A Novel Algorithm for Identifying Generalized Pustular Psoriasis Flares Using Natural Language Processing and Outpatient Electronic Health Records

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Table of Contents

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Abstract

Background: Generalized pustular psoriasis (GPP) is a systemic, neutrophilic, inflammatory disease characterized by chronic symptoms and periods of flaring, which can be potentially life-threatening. The rarity of GPP and inconsistent documentation complicate real-world identification of GPP flares.

Objective: We developed an algorithm to identify outpatient encounters indicative of GPP flares using structured data and unstructured clinical notes from electronic health records (EHRs).

Methods: De-identified patient-level EHR data (2017–2024) from six specialty dermatology networks in the USA were accessed. Eligible outpatient encounters had (1) an International Classification of Diseases, 10th Revision, Clinical Modification diagnosis code for GPP, (2) a dermatologist-defined diagnosis status of “inadequately controlled” or “worsening” disease (gold standard indicator of flare), and (3) available clinical notes. Natural language processing (NLP) of clinical notes identified the most common terms (eg, clinical manifestations, treatment) by flare status.

Results: Multivariable logistic regression models and leave pair-out cross-validation selected models yielding the highest area under the receiver-operating characteristic plot (AUROC) (discriminative ability for flares) from 1,354 encounters (679 patients: 81% female, 84% Caucasian, mean age 58 years). The final model combined NLP terms and EHR variables and yielded a higher discriminative ability (AUROC=0.72; sensitivity=0.68; specificity=0.66) than either NLP terms or EHR data alone.

Conclusions: Although not fully discriminative, the model could be used in future to identify GPP flares from EHR data. Clinical Trial: N/A

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ABSTRACT (220/450 words)

Background: Generalized pustular psoriasis (GPP) is a systemic, neutrophilic, inflammatory disease characterized by chronic symptoms and periods of flaring, which can be potentially life-threatening. The rarity of GPP and inconsistent documentation complicate real-world identification of GPP flares.
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Conclusions: Although not fully discriminative, the model could be used in future to identify GPP flares from EHR data.
Trial registration: N/A

Keywords: Generalized pustular psoriasis; flare; algorithm; real-world data; natural language processing

Introduction

Generalized pustular psoriasis (GPP) is a systemic, neutrophilic, inflammatory skin disease associated with a higher burden of illness compared with plaque psoriasis [1,2]. Its clinical course is heterogeneous and unpredictable, characterized by chronic symptoms and flares that manifest as rapidly disseminating painful skin manifestations including pustules and erythema, often accompanied by systemic symptoms such as pain, fever, and fatigue [3-6]. GPP is potentially life-threatening, owing to flare-related complications including sepsis and respiratory, heart, liver, and kidney failure [3,7]. Understanding and characterizing flare burden among patients with GPP is therefore of high importance to clinical practice.

Accurate patient cohort identification from real-world data is key to performing epidemiologic research [8]. However, the rarity of GPP and lack of standardized criteria for flare documentation make it difficult to identify and study GPP flares in the real-world setting. Furthermore, GPP flares may often go unreported because no specific procedure code exists for them in structured electronic health records (EHRs). As a result, few studies examining GPP flares in the outpatient dermatology setting have been published. In a large, US-based population-level study, string-based keyword searches of clinical notes from EHRs identified potential GPP flares; however, only approximately half of patients were identified in the outpatient setting during routine clinical care, with the other half identified from inpatient, emergency, and other settings [9].

The objective of this study was to develop a novel algorithm to identify patient healthcare encounters indicative of GPP flares, specifically in the outpatient dermatology setting, using natural language processing (NLP) of unstructured clinical notes and structured data available in EHRs.

