

Predictors of nonresponse to dupilumab in patients with atopic dermatitis

A machine learning analysis

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ABSTRACT

Background: Many patients with atopic dermatitis (AD) have a suboptimal response to systemic therapy.

Objective: This study assessed predictors of nonresponse to dupilumab in patients with AD.

Methods: Data (April 2017 through June 2019) for patients aged 12 years and above with AD (International Classification of Diseases–9/10–Clinical Modification: 691.8/L20.x) who initiated dupilumab on or after April 1, 2017 (index date) were collected from an electronic health record and insurance claims database. Nonresponse indicators (dupilumab discontinuation, addition of another systemic therapy or phototherapy, addition of a high-potency topical corticosteroid, AD-related hospital visit, AD-related emergency department visit, incident skin infection) were predicted from available demographic and clinical variables using machine learning.

Results: Among 419 patients (mean age: 45 years), 145 (35%) experienced at least 1 indicator of nonresponse in the 6-month postindex period. In patients with at least 1 indicator, the most common was dupilumab discontinuation (47% [68/145]). Of note, this analysis could not capture nonmedical reasons for dupilumab discontinuation (eg, cost, access). The most common predictors of nonresponse were a claim for ibuprofen (in 69% of patients with a nonresponse indicator) and a Quan-Charlson Comorbidity Index value of 3 to 4 (59%).

Conclusion: Systemic dupilumab therapy for AD can be associated with a relatively high prevalence of nonresponse indicators. Factors associated with these indicators—that is, predictors of nonresponse—may be used to optimize disease management.

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Introduction

Atopic dermatitis (AD) is a heterogeneous, long-term, inflammatory disease of the skin characterized by red and itchy rashes occurring anywhere on the body, in either a persistent or relapsing manner.¹ It is common, affecting up to 36% of the pediatric population and up to 23% of the adult population worldwide.² In the United States, the prevalence is up to 15% in the pediatric population^{3,4} and 10% among adults.^{5,6} In recent studies, AD has been associated with anxiety, depression, sleep disruption, increased economic burden, and decreased quality of life, particularly when moderate or severe.^{7–10}

Nonpharmacologic topical therapies (eg, emollients), along with medicated topical therapies that include topical corticosteroids (TCs), topical calcineurin inhibitors (TCIs), phosphodiesterase 4

inhibitors, or a Janus kinase (JAK) inhibitor, are often sufficient for maintaining disease control.^{11–13} However, some patients may require treatment intensification with phototherapy, off-label systemic immunosuppressants (methotrexate, cyclosporine, azathioprine, mycophenolate mofetil),¹⁴ or AD-approved systemic therapies such as biologics (dupilumab and tralokinumab)^{15,16} or JAK inhibitors (abrocitinib, baricitinib, and upadacitinib).^{13,17}

As the armamentarium of AD therapies continues to expand, it is becoming increasingly important to optimize treatments for individual patients. Dupilumab is a subcutaneously administered antibody that blocks interleukin (IL)-4 and IL-13 receptor activation through binding of the IL-4 receptor α subunit, and it is currently the most typically used systemic AD therapy in the United States.⁸ However, randomized trial data reveal that approximately half of the patients with AD treated with dupilumab for 16 weeks may not achieve a notable response in key symptoms such as itch.¹⁸

This study aimed to identify potential predictors of nonresponse to dupilumab on the basis of electronic health records (EHR) and claims data, using machine learning (ML). Compared with more traditional, regression-based approaches, ML methods are better suited for prediction in complex circumstances with many possible variables, the attendant nonlinear relationships, and the outcomes of interest.

Methods

Study Design and Data Source

The Optum Market Clarity database, which includes data from more than 63 million individuals in the United States, was selected as the data source for this retrospective cohort study. Through the integration of the Optum EHR system and several individual payer claims data sets, the Market Clarity database allows for the analysis of patient demographics (eg, race, ethnicity), clinical notes (eg, health behaviors such as smoking history or status, alcohol consumption or exercise level), laboratory values, medications, and health care resource use and costs. Data were deidentified, in compliance with the Health Insurance Portability and Accountability Act. Therefore, approval from institutional review boards or independent ethics committees was not needed.

Study Sample

We included all patients aged at least 12 years who had initiated dupilumab between April 1, 2017 (the first full month after the US approval of dupilumab) and June 30, 2019 (the most recent Market Clarity data cut available that allowed at least a 6-month follow-up period). Additional inclusion criteria were as follows: (1) at least 2 claims for dupilumab during this observation window, with the first claim representing the index date; (2) at least 6 months of continuous administrative eligibility before and after this index date; and (3) at least 2 AD diagnosis codes during the study period with at least 1 preceding the index date. Patients were excluded if they had participated in a clinical trial (International Classification of Diseases [ICD] –9-Clinical Modification [CM]: V70.7, ICD-10-CM: Z00.6) in the 6-month preindex baseline and 6-month postindex follow-up periods, because their treatment patterns may not reflect real-world practice.

Indicators of Nonresponse

The standard measures of clinical response in AD (eg, those on the basis of eczema area and severity index [EASI] or investigator's global assessment scores) are not routinely captured in real-world databases. Instead, using expert opinion and previous research,¹⁷ we identified 6 indicators that might suggest a lack of response to dupilumab, including the following: (1) discontinuation of dupilumab (defined as a gap of >60 days' supply); (2) the addition of a new

systemic therapy (oral prednisone, methotrexate, cyclosporine, mycophenolate, azathioprine) or phototherapy; (3) the addition of a topical high-potency (class 1 or 2) TCS not previously used; (4) an AD-related hospitalization; (5) an AD-related emergency department (ED) visit; or (6) an incident skin infection (*Staphylococcus* or *Streptococcus* skin infection, eczema herpeticum, impetigo, cellulitis, or eczema coxsackium [ICD-9-CM: 041.01, 041.1x, 054.0, 684, 682.0; ICD-10-CM: B95.0, B95.6x-B95.8, B00.0, L01.x, L03.x, K12.2]) in the follow-up period. In this study, the presence of any of the 6 indicators was considered suggestive of treatment nonresponse.

Predictors of Nonresponse

All available data from the EHR and claims database were used as potential predictors, including demographics (eg, age, sex, race, ethnicity, geographic region, insurance), general health history (eg, body mass index, smoking history, alcohol use, Quan-Charlson Comorbidity Index,^{19,20} individual system organ class disorders, or concomitant medications), and AD-related health history (eg, duration of disease, number of dermatology visits). The full list of data considered as predictors is provided in eTable 1.

