*HLA-C*06:02* genotype is a predictive biomarker of biologic treatment response in psoriasis

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Background: Biologic therapies can be highly effective for the treatment of severe psoriasis, but response for individual patients can vary according to drug. Predictive biomarkers to guide treatment selection could improve patient outcomes and treatment cost-effectiveness.

Objective: We sought to test whether *HLA-C*06:02*, the primary genetic susceptibility allele for psoriasis, predisposes patients to respond differently to the 2 most commonly prescribed biologics for psoriasis: adalimumab (anti–TNF-α) and ustekinumab (anti–IL-12/23).

Methods: This study uses a national psoriasis registry that includes longitudinal treatment and response observations and detailed clinical data. HLA alleles were imputed from genome-wide genotype data for 1326 patients for whom 90% reduction in Psoriasis Area and Severity Index score (PASI90) response status was observed after 3, 6, or 12 months of treatment. We developed regression models of PASI90 response, examining the interaction between *HLA-C*06:02* and drug type (adalimumab or ustekinumab) while accounting for potentially confounding clinical variables.

Results: *HLA-C*06:02*–negative patients were significantly more likely to respond to adalimumab than ustekinumab at all time points (most strongly at 6 months: odds ratio [OR], 2.95; $P = 5.85 \times 10^{-7}$), and the difference was greater in *HLA-C*06:02*–negative patients with psoriatic arthritis (OR, 5.98; $P = 6.89 \times 10^{-5}$). Biologic-naive patients who were *HLA-C*06:02* positive and psoriatic arthritis negative demonstrated significantly poorer response to adalimumab at

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12 months (OR, 0.31; $P = 3.42 \times 10^{-4}$). Results from HLA-wide analyses were consistent with *HLA-C*06:02* itself being the primary effect allele. We found no evidence for genetic interaction between *HLA-C*06:02* and *ERAP1*.
Conclusion: This large observational study suggests that reference to *HLA-C*06:02* status could offer substantial clinical benefit when selecting treatments for severe psoriasis. (J Allergy Clin Immunol 2019;■■■:■■■-■■■.)

Key words: *Psoriasis, psoriatic arthritis, biologic therapy, genetics, pharmacogenetics, treatment response, HLA, adalimumab, ustekinumab, skin disease*

Abbreviations used
BAD: British Association of Dermatologists
BADBIR: British Association of Dermatologists Biologic and Immunomodulators Register
BSTOP: Biomarkers of Systemic Treatment Outcomes in Psoriasis
GxE: Gene-environment interaction
OR: Odds ratio
PASI: Psoriasis Area and Severity Index
PASI75: 75% reduction in Psoriasis Area and Severity Index score
PASI90: 90% reduction in Psoriasis Area and Severity Index score
PASI100: 100% reduction in Psoriasis Area and Severity Index score
PsA: Psoriatic arthritis
UK: United Kingdom

Psoriasis is a chronic immune-mediated skin disease with a prevalence of up to 3% in developed nations.[1] It is responsible for a high global burden of disability,[2] and the economic effect in the United States alone runs into the tens of billions of dollars.[3] Psoriasis is caused by a complex interplay of genetic and environmental factors not yet fully understood,[4,5] and molecular genetics studies have identified more than 60 genomic loci at which variation confers risk of the disease in European populations.[6,7]

In recent years, the clinical management of psoriasis has been revolutionized by a series of highly effective mAb therapies.[8] The most widely adopted of these biologics include adalimumab, which targets TNF-α, and ustekinumab, which targets the p40 subunit common to IL-12 and IL-23 and thus inhibits downstream IL-17 signaling. Clinical trials demonstrate that 71% of patients with moderate-to-severe psoriasis achieve a 75% reduction in Psoriasis Area and Severity Index (PASI; PASI75 response) after 16 weeks of adalimumab treatment, with 45% achieving the superior 90% reduction (PASI90 response) that is consistent with being "clear" or "nearly clear" of disease.[9] Similarly, ustekinumab induces a PASI75 response within 12 weeks for 67% of patients and a PASI90 response for 39% across dosing groups.[10] British Association of Dermatologists (BAD) guidelines recommend that in the absence of relevant contraindications, both drugs should be considered equally as first-line biologic therapy for psoriasis, unless active psoriatic arthritis (PsA) is present, in which case adalimumab is preferred.[11] Both drugs are indicated more widely for other immune-mediated inflammatory diseases.[12]