Methods

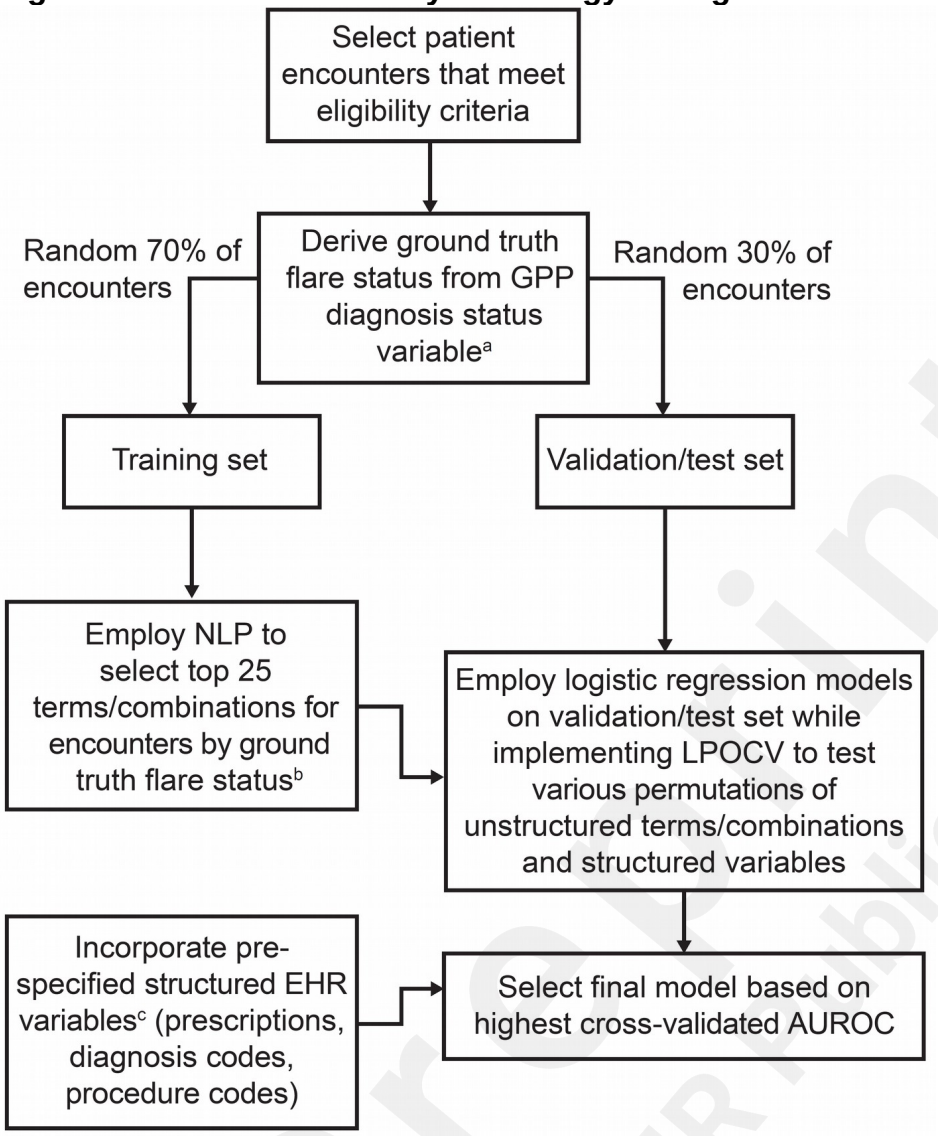
Study design and participants

This non-interventional cohort study was a secondary analysis of EHR data from US-based outpatient dermatology clinics from January 2017 to January 2024. De-identified patient-level EHR data from six specialty dermatology networks in the OMNY Health real-world data platform were accessed. In addition to standard structured EHR fields, this data source included access to de-identified, unstructured clinical notes at the encounter level. The dermatology-specific EHR system used to collect data also included an eight-level categorical variable depicting the diagnosis status associated directly with each diagnosis code. Dermatologists used this diagnosis status variable to characterize the GPP disease state (ie, flare status) of the patient at the specific encounter as “well controlled,” “improved,” “resolving,” “resolved,” “unchanged,” “stable,” “inadequately controlled,” or “worsening.” Patient encounters were included if they met all of the following criteria: (1) had an EHR diagnosis code for GPP (International Classification of Diseases, 10th Revision [ICD-10], Clinical Modification: L40.1), (2) had a recorded diagnosis status associated directly with the GPP diagnosis code, and (3) had accessible clinical notes available for analysis.