Statistical Analysis

The characteristics of the overall sample and the indicators of nonresponse were reported descriptively (means and SDs for continuous variables and frequencies and percentages for categorical variables). Predictors were identified using 4 ML classification methods (models), on the basis of their past use in similar studies: lasso logistic regression, elastic net logistic regression, random forests, and gradient boosted trees.^{21–24} Lasso logistic regression is an ML model with a single tuning parameter, the cross-validation number; it penalizes the logistic regression coefficients into absolute values using the L-1 norm and automatically selects the variables of interest. Elastic net is a combination of 2 approaches, ridge regression, from which it uses the alpha parameter (a positive value that limits the minimization of the sums of squares in the regression solution), and lasso regression, from which it uses the lambda parameter (the multiplier in the Lagrangian expression of the minimization the lasso regression performs). Random forest is an ensemble tree-based method that has predictive abilities and, through Shapley Additive Explanation (SHAP) plots, can be used to interpret the importance of each variable. Gradient boosted trees are also an ensemble tree-based method, which focuses on updating the classification error using a boosting mechanism and can provide excellent predictive accuracy, with limited interpretability. The data set was randomly split into a training data set (80%) and a test data set (20%); the former was used to develop the parameters for each ML model and the latter was used to generate the final performance for each model. Only the results from the best fitting of the 4 models are reported. The most influential predictors were based on absolute values of SHAPs.²⁵ The SHAP values are quantitative estimates of the change of prediction power of a model when a certain feature is removed from it. The SHAPs are calculated for each value of a given feature (eg, age) and then summarized by calculating SHAP mean values. A larger SHAP mean value for a given feature indicates the higher importance of that feature in the model. Missing values for baseline parameters were not imputed. Statistical analyses were conducted using the Statistical Analysis System, version 9.4 (SAS Institute, Cary, North Carolina) and R software version 3.5.

Results

Patient Characteristics

A total of 419 patients met the selection criteria (eFig 1). These patients were relatively young (age, mean $\pm$ SD: 45 $\pm$ 17 years), and

Table 1
Demographic and Health History of the Dupilumab Cohort (N = 419) at Baseline (Index Date)

Variable	N = 419
Index year, n (%)	
2017	156 (37)
2018	193 (46)
2019	70 (17)
Age, mean (SD), y	44.8 (17.3)
Sex, n (%)	
Male	183 (44)
Female	236 (56)
Race, n (%)	
White	290 (69)
African American	67 (16)
Asian	24 (6)
Unknown (missing)	38 (9)
Ethnicity, n (%)	
Non-Hispanic	364 (87)
Hispanic	18 (4)
Unknown (missing)	37 (9)
Census region, n (%)	
East North Central	117 (28)
East South Central	18 (4)
Middle Atlantic	112 (27)
Mountain	12 (3)
New England	12 (3)
Pacific	15 (4)
South Atlantic or West South Central	82 (20)
West North Central	40 (10)
Unknown (missing)	11 (3)
Integrated delivery network, n (%)	
Out of network	27 (6)
In network	392 (94)
Insurance coverage, n (%)	
Commercial	308 (74)
Medicaid	66 (16)
Medicare	40 (10)
Other (uninsured, missing)	5 (1)
AD family history ^a , n (%)	26 (6)
Disease duration, n (%)	
<6 mo	107 (26)
6–12 mo	43 (10)
1–2 y	60 (14)
2–5 y	116 (28)
5+ y	93 (22)
Body mass index, n (%)	
Underweight (≤ 18.5 kg/m ²)	7 (2)
Normal weight (> 18.5 to ≤ 25 kg/m ²)	59 (14)
Overweight (> 25 to ≤ 30 kg/m ²)	54 (13)
Obesity (> 30 kg/m ²)	91 (22)
Unknown (missing)	208 (50)
Alcohol consumption ^b , n (%)	
Does not consume alcohol	58 (14)
Consumes alcohol	86 (21)
Unknown (missing)	275 (66)
Smoking, n (%)	
Never smoked	127 (30)
Smoked previously	47 (11)
Current smoker	34 (8)
Currently not smoking	14 (3)
Unknown (missing)	197 (47)
Quan-Charlson Comorbidity Index, mean (SD)	0.93 (1.44)

Abbreviation: AD, atopic dermatitis.

^aPatients without evidence or record of a family history of AD were considered to have no family history of AD.

^bAlcohol consumption was captured through clinical notes.

most were women (56%) and White (69%). The index year (and, therefore, follow-up time) varied: 37% of patients initiated dupilumab in 2017, 46% in 2018, and 17% in 2019. The complete demographic and health history characteristics at the index date (baseline) are detailed in Table 1.

The most frequently reported system organ class disorders at index date were infections and infestations (47%), psychiatric disorders (41%), and respiratory, thoracic, and mediastinal disorders (38%)

(eTable 2). Overall, medication history was substantial, with a mean ($\pm$ SD) of 23.3 ($\pm$ 21.2) medication claims in the 6 months before the initiation of dupilumab. The most common medications used at baseline, regardless of their indication, are detailed in eTable 2. Although the database does not capture intended use, several of those medications are typically used for the treatment of AD (triamcinolone, 52% of participants; prednisone, 45%; topical tacrolimus ointment, 23%; 2.5% hydrocortisone cream or ointment, 13%; crisaborole, 13%; methylprednisolone, 12%).

Indicators of Nonresponse

Out of 419 patients in the study sample, 145 (35%) experienced at least 1 indicator of nonresponse in the 6-month postindex period (Fig 1), and 26 out of 419 (6%) experienced more than 1. Only 1 in 419 patients (0.2%) had more than 3 indicators. The most common individual indicators were discontinuation of dupilumab (53/145 [37%]), add-on of systemic therapy or phototherapy (27/145 [19%]), and an incident skin infection (22/145 [15%]) (Table 2).

Predictors of Nonresponse

Out of the 4 ML models tested, the random forest exhibited the highest level of accuracy (69%) and was selected for the subsequent analyses (eTable 3). The most influential predictors are illustrated in Figure 2a, and the direction of the relationship between predictor and outcome is illustrated in Figure 2b.

The prevalence of nonresponse indicators for each of the key predictor variables from the ML model is detailed in eTable 4. Patients who were least likely ($<30\%$) to experience a nonresponse indicator were those who had few (but at least 1) AD-related physician visits (29%), were aged 25 years or younger (28%), were of male sex (28%), were from the Middle Atlantic census region (28%), had some AD-related out-of-pocket medical costs (27%), belonged to the lowest tertile in terms of all-cause physician visits (26%), had used prednisone (26%), had few (but at least 1) allergist visits (21%), and were Asian (17%) or were from the New England census region (17%). The specific reasons for the lower prevalence of nonresponse indicators in these patients were varied (eg, younger patients were disproportionately less likely than older patients to have an incident skin infection, and men were less likely than women to discontinue or add on another systemic therapy) (eTable 4).