Because patients can respond differently to different biologics, there is great potential to improve patient outcomes and optimize use of these expensive therapies[13] through identification of biomarkers that can inform which therapies are most likely to be efficacious. The MHC class I allele *HLA-C*06:02* is a promising candidate biomarker. *HLA-C*06:02* is the genetic variant that makes the largest contribution to psoriasis susceptibility: it accounts for more than 6% of variance in disease risk,[14] and each copy of the *HLA-C*06:02* allele carried increases a subject's risk of psoriasis 5-fold.[15] Its effect is modified by an interaction with genetic variants in the gene *ERAP1*, which encodes endoplasmic reticulum aminopeptidase 1, a peptide-trimming protein involved in MHC antigen presentation.[15]

*HLA-C*06:02* status has also been reported to be associated with differences in clinical presentation of psoriasis, with *HLA-C*06:02*–positive patients experiencing earlier onset, differences in lesion severity and distribution, higher incidence of the Koebner phenomenon, and increased likelihood of exacerbation caused by streptococcal throat infection.[16-18] These differences hint at distinct pathophysiologies, and differential response to treatment might therefore be expected. Some evidence has recently accumulated in support of this, with several studies reporting better response to ustekinumab among *HLA-C*06:02*–positive patients than among *HLA-C*06:02*–negative patients.[19-21] The relationship between *HLA-C*06:02* and response to anti-TNF agents is unclear.[22]

Therefore, with the aim of improving outcomes in patients with moderate-to-severe psoriasis, we sought to test the hypothesis that *HLA-C*06:02* status is an effective predictive biomarker of response that could be used to inform treatment selection between the 2 most commonly used biologics: adalimumab and ustekinumab. As such, we have undertaken a retrospective evaluation of *HLA-C*06:02* as a predictive biomarker in a large prospective observational study of biologic interventions in the United Kingdom (UK) population of patients with psoriasis. Our primary definition of positive treatment response is achievement of PASI90 because it correlates with the clinically important status of being "clear" or "nearly clear" of psoriasis.[23] We consider response at 3, 6, and 12 months after treatment initiation and secondary outcomes of PASI75 and 100% reduction in PASI score (PASI100).

METHODS

Patient population

The study was conducted in accordance with the 2008 Declaration of Helsinki and in the spirit of the 1996 International Conference on Harmonisation in Good Clinical Practice. Ethical approval for this study was granted by The South East London REC 2 Ethics Committee (11/H0802/7). Written informed consent was obtained from all subjects before enrollment.

All participants are adults (>16 years) enrolled in the Biomarkers of Systemic Treatment Outcomes in Psoriasis (BSTOP) study (https://www.kcl.ac.uk/lsm/research/divisions/gmm/departments/dermatology/Research/stru/groups/bstop/index.aspx) and the British Association of Dermatologists Biologic and Immunomodulators Register (BADBIR; www.badbir.org). The BSTOP study is a prospective observational study across 60 UK dermatology centers that includes biological sample collection. It aims to establish clinically relevant markers of outcomes to systemic therapies in patients with severe psoriasis (study protocol: https://www.kcl.ac.uk/ContensisManagedLinks/BSTOP-Protocol-Version-5.pdf). BADBIR is a pharmacovigilance register that has recruited more than 16,000 patients with psoriasis undertaking systemic conventional or biological therapy in the UK and Ireland. It seeks to assess the long-term safety of biologic treatments for psoriasis. Enrollment

criteria for the biologic arm for both the BSTOP study and BADBIR include diagnosis and prescription of systemic therapy by a dermatologist.

Clinical data

Detailed clinical data are recorded by the BSTOP study and BADBIR at registration and at regular follow-up assessments during the course of routine clinical care. These data include demographics, Psoriasis Area and Severity Index (PASI) assessments of disease severity, treatment details, adverse events, and comorbidities. Clinical data were extracted on July 1, 2017. Data derived from the BSTOP study and BADBIR were merged, and processes were established to identify and resolve inconsistencies between data sources in collaboration with local clinical teams. For a minority of patients, appropriate assumptions were used to demarcate periods of treatment: treatment was considered ongoing where treatment episodes for the same biologic were separated by less than 90 days[24]; missing treatment end dates were imputed based on the start date of subsequent biologic treatment, allowing a 28-day washout period; and patients were considered to be continuing treatment at the data extract date where no end date was recorded. Age of psoriasis onset was inferred from the recorded year of onset. Patients were assumed to be positive for PsA if reported at BADBIR registration or at any subsequent follow-up before the data extract date (92.8% diagnosed by a rheumatologist).

Genotype data and HLA imputation

DNA was isolated from blood using standard methods. Genotyping was performed with Illumina HumanOmniExpressExome-8 v1.2 and v1.3 BeadChips, followed by quality control with standard tools[25-28] and procedures, as detailed in the Methods section in this article's Online Repository at www.jacionline.org. The final data set was limited to patients of European ancestry. Classical HLA alleles were imputed using SNP2HLA (version 1.0.3) based on the Type 1 Diabetes Genetics Consortium reference panel.[29] We excluded poorly imputed alleles ($R^2 < 0.9$) and alleles with a frequency of less than 0.01, resulting in a total of 142 distinct 2- and 4-digit imputed alleles.