Analytic methods

The main goal of the algorithm development process was to select a set of variables that, when included together in a model, would yield the highest predictive ability to discriminate between encounters that were and were not GPP flares. A schematic of the analytic strategy for algorithm development is presented in Figure 1.

Figure 1. Schematic of analytic strategy for algorithm development



AUROC: area under the receiver-operating characteristic plot; EHR: electronic health record; GPP: generalized pustular psoriasis; LPOCV: leave pair-out cross-validation; NLP: natural language processing.

[a]The diagnosis status variable was an eight-level categorical variable in the EHR that dermatologists used to characterize GPP disease state of the patient at the specific encounter as flare (“inadequately controlled,” or “worsening”) or not flare (“well controlled,” “improved,” “resolving,” “resolved,” “unchanged,” “stable”).

[b]Ground truth or gold standard represents information accepted to be true, in this case based on the diagnosis status variable.

[c]Structured variables at the same encounter were considered as candidate predictors of true GPP flare status were as follows: procedure codes indicative of moderate or complex disease management, diagnosis codes for plaque psoriasis, psoriatic arthritis, other autoimmune conditions (Crohn’s disease or ulcerative colitis, rheumatoid arthritis, ankylosing spondylitis, uveitis, hidradenitis suppurativa, scleroderma), prescriptions for systemic steroids, other systemic agents (apremilast, acitretin, tofacitinib, methotrexate, cyclosporine, sulfasalazine, azathioprine, hydroxyurea, isotretinoin, methoxsalen, mycophenolate mofetil, thioguanine), and biologics.

Descriptive statistics were used to characterize the study population. Encounters with GPP

diagnosis statuses marked as “inadequately controlled” or “worsening” were labeled as ground truth or gold standard (information accepted to be true) flares. Encounters with other GPP diagnosis statuses (“well controlled,” “improved,” “resolving,” “resolved,” “unchanged,” and “stable”) were labeled as not ground truth flares. Patient encounters were randomly divided into training (70%) and validation/test (30%) sets.

NLP was performed on the clinical notes of the training set to identify the most frequently appearing single-, double-, and triple-term combinations by ground truth flare status. For each term or term combination, the ratio of its appearance in encounters that were true flares to encounters that were not true flares was computed. Terms or term combinations were ranked in descending order of this ratio, and combinations of terms with similar concepts (eg, “pustular ps,” “pustular pso,” “pustular psoriasis”) were aggregated. The top and bottom 25 aggregated terms (ie, NLP flare-related terms [NLP-F] and NLP non-flare-related terms [NLP-NF]) were considered candidate terms in subsequent models.

Structured variables at the same encounter that were considered as candidate predictors of true GPP flare status were as follows: procedure codes indicative of moderate or complex disease management, diagnosis codes for plaque psoriasis, psoriatic arthritis, other autoimmune conditions (Crohn’s disease or ulcerative colitis, rheumatoid arthritis, ankylosing spondylitis, uveitis, hidradenitis suppurativa, scleroderma), prescriptions for systemic steroids, other systemic agents (apremilast, acitretin, tofacitinib, methotrexate, cyclosporine, chloroquine, hydroxychloroquine, sulfasalazine, azathioprine, hydroxyurea, isotretinoin, methoxsalen, mycophenolate mofetil, thioguanine), and biologics.