Conversely, a high prevalence of nonresponse indicators was associated with a claim for ibuprofen (69%), Quan-Charlson Comorbidity Index value of 3 to 4 (59%), residence in Mountain (58%) or East South Central (50%) census regions, no concomitant medication claims (55%), no claim for prednisone (41%), no AD-related visits (40%), female sex (39%), age older than 65 years (38%), respiratory comorbidity (38%), upper tertile in terms of all-cause physician visits (38%) or allergist visits (38%), African American race (37%), or presence of psychiatric comorbidity (37%) (eTable 4). The reasons for the higher prevalence of nonresponse indicators in these patients were also varied. For example, older individuals were disproportionately more likely to discontinue treatment, have an incident skin infection, or have an AD-related ED visit than younger patients, whereas those with psychiatric comorbidity were disproportionately likely to add on another systemic therapy than those without.

Discussion

This study reinforces what is known regarding patients who initiate a systemic therapy (dupilumab in this case) for AD (ie, they are young and predominantly of the female sex) and the challenges they face in disease management.^{8,26} More than 40% of patients had psychiatric comorbidity, consistent with survey-based research

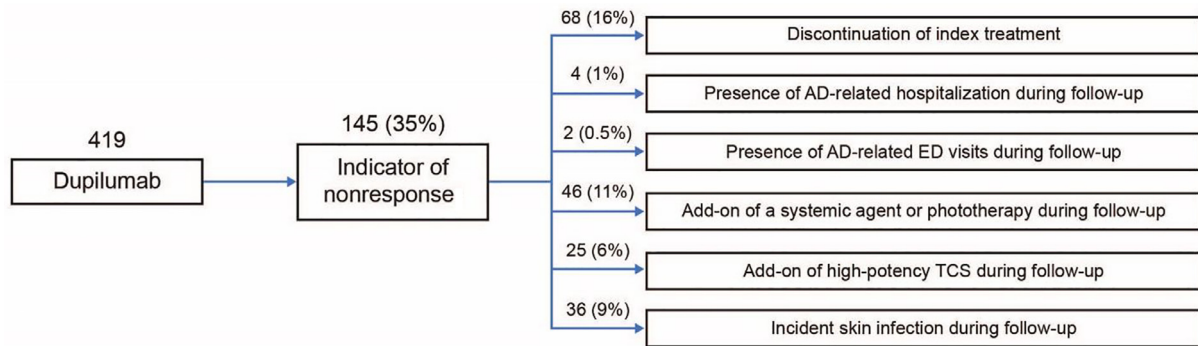


Figure 1. Indicators of nonresponse to dupilumab in patients with AD during the postindex follow-up period. AD, atopic dermatitis; ED, emergency department; TCS, topical corticosteroid.

Table 2
Frequency of Specific Indicators and Combination of Indicators of Nonresponse Among Patients Who Experienced Nonresponse

Indicators of nonresponse, n (%)	Patients who experienced nonresponse n = 145
Individual indicators	
Discontinuation of index treatment in follow-up only	53 (37)
Add-on of a systemic agent or phototherapy in follow-up only	27 (19)
Incident skin infection in follow-up only	22 (15)
Add-on of high potency TCS in follow-up only	15 (10)
Presence of AD-related hospitalization in follow-up only	2 (1)
Presence of AD-related ED visit in follow-up only	0
Indicator combinations	
Any 2 of the 6 above individual indicators	18 (12)
Any 3 of the 6 above individual indicators	7 (5)
Any 4 of the 6 above individual indicators	0
Any 5 of the 6 above individual indicators	1 (1)
All 6 of the above individual indicators	0

Abbreviations: AD, atopic dermatitis; ED, emergency department; TCS, topical corticosteroids.

reporting the connection between moderate-to-severe AD and a considerable psychosocial burden.^{9,10} Furthermore, these patients frequently rely on various topical therapies to help control their disease, even after initiating a systemic therapy, as previously reported,⁸ and 45% used systemic prednisone.

More specific to our objectives, we found that 35% of patients newly initiating dupilumab experienced at least 1 indicator of nonresponse within 6 months, highlighting the difficulties in treating patients with moderate-to-severe AD. For a plurality of patients, discontinuing dupilumab was the sole indicator of nonresponse; however, other indicators such as adding-on systemic therapy, adding-on a high-potency TCS, or having an incident skin infection, were also common. AD-related hospitalizations or ED visits were infrequently observed, consistent with previous literature.⁸

The use of ML can help generate hypotheses as to which patients may be more or less likely to respond to dupilumab. The models used in this study, random forest, in particular, were adequately able to predict the future occurrence of an indicator of nonresponse. In some cases, these factors may represent patients with more severe disease; for example, psychiatric comorbidities were found to correlate with an increase in AD severity.⁹ The use of ibuprofen may be associated with increased skin-related pain, which also would be associated with greater disease severity. In turn, patients with severe disease may be less likely to respond and sustain their response with dupilumab in the real world. Other factors, such as race, may reflect a complex relationship among disease severity, heterogeneity in the

clinical manifestations of AD, access to dermatologic care, and the resultant impact of those aspects on patient outcomes.

Although additional research would be needed to verify these findings, studies such as this one can help identify new lines of inquiry into understanding which patients may be more or less likely to respond to dupilumab and other systemic therapies.

Limitations

Several limitations should be noted. First, retrospective, non-randomized studies are inherently susceptible to selection bias. As is often the case with real-world data sets, reference-standard clinical measures for response, or notes related to the lack of eczema improvement, were not available and we had to rely on proxy variables. The choice of these proxy variables (ie, our indicators of nonresponse) was also dictated by the parameters that were available in the database. Furthermore, the extent to which our indicators of nonresponse accurately correspond to nonresponse measures on the basis of EASI or investigator's global assessment is unclear. For example, discontinuation of dupilumab may occur for reasons that are unrelated to efficacy (eg, access, cost), or related, but difficult to capture, such as the absence of symptoms. Of note, clinical trial data suggest that the absence of symptoms (defined as 100% improvement on the EASI) after 16 weeks of dupilumab therapy would be attained in approximately 8% of patients with moderate-to-severe AD.²⁷ Also, we only focused on baseline variables, which means that treatment adherence to previously administered topical therapies is not featured in our analysis (it is important to note that adherence to topical therapies is difficult to assess and that all the patients were new to systemic therapies, so there was no history of adherence to dupilumab). Moreover, the prescription claims data do not capture intended use. Health history data for factors that have been associated with an increased risk of AD, such as obesity²⁸ and smoking,²⁹ were also missing in approximately half of the participants (Table 2). It should also be mentioned that, in studies of this type, any associations designated as statistically substantial are merely hypothesis-generating and may not necessarily reflect anything regarding the treatment in question. For example, our data suggest that patients with a more pronounced comorbidity burden are more likely to have an indicator of nonresponse to dupilumab. This could be owing to many reasons: patients with more comorbidities may be more likely to discontinue treatment because of tolerability issues, various concomitant medications for comorbidities may influence adherence and, therefore, treatment effect, etc. Finally, a relatively small sample in our study is the likely reason for relatively low accuracy values (eTable 3), which limits the generalizability of our findings. Ultimately, this study was exploratory, and replicate studies with larger sample sizes and in different data sets would be needed to verify our findings.