Data integration and definition of response

Patients with both genotype and response data for the first course of treatment for either drug (adalimumab or ustekinumab) were considered for analysis. Patients were required to have a baseline PASI score (up to 6 months before treatment initiation) of greater than 10 and a response PASI score recorded sufficiently close to at least 1 response time point (±30 days from the 3-month and ±60 days from the 6- and 12-month time points) while still receiving treatment. One hundred one patients with eligible records for both treatments were randomly assigned to the adalimumab or ustekinumab groups (50/51 patients, respectively), with their other records being excluded from the analysis. This did not materially affect results (see Table E18 in this article's Online Repository at www.jacionline.org). The final integrated data set included observations for 1326 patients.

For each patient observed at each response time point, the primary outcome of PASI90 response was achieved if the response PASI score represented a reduction of 90% or more relative to the baseline PASI score. Secondary responses of PASI75 and PASI100 were defined similarly.

Statistical modeling

All statistical models were implemented in R software.[27,30] Associations between patients' characteristics and drug type were established through regression modeling (linear regression for continuous characteristics and logistic regression for binary characteristics), with drug type (adalimumab vs ustekinumab) as the sole explanatory variable. Associations with *HLA-C*06:02* were established by using regression models based on imputed *HLA-C*06:02* dosage with 5 ancestry principal component covariates based on 108,319 independent single nucleotide polymorphisms genome wide.[26,31,32]

At each response time point, multivariable logistic regression modeling was used with binary PASI90 response as the dependent variable (PASI75/PASI100 for secondary outcomes) and baseline PASI score as a covariate. Drug type and *HLA-C*06:02* dosage were included as main effects and as a drug × *HLA-C*06:02* interaction term: a statistically significant nonzero interaction effect would implicate *HLA-C*06:02* as a predictive biomarker.

To generate the full multivariable model accounting for potential clinical confounders, main effect and interaction covariate terms were added based on correlations with *HLA-C*06:02* or drug (Table I). For variables significantly correlated with *HLA-C*06:02* (age of onset, baseline PASI score, disease duration, and PsA), an interaction term with drug was included, and for variables significantly correlated with drug (PsA and biologic naive status), an interaction term with *HLA-C*06:02* was included. The full model is described in the Methods section in this article's Online Repository. Missing observations for age of onset or PsA status covariates were replaced by mean-imputed values derived from the *HLA-C*06:02*–positive and *HLA-C*06:02*–negative subgroups. Models of response were fitted within the *HLA-C*06:02*– and PsA-defined subgroups; these included a term for drug type and a covariate term for baseline PASI only.

To confirm that our full multivariable model adequately controlled for potential confounding through covariates influencing treatment selection, we repeated the regression analysis with inverse probability of treatment weighting using the propensity score.[33] Weighted regression was implemented with the "survey" package in R software.[34] See the Methods section in this article's Online Repository for full details.

HLA-wide analysis was performed for 142 2- and 4-digit alleles having a frequency of greater than 1% in our full genotyped cohort of 3320 patients. The full interaction model was fitted based on imputed dosage for each allele in turn, substituting the *HLA-C*06:02* main effect and interaction terms. Conditional analysis was performed by including main effect and interaction terms for both *HLA-C*06:02* and the alternative alleles.

ERAP1 interaction analysis was based on the genotyped variant rs27524.[15] Psoriasis susceptibility epistasis was confirmed by using case-only association testing in the full cohort of 3320 patients, treating *HLA-C*06:02* status as a binary trait. To test for interaction with respect to adalimumab and ustekinumab response, the full gene-environment interaction (GxE) model was supplemented with a main effect term for rs27524 genotype, the first-order interaction terms rs27524 genotype × *HLA-C*06:02* dosage and rs27524 genotype × drug, and the second-order interaction term rs27524 genotype × *HLA-C*06:02* dosage × drug. Power analysis for the *ERAP1* interaction test conducted in the *HLA-C*06:02*–negative subgroup was conducted by using the method of Demidenko (https://www.dartmouth.edu/~eugened/power-samplesize.php).[35] Assumptions of the method required rs27524 genotype to be collapsed to a binary variable (for the purposes of power estimation only); therefore estimates are approximate.

RESULTS

A prospective observational data resource facilitating predictive genetic biomarker identification in psoriasis

To assess the ability of *HLA-C*06:02* to predict different rates of response to adalimumab and ustekinumab, we considered 3320 patients enrolled in the BSTOP study and BADBIR for whom genotype data were available (see the main Methods section). Of these patients, 53.4% were *HLA-C*06:02* positive (carrying ≥1 copy of the allele), with 46.6% being *HLA-C*06:02* negative. After applying eligibility criteria to ensure that valid baseline and response PASI scores were available, 1326 participants were included in the final analyses (Fig 1).