Multivariable logistic regression models were employed where the true GPP flare status was modeled as a function of the relevant subset of candidate variables. Each model output included the area under the receiver-operating characteristic plot (AUROC), which quantified the ability of the model to discriminate between encounters that were and were not true GPP flares. To derive the most discriminative model with external validation, various permutations of candidate variables were attempted while implementing leave pair-out cross-validation (LPOCV) on the validation/test set, which is the least biased validation technique for estimating the AUROC [10].

Through the LPOCV process, two separate sets of terms were selected from the subset of terms derived from NLP of the clinical notes: one set associated with notes from encounters that were flares (NLP-F terms) and another set associated with notes from encounters that were not flares (NLP-NF terms). Indicator variables for whether the note contained any of the NLP-F terms or NLP-NF terms were created as separate entities in the subsequent modeling while also considering structured EHR variables.

Models yielding the highest AUROC values using (1) only NLP indicator variables, (2) only structured EHR data, and (3) both NLP indicator variables and structured EHR data were selected for comparison. The overall model with the highest LPOCV AUROC was selected as the final model, and the receiver-operating characteristic plot was generated to select the operating point that optimized the tradeoff between sensitivity and specificity.

Ethics statement

Per US federal regulations [45 CFR 46.102(e)(5)], studies conducted in de-identified databases like the one used in this study are exempt from study-specific investigational review board reviews as they do not meet the definition of research on human subjects. De-identified data were obtained through partnership agreements with each data holder.

Results

Of approximately 38 million patient encounters from specialty dermatology networks, 8,249 had a diagnosis code for GPP (ICD-10 code: L40.1) and 1,354 of these also had a GPP-specific diagnosis status (one of eight categorical variables: see methods) and accessible clinical notes. These 1,354 encounters from 679 unique patients comprised the study population. The patient population was majority female (81%) and Caucasian (84%), with a mean (standard deviation) age of 58 (±15) years (37% of patients were aged 65 years and older [Table 1]).

Table 1. Patient characteristics at index GPP[a] diagnosis code

Characteristic	Study population N=679
Sex, n (%)	
Female	551 (81.3)
Male	127 (18.7)
Age, mean (±SD), years	58 (±15)
Age (years), n (%)	
<18	8 (1.2)
18 to 34	44 (6.5)
35 to 49	107 (15.8)
50 to 64	268 (39.5)
≥65	252 (37.1)
Race, n (%)	
Asian or Pacific Islander	6 (2.1)
Black or African American	29 (9.9)
White	245 (83.9)
Other[b]	5 (4.1)
Ethnicity, n (%)	
Hispanic or Latino	22 (11.1)
Not Hispanic or Latino	177 (88.9)
Body surface area percentage (%)	N=189
Mean (±SD)	11 (±17)
Median (Q1–Q3)	5 (2–10)
Physician global assessment, n (%)	
Clear	22 (11.5)
Almost clear	28 (14.7)
Mild	40 (20.9)
Moderate	72 (37.7)
Severe	29 (15.2)
Pain VAS[c]	N=112
Mean (±SD)	1.7 (±2.5)
Median	0

[a]GPP: generalized pustular psoriasis.
[b]The specific race/ethnicity of patients who chose 'Other' was not available in the EHR[d].
[c]VAS: visual analog scale.
[d]EHR: electronic health record.
Some variables have missing data; statistics were based on non-missing data.

NLP-F terms (10 in total) generally described a treatment (eg, "prednisone", "ointment", or "apply") or clinical manifestation (eg, "rash", "pustular"), whereas NLP-NF terms (two in total) comprised "folic" and "prn" (meaning "as needed"; Table 2). LPOCV using only NLP-F and NLP-NF indicator variables as predictors of flare yielded an AUROC of 0.61, indicating poor discrimination derived from NLP alone. The most predictive structured EHR variable was a procedure code for moderate or complex disease management, which, by itself, yielded an LPOCV AUROC of 0.61 (equivalent to that of the NLP indicators alone). The most discriminative model consisting only of structured EHR variables yielded an AUROC of 0.69 and contained the following variables: procedure code for moderate or complex

disease management, systemic steroid prescription, plaque psoriasis diagnosis code, and other autoimmune condition diagnosis code.