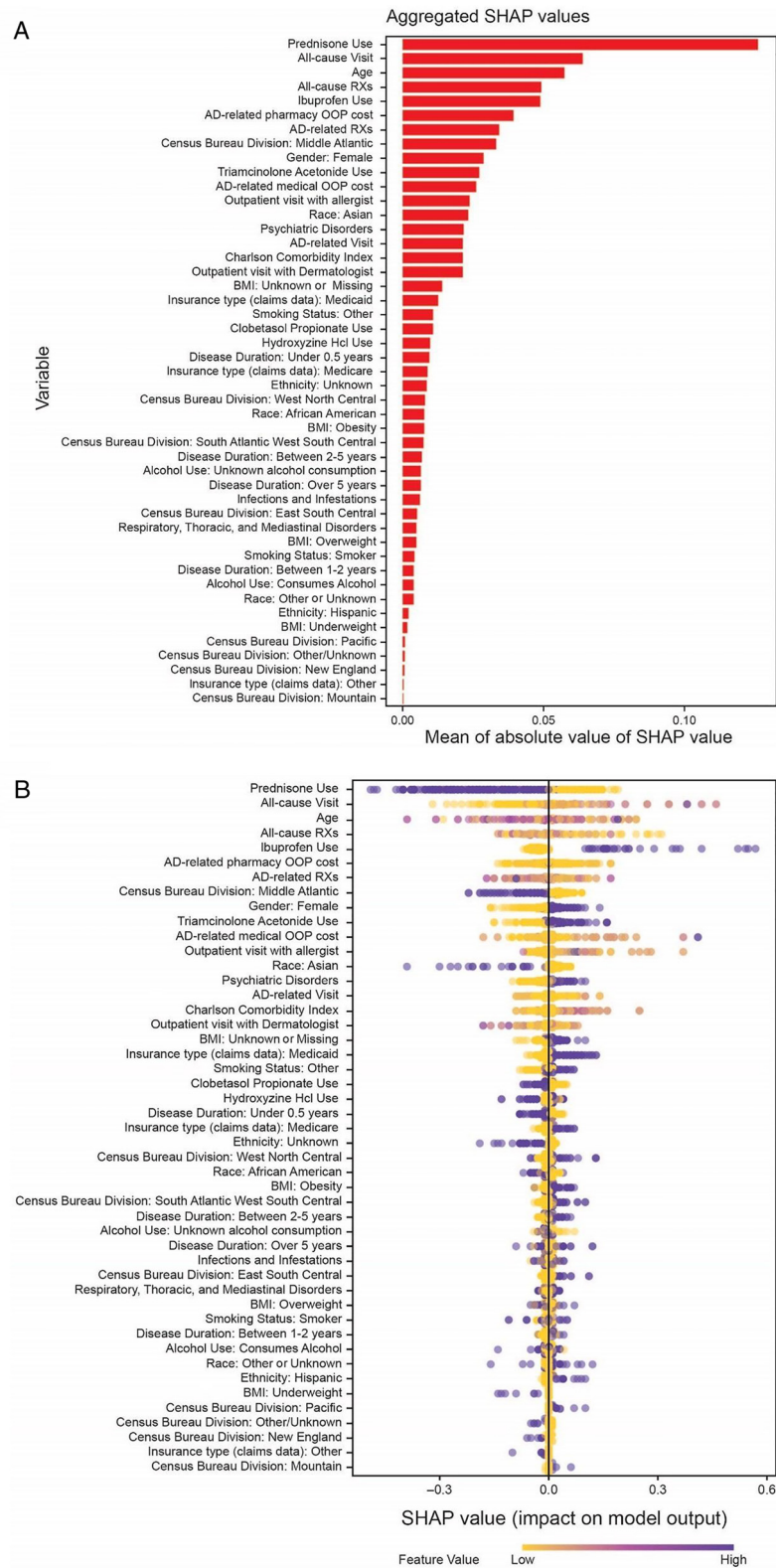


Figure 2. Importance and impact of top predictors among the dupilumab cohort on the basis of the following: (A) mean absolute SHAP values, and (B) individual SHAP values. Features or predictors are ordered by declining influence. Blue dots with positive value indicate a positive association with a higher prevalence of nonresponse indicators. AD, atopic dermatitis; BMI, body mass index; OOP, out-of-pocket; RX, prescription; SHAP, Shapley Additive Explanation.

Conclusion

The results of this study support clinical trial findings, which indicate that a substantial subset of patients with AD who initiate dupilumab treatment will have a suboptimal response. In real-world

clinical practice, predicting which patients may be more or less likely to experience a nonresponse is challenging, and our findings suggest that many factors can contribute to such an outcome. Although more research is necessary to confirm these findings, they may be used to support clinical decision-making and optimize disease management.

Supplementary Data

Supplementary material associated with this article can be found in the online version at <https://doi.org/10.1016/j.anai.2022.05.025>.

