniques is that PSEVs (and therefore SPOKEsigs) are based on a “clear box” algorithm that constructs machine-readable vectors while maintaining human interpretability. This means each element in the vector corresponds to a node in SPOKE and it is possible to trace back how information travels from sparse EHRs to downstream nodes. The diffusion of EHRs through SPOKE enabled the prioritization of the MS Disease node in the SPOKEsigs of MS patients compared with controls. Additionally, the significance of this differential prioritization increases as the time to diagnosis decreases. Further, we have shown that the known biological underpinnings of MS could be abstracted using these sparse clinical data. This is evident by the prioritization of myelin-related nodes within the SPOKEsigs of MS patients—whose disease is characterized by demyelination in the CNS—compared with controls up to 7 years prior to MS diagnosis.

We hypothesized that SPOKEsigs contained deeper information about a patient than the equivalent EHR vectors (SEPs). Remarkably, SPOKEsigs outperformed SEPs (ie, EHR-only information) at all time points for both the All-Visits and PCP-Only analyses. The All-Visit AUCs were always higher than the PCP-Only AUCs due to the greater power of the All-Visit group in both the number of patients and encounters. This difference was minimized by the addition of SPOKE, which enabled the use of PCP-Only data to achieve results closer to using All-Visit data using the SEPs alone. This enhancement of EHRs using SPOKE was particularly striking for the PCP-Only analysis performed 3 years before diagnosis, which showed a 12% improvement in AUC (over SEPs alone). These results hint at a future where, after adequate validation including consideration of possible biases, SPOKE could be used at the point of care to support or target supplementary evaluation for primary care providers.

The top biological drivers of the classifier were split into 2 groups (MS significant or non-MS significant) according to whether they were ranked higher in the MS or Control SPOKEsigs. Notably, SPOKEsigs outperformed SEPs (ie, EHR-only information) at all time points for both the All-Visits and PCP-Only analyses. The All-Visit AUCs were always higher than the PCP-Only AUCs due to the greater power of the All-Visit group in both the number of patients and encounters. This difference was minimized by the addition of SPOKE, which enabled the use of PCP-Only data to achieve results closer to using All-Visit data using the SEPs alone. This enhancement of EHRs using SPOKE was particularly striking for the PCP-Only analysis performed 3 years before diagnosis, which showed a 12% improvement in AUC (over SEPs alone). These results hint at a future where, after adequate validation including consideration of possible biases, SPOKE could be used at the point of care to support or target supplementary evaluation for primary care providers.

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CONCLUSIONS

This work presents a strategy to embed EHR data onto a knowledge graph (SPOKE) to obtain high-dimensional health status profiles (SPOKEsigs). SPOKEsigs were computed for hundreds of thousands of individuals and a random-forest classifier was trained to identify individuals at risk of MS. This approach was able to detect MS up to 5 years prior to their documented diagnosis in the clinic. SPOKEsigs represent a new kind of “clear box” explainable predictive models with broad applicability to other chronic medical conditions where early diagnosis can benefit patients.

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AUTHOR CONTRIBUTIONS

CAN: developed methods for analysis, gathered data, and performed analysis. Created Figures, and drafted article. RB: analyzed clinical data, ensured medical accuracy, and edited article. AJB: contributed to the study design, methods development and article revision, and editing. SEB: study conception, design, and supervision. Data analysis and Figure design. Drafted and edited article. Accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
SUPPLEMENTARY MATERIAL

Supplementary material is available at Journal of the American Medical Informatics Association online.

CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY

Due to the sensitive nature of EHR, we are not able to share patient data, even in deidentified form. To facilitate the reproducibility and advancement of this research, we have created an API for generating SPOKEsigs alongside a jupyter notebook with instructions on how to use it, which can be accessed at https://github.com/BaranziniLab/SPOKEsigs. Anyone with access to EHRs can now create SPOKEsigs for their own patient populations and test the concepts presented in this work. SPOKE can be accessed at https://spoke.rvb.ucsf.edu/neighborhood.html.

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