Table 2. Selected terms from unstructured clinical notes based on frequency of appearance from encounters with flares (NLP-F)[a,b] and without flares (NLP-NF)[c]

NLP-F terms	NLP-NF terms
Biologic[d]	Folic
Rash	Prn
Pustular	
Consider	
Prednisone	
Follow	
Biopsy	
Ointment or apply	
Started	
Flare	

[a]NLP: natural language processing.
[b]NLP-F: terms most uniquely appearing in notes from encounters with flares.
[c]NLP-NF: terms most uniquely appearing in notes from encounters without flares.
[d]Also includes “biologics” or the generic or brand name of any biologic for treatment of psoriasis (eg, “Tremfya”, “Taltz”, etc.).

The overall final model combined NLP elements and structured EHR variables, yielding an AUROC of 0.72. It comprised a different combination of variables (Table 3). In addition to the NLP-F and NLP-NF indicator variables, the procedure codes for moderate or complex disease management, systemic steroid prescription, other systemic agent prescription, and interaction terms between the procedure code and each NLP indicator variable were selected as the final variables.

Table 3. Variables selected for the final model and their coefficients

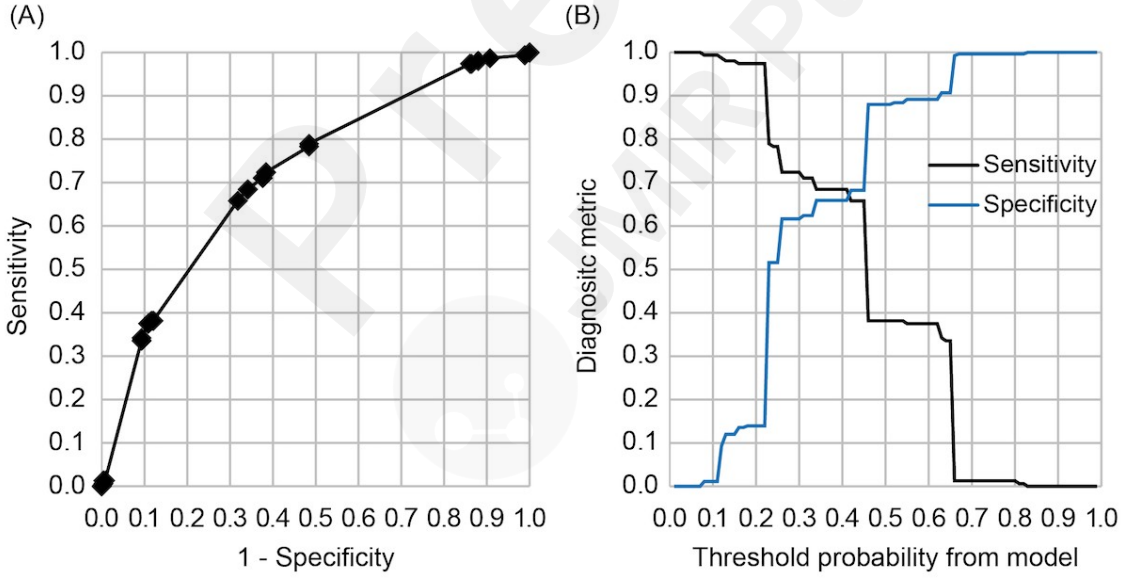
Characteristic	Coefficient
(Intercept)	-1.231
NLP-F[a,b]	0.142
NLP-NF[c]	-0.841
Moderate/complex procedure code	1.033
Systemic steroid prescription	0.900
Other systemic agent prescription	-0.475
NLP-F x Moderate/complex procedure code	0.713
NLP-NF x Moderate/complex procedure code	0.705