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Supplementary Data

eTable 1

Baseline Characteristics Assessed as Potential Predictors of Nonresponse

Abbreviation	Definition
AGE	Age at index date, y
SEX	Sex
RACE	Race
ETHNICITY	Ethnicity
BL_BMI_BIN	BMI (closest to index date in 6-mo preindex baseline) binned into categories
DIVISION	Census Bureau divisions
BL_TOP25_25	fluticasone propionate plus salmeterol use during 6-mo preindex (rank: 25)
BL_TOP25_5	albuterol sulfate use during 6-mo preindex (rank: 5)
BL_TOP25_9	hydrocortisone use during 6-mo preindex (rank: 9)
BL_TOP25_14	levothyroxine sodium use during 6-mo preindex (rank: 14)
BL_TOP25_2	prednisone use during 6-mo preindex (rank: 2)
BL_TOP25_1	triamcinolone acetonide use during 6-mo preindex (rank: 1)
BL_TOP25_10	fluticasone propionate use during 6-mo preindex (rank: 10)
BL_TOP25_12_1	atorvastatin calcium use during 6-mo preindex (rank: 12)
BL_TOP25_13	hydrocodone plus acetaminophen use during 6-mo preindex (rank: 13)
BL_TOP25_15_1	doxycycline hyclate use during 6-mo preindex (rank: 15)
BL_TOP25_15_2	fluocinonide use during 6-mo preindex (rank: 15)
BL_TOP25_16	sulfamethoxazole plus trimethoprim use during 6-mo preindex (rank: 16)
BL_TOP25_18_1	0.9 % sodium chloride use during 6-mo preindex (rank: 18)
BL_TOP25_22	gabapentin use during 6-mo preindex (rank: 22)
BL_TOP25_24_2	amoxicillin plus potassium clav use during 6-mo preindex (rank: 24)
BL_TOP25_3	hydroxyzine HCl use during 6-mo preindex (rank: 3)
BL_TOP25_7	montelukast sodium use during 6-mo preindex (rank: 7)
BL_TOP25_4	clobetasol propionate use during 6-mo preindex (rank: 4)
BL_TOP25_11	methylprednisolone use during 6-mo preindex (rank: 11)
BL_TOP25_8	cephalexin use during 6-mo preindex (rank: 8)
BL_TOP25_6	tacrolimus use during 6-mo preindex (rank: 6)
BL_TOP25_18_2	azithromycin use during 6-mo preindex (rank: 18)
BL_TOP25_12_2	mupirocin use during 6-mo preindex (rank: 12)
BL_TOP25_18_3	omeprazole use during 6-mo preindex (rank: 18)
BL_TOP25_19	folic acid use during 6-mo preindex (rank: 19)
BL_TOP25_20	methotrexate sodium use during 6-mo preindex (rank: 20)
BL_TOP25_17	crisaborole use during 6-mo preindex (rank: 17)
BL_TOP25_21	ibuprofen use during 6-mo preindex (rank: 21)
BL_TOP25_23	cetirizine HCl use during 6-mo preindex (rank: 23)
BL_TOP25_24_1	amlodipine besylate use during 6-mo preindex (rank: 24)
BL_CCI11	Diabetes with long-term complications during 6-mo bl
BL_CCI14	Any malignancy, including leukemia and lymphoma during 6-mo bl
BL_CCI	Charlson Comorbidity Index during 6-mo bl
INS_C	Insurance type (claims data)
BL_SMOKE	Smoking status (closest to index date in 6-mo preindex baseline)
BL_ALCOHOL	Alcohol Use (closest to index date in 6-mo preindex baseline)
BL_RX_C	Number of all-cause RXs during 6-mo preindex baseline (claims)
BL_REL_RX_C	Number of AD-related RXs during 6-mo preindex baseline (claims)
BL_REL_RX_OOP_COST	AD-related pharmacy out-of-pocket cost during 6-mo preindex baseline
BL_REL_MEDICAL_OOP_COST	AD-related medical out-of-pocket cost during 6-mo preindex baseline
BL_DERM_VISIT_BOTH	Number of outpatient visits with a dermatologist during variable-length preindex baseline (claims and EMR)
BL_ALLERG_VISIT_BOTH	Number of outpatient visits with an allergist during 6-mo preindex baseline (claims and EMR)
OUTCOME	Flag if a patient discontinued on the basis of 6 possible conditions as disclosed in SAP
family_history_AD	Categorize if a patient has a family history of AD, no family history, or missing
BL_REL_VISIT_BOTH	Combination of BL_REL_ER_VISIT_BOTH + BL_REL_OP_VISIT_BOTH + BL_REL_IP_VISIT_BOTH
BL_VISIT_BOTH	Combination of BL_ER_VISIT_BOTH + BL_IP_VISIT_BOTH + BL_OP_VISIT_BOTH
BIN_BLALL_ADDX_DURATION	BLALL_ADDX_DURATION placed into bins on the basis of boxplot
SOC_Cardiac_Disorders	Grouping of certain AD comorbidities to SOC group Cardiac Disorders
SOC_Endocrine_Disorders	Grouping of certain AD comorbidities to SOC group Endocrine Disorders
SOC_Gastrointestinal_Disorders	Grouping of certain AD comorbidities to SOC group Gastrointestinal Disorders
SOC_Hepatobiliary_Disorders	Grouping of certain AD comorbidities to SOC group Hepatobiliary Disorders
SOC_Immune_System_Disorders	Grouping of certain AD comorbidities to SOC group Immune System Disorders
SOC_Infections_And_Infestations	Grouping of certain AD comorbidities to SOC group Infections and Infestations
SOC_Metabolism_And_Nutrition_Disorders	Grouping of certain AD comorbidities to SOC group Metabolism and Nutrition Disorders
SOC_Psychiatric_Disorders	Grouping of certain AD comorbidities to SOC group Psychiatric Disorders
SOC_Renal_And_Urinary_Disorders	Grouping of certain AD comorbidities to SOC group Renal and Urinary Disorders
SOC_Respiratory_Thoracic_Mediastinal_Disorders	Grouping of certain AD comorbidities to SOC group Respiratory, Thoracic, and Mediastinal Disorders
SOC_Skin_And_Subcutaneous_Tissue_Disorders	Grouping of certain AD comorbidities to SOC group Skin and Subcutaneous Tissue Disorders
SOC_Vascular_Disorders	Grouping of certain AD comorbidities to SOC group Vascular Disorders

Abbreviations: AD, atopic dermatitis; bl, baseline; BMI, body mass index; clav, clavulanic acid; EMR, electronic medical record; HCl, hydrochloride; RX, prescription; SAP, systems, applications, and products data processing software; SOC, system organ class.

eTable 2

Comorbidities, Concomitant Medications, and Health Care Resource Use of the Dupilumab Cohort at Baseline (N = 419)

Variables	N = 419
System organ class disorders, n (%)	
Infections and infestations	196 (47)
Psychiatric disorders	171 (41)
Respiratory, thoracic, and mediastinal disorders	159 (38)
Metabolism and nutrition disorders	53 (13)
Skin and subcutaneous tissue disorders	31 (7)
Cardiac disorders	29 (7)
Immune system disorders	26 (6)
Endocrine disorders	25 (6)
Renal and urinary disorders	22 (5)
Hepatobiliary disorders	16 (4)
Vascular disorders	13 (3)
Gastrointestinal disorders	10 (2)
Most frequent concomitant medications, n (%)	
Triamcinolone acetonide	219 (52)
Prednisone	189 (45)
Hydroxyzine HCl	127 (30)
Albuterol sulfate	120 (29)
Clobetasol propionate	105 (25)
Tacrolimus	99 (24)
Montelukast sodium	84 (20)
Cephalexin	71 (17)
Fluticasone propionate	60 (14)
Hydrocortisone	56 (13)
Mupirocin	54 (13)
Crisaborole	54 (13)
Methylprednisolone	51 (12)
Doxycycline hyclate	49 (12)
Azithromycin	49 (12)
Atorvastatin calcium	47 (11)
Hydrocodone plus acetaminophen	47 (11)
Sulfamethoxazole plus trimethoprim	47 (11)
Fluocinonide	43 (10)
Omeprazole	41 (10)
Methotrexate sodium	40 (10)
Fluticasone propionate plus salmeterol	41 (10)
Levothyroxine sodium	40 (10)
Gabapentin	39 (9)
Folic acid	38 (9)
Cetirizine HCl	37 (9)
Ibuprofen	36 (9)
0.9% sodium chloride	34 (8)
Amoxicillin plus potassium clav	34 (8)
Amlodipine besylate	28 (7)
Topical medications, n (%)	
Topical corticosteroids, lower-medium or medium potency	218 (52)
Topical corticosteroids, high or very high potency	204 (49)
Topical corticosteroids, lowest or low potency	103 (25)
Tacrolimus	96 (23)
Crisaborole	54 (13)
Pimecrolimus	42 (10)
Health care resource use, mean (SD)	
Number of AD-related physician visits	2.7 (6.7)
Total number of physician visits	24.7 (26.2)
Number of AD-related medications	5.2 (4.2)
Total number of medications	23.3 (21.2)
Number of dermatology visits	3.8 (5.3)
Number of allergist visits	1.2 (3.5)
AD-related medical out-of-pocket costs, USD ^a	62 (193)
AD-related prescription medication out-of-pocket costs, USD ^a	79 (289)

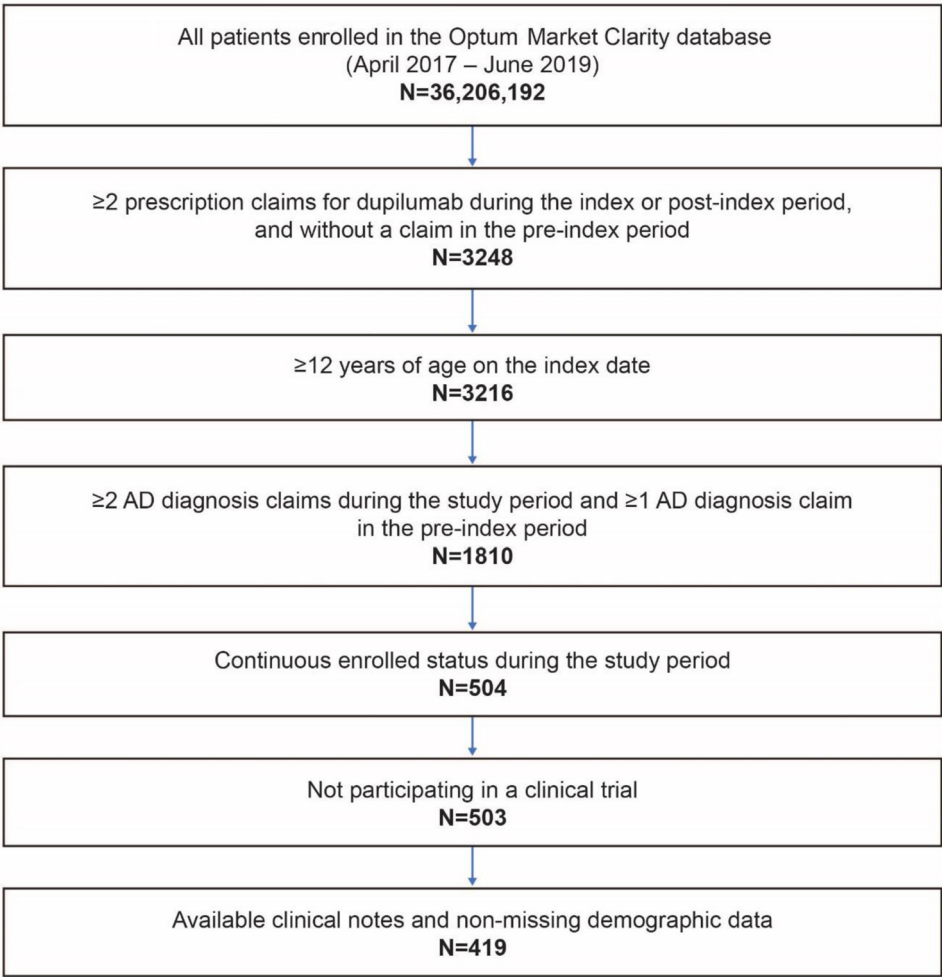
Abbreviations: AD, atopic dermatitis; clav, clavulanic acid; HCl, hydrochloride; USD, US dollars.

^aIndividual costs of care were calculated using 2017 or 2018 USD values, depending on data capture. No adjustments for inflation were made.

eTable 3
Accuracy Statistics of Various Machine Learning Models for the Dupilumab Cohort

Parameter	Lasso logistic regression	Elastic net logistic regression	Random forest	Gradient boosted trees
Accuracy	0.590	0.663	0.687	0.602
AUC ROC	0.574	0.669	0.704	0.587
Sensitivity (recall)	0.551	0.586	0.724	0.483
Specificity	0.611	0.704	0.667	0.667
PPV (precision)	0.436	0.515	0.538	0.438
NPV	0.717	0.760	0.818	0.706

Abbreviations: AUC, area under the curve; NPV, negative predictive value; PPV, positive predictive value; ROC, receiver operator curve.



Note: Patients were required to have demographic data captured, but there was no requirement on which data specifically had to be included.

eFigure 1. Patient selection flow chart.