[a]NLP: natural language processing.
[b]NLP-F: terms most uniquely appearing in notes from encounters with flares.
[c]NLP-NF: terms most uniquely appearing in notes from encounters without flares.
[d]GPP: generalized pustular psoriasis.
To compute the probability of GPP[d] flare, sum the intercept and applicable coefficients, then take the inverse logit. For example, if an encounter had a clinical note containing an NLP-F term, a procedure code for moderate/complex disease management, and a systemic steroid prescription, then the GPP flare probability would be computed as follows:
Coefficient sum = -1.231 + 0.142 + 1.033 + 0.900 + 0.713 = 1.557
GPP flare probability = exp (1.557) / (1 + exp [1.557]) = 0.83

Using Table 3, the probability that the encounter is a GPP flare can be computed by summing the intercept and coefficients applicable to the encounter, and then taking the inverse logit of that value. For example, if an encounter had a clinical note with any of the NLP-F terms, a procedure code for moderate or complex disease management, and a systemic steroid prescription, the probability that the encounter is a GPP flare would be 83%, as outlined in the table footnote.

Because the multivariable logistic regression model yielded a continuous probability of GPP flare, the threshold probability (ie, operating point on the receiver-operating characteristic plot) to dichotomize each encounter as GPP flare or not GPP flare could be drawn at multiple locations of the receiver-operating characteristic plot (Figure 2A). The best operating point to choose depends largely on the potential consequences of incorrectly classifying an observation in a particular direction versus the other. In the absence of this scenario, the operating point closest to the top left corner of the plot may be chosen because it optimizes the tradeoff between sensitivity and specificity. This optimized operating point corresponded to a GPP flare probability of 40%. Thus, GPP flare probabilities ≥40% would be categorized as flares, whereas probabilities below this threshold would not be categorized as flares. The resulting diagnostic metrics at this threshold were a sensitivity of 0.68 and a specificity of 0.66. Sensitivity and specificity values were plotted as a function of threshold probability derived from the model, further illustrating the sensitivity–specificity tradeoff and allowing for the selection of the appropriate threshold probability for any particular use case of interest (Figure 2B).

Figure 2. Diagnostic metrics for final selected model (A) receiver-operating characteristic plot; (B) sensitivity–specificity tradeoff for different threshold probabilities



The area under the receiver-operating characteristics curve was 0.72, and threshold probability that optimized the sensitivity–specificity tradeoff was 0.40, yielding a sensitivity of 0.68 and a specificity of 0.66.

Discussion

Identification of GPP flares in EHR data is important to understand disease progression and health outcomes in the real-world setting, but discriminating accurately between encounters

associated and not associated with flares in the outpatient setting remains challenging. In this study, we developed a novel algorithm for flare identification based on NLP of unstructured clinical notes and structured data available in outpatient EHRs. The least discriminative model was derived from the use of NLP alone to detect the presence of terms or term combinations in the unstructured clinical notes without considering the structured data (AUROC=0.61). The use of structured EHR data alone (procedure codes and prescriptions) yielded a slightly higher AUROC of 0.69, but both the unstructured and structured EHR data together yielded the most discriminative model (AUROC=0.72).

Other approaches to increase the overall discriminative ability of the model were considered but not pursued because they had limited utility in external data sources. For example, transformer-based NLP models implementing more sophisticated machine learning techniques have performed better in detecting GPP flares [11] and could be useful in analyzing this database; however, the “black box” nature of these models is not transportable to other datasets, and therefore may not be useful for other researchers studying GPP flares in their data. Similarly, the inclusion of other structured EHR variables over longer time intervals was considered to improve model performance; however, the inclusion of these variables would require patients to have a requisite amount of follow-up data for evaluation, which may limit its use in other EHR data sources.

GPP flares in the outpatient dermatology setting may be harder to identify than in other settings, which could contribute to models being less discriminative. In the inpatient and emergency department settings, GPP flare identification is likely more straightforward given that the patient is being seen in one of those settings with a documented diagnosis code for GPP, whereas in the outpatient setting, GPP flares may be more heterogeneous in their presentation.