eTable 4
Predictors of Specific Indicators of Nonresponse

Parameter	Any indicator of nonresponse		Discontinuation		Add-on systemic agent or phototherapy		Add-on high-potency TCS		Incident skin infection		AD-related hospitalization		AD-related ED visit	
	No indicator	Any indicator	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes
Age (y)														
Age ≤25	58 (73)	22 (28)	68 (85)	12 (15)	74 (85)	6 (15)	74 (93)	6 (8)	75 (94)	5 (6)	79 (99)	1 (1)	80 (100)	0 (0)
Age ≥26 to <55	127 (63)	76 (37)	168 (83)	35 (17)	177 (83)	26 (17)	191 (94)	12 (6)	183 (90)	20 (10)	202 (100)	1 (0)	203 (100)	0 (0)
Age 55 to ≤65	64 (67)	32 (33)	83 (86)	13 (14)	86 (86)	10 (14)	91 (95)	5 (5)	90 (94)	6 (6)	95 (99)	1 (1)	96 (100)	0 (0)
Age >65	25 (63)	15 (38)	32 (80)	8 (20)	36 (90)	4 (10)	38 (95)	2 (5)	35 (88)	5 (13)	39 (98)	1 (3)	38 (95)	2 (5)
Sex														
Female	143 (61)	93 (39)	189 (80)	47 (20)	204 (86)	32 (14)	222 (94)	14 (6)	216 (92)	20 (8)	236 (100)	0 (0)	236 (100)	0 (0)
Male	131 (72)	52 (28)	162 (89)	21 (11)	169 (92)	14 (8)	172 (94)	11 (6)	167 (91)	16 (9)	179 (98)	4 (2)	181 (99)	2 (1)
Race														
African American	42 (63)	25 (37)	55 (82)	12 (18)	58 (87)	9 (13)	64 (96)	3 (4)	61 (91)	6 (9)	67 (100)	0 (0)	67 (100)	0 (0)
Asian	20 (83)	4 (17)	24 (100)	0 (0)	23 (96)	1 (4)	23 (96)	1 (4)	22 (92)	2 (8)	24 (100)	0 (0)	24 (100)	0 (0)
White	188 (65)	102 (35)	241 (83)	49 (17)	257 (89)	33 (11)	272 (94)	18 (6)	265 (91)	25 (9)	286 (99)	4 (1)	288 (99)	2 (1)
Other or unknown	24 (63)	14 (37)	31 (82)	7 (18)	35 (92)	3 (8)	35 (92)	3 (8)	35 (92)	3 (8)	38 (100)	0 (0)	38 (100)	0 (0)
Census region														
East North Central	71 (61)	46 (39)	94 (80)	23 (20)	101 (86)	16 (14)	110 (94)	7 (6)	107 (91)	10 (9)	115 (98)	2 (2)	116 (99)	1 (1)
East South Central	9 (50)	9 (50)	15 (83)	3 (17)	15 (83)	3 (17)	17 (94)	1 (6)	14 (78)	4 (22)	18 (100)	0 (0)	17 (94)	1 (6)
Middle Atlantic	81 (72)	31 (28)	99 (88)	13 (12)	103 (92)	9 (8)	106 (95)	6 (5)	105 (94)	7 (6)	110 (98)	2 (2)	112 (100)	0 (0)
Mountain	5 (42)	7 (58)	8 (67)	4 (33)	10 (83)	2 (17)	10 (83)	2 (17)	11 (92)	1 (8)	12 (100)	0 (0)	12 (100)	0 (0)
New England	10 (83)	2 (17)	11 (92)	1 (8)	11 (92)	1 (8)	12 (100)	0 (0)	10 (83)	2 (17)	12 (100)	0 (0)	12 (100)	0 (0)
Pacific	9 (60)	6 (40)	13 (87)	2 (13)	14 (93)	1 (7)	15 (100)	0 (0)	12 (80)	3 (20)	15 (100)	0 (0)	15 (100)	0 (0)
S. Atlantic or West South Central	54 (66)	28 (34)	64 (78)	18 (22)	73 (89)	9 (11)	79 (96)	3 (4)	78 (95)	4 (5)	82 (100)	0 (0)	82 (100)	0 (0)
West North Central	26 (65)	14 (35)	37 (92)	3 (8)	36 (90)	4 (10)	35 (88)	5 (12)	36 (90)	4 (10)	40 (100)	0 (0)	40 (100)	0 (0)
Other or unknown	9 (82)	2 (18)	10 (91)	1 (9)	10 (91)	1 (9)	10 (91)	1 (9)	10 (91)	1 (9)	11 (100)	0 (0)	11 (100)	0 (0)
Quan-Charlson Comorbidity Index														
0	142 (68)	68 (32)	175 (83)	35 (17)	182 (87)	28 (13)	201 (96)	9 (4)	194 (92)	16 (8)	209 (100)	1 (0)	209 (100)	1 (0)
1-2	110 (67)	55 (33)	139 (84)	26 (16)	153 (93)	12 (7)	153 (93)	12 (7)	155 (94)	10 (6)	164 (99)	1 (1)	165 (100)	0 (0)
3-4	12 (41)	17 (59)	23 (79)	6 (21)	25 (86)	4 (14)	25 (86)	4 (14)	23 (79)	6 (21)	27 (93)	2 (7)	28 (97)	1 (3)
>4	10 (67)	5 (33)	14 (93)	1 (7)	13 (87)	2 (13)	15 (100)	0 (0)	11 (73)	4 (27)	15 (100)	0 (0)	15 (100)	0 (0)
Psychiatric disorders														
No	166 (67)	82 (33)	206 (83)	42 (17)	225 (91)	23 (9)	235 (95)	13 (5)	227 (92)	21 (8)	247 (100)	1 (0)	247 (100)	1 (0)
Yes	108 (63)	63 (37)	145 (85)	26 (15)	148 (87)	23 (13)	159 (93)	12 (7)	156 (91)	15 (9)	168 (98)	3 (2)	170 (99)	1 (1)
Infections and infestations														
No	147 (66)	76 (34)	186 (83)	37 (17)	198 (89)	25 (11)	208 (93)	15 (7)	211 (95)	12 (5)	222 (100)	1 (0)	223 (100)	0 (0)
Yes	127 (65)	69 (35)	165 (84)	31 (16)	175 (89)	21 (11)	186 (95)	10 (5)	172 (88)	24 (12)	193 (98)	3 (2)	194 (99)	2 (1)
Respiratory, thoracic, and mediastinal disorders														
No	175 (67)	85 (33)	220 (85)	40 (15)	229 (88)	31 (12)	248 (95)	12 (5)	236 (91)	24 (9)	259 (100)	1 (0)	258 (99)	2 (1)
Yes	99 (62)	60 (38)	131 (82)	28 (18)	144 (91)	15 (9)	146 (92)	13 (8)	147 (92)	12 (8)	156 (98)	3 (2)	159 (100)	0 (0)
All-cause visits														
<9 visits	82 (74)	29 (26)	94 (85)	17 (15)	99 (89)	12 (11)	108 (97)	3 (3)	106 (95)	5 (5)	111 (100)	0 (0)	111 (100)	0 (0)
9-31 visits	129 (63)	77 (37)	168 (82)	38 (18)	185 (90)	21 (10)	193 (94)	13 (6)	189 (92)	17 (8)	204 (99)	2 (1)	205 (100)	1 (0)
>31 visits	63 (62)	39 (38)	89 (87)	13 (13)	89 (87)	13 (13)	93 (91)	9 (9)	88 (86)	14 (14)	100 (98)	2 (2)	101 (99)	1 (1)
AD-related visits														
0 visits	105 (60)	69 (40)	136 (78)	38 (22)	149 (86)	25 (14)	165 (95)	9 (5)	160 (92)	14 (8)	173 (99)	1 (1)	174 (100)	0 (0)
1-3 visits	108 (71)	45 (29)	133 (87)	20 (13)	140 (92)	13 (8)	142 (93)	11 (7)	142 (93)	11 (7)	151 (99)	2 (1)	151 (99)	2 (1)
>3 visits	61 (66)	31 (34)	82 (89)	10 (11)	84 (91)	8 (9)	87 (95)	5 (5)	81 (88)	11 (12)	91 (99)	1 (1)	92 (100)	0 (0)
Dermatologist visits														
0 visits	42 (65)	23 (35)	55 (85)	10 (15)	56 (86)	9 (14)	61 (94)	4 (6)	62 (95)	3 (5)	65 (100)	0 (0)	65 (100)	0 (0)
1 visit	42 (61)	27 (39)	56 (81)	13 (19)	60 (87)	9 (13)	64 (93)	5 (7)	64 (93)	5 (7)	69 (100)	0 (0)	69 (100)	0 (0)
2-4 visits	120 (66)	63 (34)	154 (84)	29 (16)	162 (89)	21 (11)	171 (93)	12 (7)	166 (91)	17 (9)	182 (99)	1 (1)	183 (100)	0 (0)
>4 visits	70 (69)	32 (31)	86 (84)	16 (16)	95 (93)	7 (7)	98 (96)	4 (4)	91 (89)	11 (11)	99 (97)	3 (3)	100 (98)	2 (2)