Zema et al. (2022) have previously published an algorithm to identify GPP flares using EHR data from all healthcare settings based on string searches in clinical notes and informed by literature review and clinical expert input [9]. When applied to our validation/test set, this algorithm yielded a sensitivity of 22% and a specificity of 81%. At this same sensitivity level (22%), our model yielded a specificity of 94%, and at this same specificity level (81%), our model yielded a sensitivity of 68%. This validation exercise supports the notion that different methods of identifying GPP flares may be needed in different healthcare settings.

This study had several limitations. GPP may be underdiagnosed in the real-world outpatient setting, introducing the potential for unnecessary exclusion of some patients. The coding of GPP in the EHR may have varied between health systems and clinicians. Additionally, documentation of flares may not have been comprehensive or consistent between healthcare providers, and clinically adjudicated chart reviews may not be performed to confirm gold standard/ground truth flare status, both of which may have led to variability in outcome ascertainment. Finally, data were limited to US-based dermatology practices, which may limit generalizability to broader populations.

In conclusion, using NLP in combination with structured data from EHRs to identify GPP flares enhances data utilization by extracting valuable information from unstructured clinical notes, reflecting real-world applicability. While the model developed in this study was not fully discriminative, implementation of this algorithm may provide researchers with the opportunity to study GPP flares in external EHR datasets where clinical notes are

accessible.

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Conflicts of interest

LR and VK are employees of and may hold stock or stock options in OMNY Health, a company contracted by Boehringer Ingelheim to provide data access and research services. SRF has received research, speaking and/or consulting support from Eli Lilly and Company, GlaxoSmithKline/Stiefel, AbbVie, Janssen, Alovtech, vTv Therapeutics, Bristol Myers Squibb, Samsung, Pfizer, Boehringer Ingelheim, Amgen, Dermavant, Arcutis Biotherapeutics, Novartis, Novan, UCB, Helsinn, Sun Pharma, Almirall, Galderma, Leo Pharma, Mylan, Celgene, Ortho Dermatology, Menlo, Merck & Co, Qurient, Forte, Arena, Biocon, Accordant, Argenx, Sanofi, Regeneron, the National Biological Corporation, Caremark, Teladoc, Ono, Micreos, Eurofins, Informa, UpToDate, and the National Psoriasis Foundation. He is founder and part owner of Causa Research and holds stock in Sensal Health. ADL is an employee of Boehringer Ingelheim International GmbH. SEW, GRC, and AL are employees of Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT, USA.

Data availability statement

Datasets related to this article were derived from de-identified electronic health record data and natural language processing of unstructured clinical notes from specialty dermatology clinics in the United States through the OMNY Health real-world data platform. Per the patient privacy regulations described in the Health Insurance Portability and Accountability Act and per individual contracts with healthcare systems providing the data, datasets related to this article cannot be made available for public use. Any inquiries about the datasets can be made to OMNY Health.

Author contributions statement
Conceptualization: LR, SEW, VK, GRC, AL, ADL

Data curation: LR, VK

Formal analysis: LR, VK

Funding acquisition: SEW, ADL

Investigation: LR, SEW, VK, GRC, AL, ADL

Methodology: LR, SEW, VK, GRC, AL, ADL, SRF

Project administration: LR, SEW, VK, GRC, AL, ADL

Resources:

Software:

Supervision:

Validation:

Visualization:

Writing – original draft: LR

Writing – review & editing: LR, SEW, VK, GRC, AL, ADL, SRF

Abbreviations

AUROC: Area under the receiver-operating characteristic plot

EHR: Electronic health records

GPP: Generalized pustular psoriasis

ICD-10: International Classification of Diseases, 10th Revision

LPOCV: Leave pair-out cross-validation

NLP: Natural language processing

NLP-F: NLP flare-related terms

NLP-NF: NLP non-flare-related terms

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