(continued)

eTable 4 (Continued)

Parameter	Any indicator of nonresponse		Discontinuation		Add-on systemic agent or phototherapy		Add-on high-potency TCS		Incident skin infection		AD-related hospitalization		AD-related ED visit	
	No indicator	Any indicator	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes
Allergist visits														
0 visits	199 (65)	106 (35)	252 (83)	53 (17)	271 (89)	34 (11)	287 (94)	18 (6)	283 (93)	22 (7)	304 (100)	1 (0)	304 (100)	1 (0)
1 visit	22 (79)	6 (21)	24 (86)	4 (14)	27 (96)	1 (4)	28 (100)	0 (0)	25 (89)	3 (11)	28 (100)	0 (0)	28 (100)	0 (0)
>1 visit	53 (62)	33 (38)	75 (87)	11 (13)	75 (87)	11 (13)	79 (92)	7 (8)	75 (87)	11 (13)	83 (97)	3 (3)	85 (99)	1 (1)
All-cause medication claims														
0 medications	5 (45)	6 (55)	8 (73)	3 (27)	8 (73)	3 (27)	9 (82)	2 (18)	10 (91)	1 (9)	11 (100)	0 (0)	11 (100)	0 (0)
1–10 medications	72 (69)	33 (31)	85 (81)	20 (19)	99 (94)	6 (6)	101 (96)	4 (4)	99 (94)	6 (6)	105 (100)	0 (0)	105 (100)	0 (0)
11–30 medications	136 (68)	65 (32)	171 (85)	30 (15)	177 (88)	24 (12)	189 (94)	12 (6)	185 (92)	16 (8)	199 (99)	2 (1)	200 (100)	1 (0)
>30 medications	61 (60)	41 (40)	87 (85)	15 (15)	89 (87)	13 (13)	95 (93)	7 (7)	89 (87)	13 (13)	100 (98)	2 (2)	101 (99)	1 (1)
AD-related medication claims														
0 medications	17 (63)	10 (37)	23 (85)	4 (15)	22 (81)	5 (19)	24 (89)	3 (11)	26 (96)	1 (4)	27 (100)	0 (0)	27 (100)	0 (0)
1–2 medications	59 (61)	38 (39)	81 (84)	16 (16)	83 (86)	14 (14)	89 (92)	8 (8)	88 (91)	9 (9)	97 (100)	0 (0)	97 (100)	0 (0)
3–7 medications	132 (67)	66 (33)	165 (83)	33 (17)	180 (91)	18 (9)	186 (94)	12 (6)	183 (92)	15 (8)	197 (99)	1 (1)	197 (99)	1 (1)
>7 medications	66 (68)	31 (32)	82 (85)	15 (15)	88 (91)	9 (9)	95 (98)	2 (2)	86 (89)	11 (11)	94 (97)	3 (3)	96 (99)	1 (1)
Ibuprofen														
No	263 (69)	120 (31)	325 (85)	58 (15)	344 (90)	39 (10)	361 (94)	22 (6)	353 (92)	30 (8)	380 (99)	3 (1)	381 (99)	2 (1)
Yes	11 (31)	25 (69)	26 (72)	10 (28)	29 (81)	7 (19)	33 (92)	3 (8)	30 (83)	6 (17)	35 (97)	1 (3)	36 (100)	0 (0)
Prednisone														
No	135 (59)	95 (41)	188 (82)	42 (18)	193 (84)	37 (16)	216 (94)	14 (6)	208 (90)	22 (10)	230 (100)	0 (0)	229 (100)	1 (0)
Yes	139 (74)	50 (26)	163 (86)	26 (14)	180 (95)	9 (5)	178 (94)	11 (6)	175 (93)	14 (7)	185 (98)	4 (2)	188 (99)	1 (1)
Triamcinolone acetonide														
No	141 (70)	59 (30)	171 (86)	29 (14)	179 (90)	21 (10)	188 (94)	12 (6)	191 (96)	9 (4)	199 (100)	1 (0)	200 (100)	0 (0)
Yes	133 (61)	86 (39)	180 (82)	39 (18)	194 (89)	25 (11)	206 (94)	13 (6)	192 (88)	27 (12)	216 (99)	3 (1)	217 (99)	2 (1)
AD-related RX OOP cost														
No cost	94 (59)	64 (41)	121 (77)	37 (23)	139 (88)	19 (12)	151 (96)	7 (4)	147 (93)	11 (7)	157 (99)	1 (1)	158 (100)	0 (0)
>0 cost	180 (69)	81 (31)	230 (88)	31 (12)	234 (90)	27 (10)	243 (93)	18 (7)	236 (90)	25 (10)	258 (99)	3 (1)	259 (99)	2 (1)
AD-related medical OOP cost														
No cost	168 (61)	106 (39)	218 (80)	56 (20)	242 (88)	32 (12)	257 (94)	17 (6)	251 (92)	23 (8)	271 (99)	3 (1)	273 (100)	1 (0)
>0 cost	106 (73)	39 (27)	133 (92)	12 (8)	131 (90)	14 (10)	137 (94)	8 (6)	132 (91)	13 (9)	144 (99)	1 (1)	144 (99)	1 (1)

Abbreviations: AD, atopic dermatitis; ED, emergency department; OOP, out-of-pocket; RX, prescription; TCS, topical corticosteroids.

NOTE. All units are number (percentage).