Participants' baseline characteristics are summarized in Table I. Because our investigation concerns the relationship between *HLA-C*06:02* and drug used for treatment (adalimumab or ustekinumab), we sought to identify clinical variables correlated with either of these. We found a strong association between age of

TABLE I. Summary statistics for baseline characteristics and potential confounding clinical variables

	All patients	By drug			By HLA-C*06:02 status		
		Adalimumab	Ustekinumab	*P* value	Negative	Positive	*P* value
No.	1326	839	487		622	704	
Baseline PASI score, mean ± SD	16.7 ± 6.4	16.8 ± 6.5	16.6 ± 6.3	.551	17.1 ± 6.6	16.4 ± 6.3	.031
Age of disease onset (y), mean ± SD*	21.8 ± 12.6	21.4 ± 12.2	22.4 ± 13.2	.173	25.6 ± 12.8	18.5 ± 11.4	9.38×10^{-22}
Disease duration at treatment start (y), mean ± SD*	23.3 ± 12.6	22.8 ± 12.1	24.0 ± 13.4	.121	20.7 ± 11.5	25.5 ± 13.1	3.61×10^{-9}
PsA (%)†	28.2	30.5	24.2	.017	32.3	24.6	8.44×10^{-3}‡
Biologic naive (%)	69.8	81.5	49.5	2.12×10^{-32}	69.3	70.2	.411
Methotrexate cotherapy at treatment start (%)	11.3	12.4	9.4	.103	13.7	9.2	.027§

Negative *HLA-C*06:02* status is defined as having no copies of the allele; positive *HLA-C*06:02* status is defined as having 1 or 2 copies of the allele. The indicated *P* values are derived from regression modeling (linear/logistic regression for continuous/binary characteristics, respectively); in particular, *HLA-C*06:02 P* values are based on imputed *HLA-C*06:02* dosage after controlling for 5 ancestry principal components.
*Based on 1177 (89%) patients with age of disease onset recorded.
†Based on 1275 (96%) patients with PsA status recorded.
‡$P = 3.98 \times 10^{-3}$ when controlling for age of onset.
§$P = .097$ when controlling for the presence of PsA.

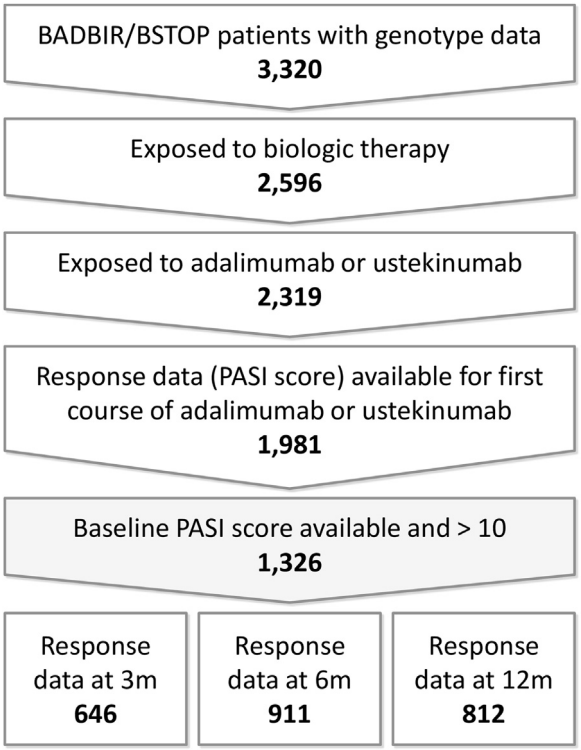

FIG 1. Flow diagram of study eligibility.

psoriasis onset and imputed *HLA-C*06:02* dosage (ie, a probability-weighted estimate of the number of copies of *HLA-C*06:02* that a patient carries; $P = 9.38 \times 10^{-22}$), as expected.[17] *HLA-C*06:02* was also associated with baseline PASI score and with duration of disease at treatment initiation ($P = .031$ and $P = 3.61 \times 10^{-9}$, respectively). The relationship between *HLA-C*06:02* and the presence of PsA is complex,[36] but we observed a statistically significant correlation ($P = 8.44 \times 10^{-3}$) that persisted even after controlling for age of psoriasis onset ($P_{adjusted} = 3.98 \times 10^{-3}$). PsA was also significantly associated with drug type ($P = .017$), likely reflecting a tendency toward prescription of anti-TNF therapy for patients with PsA because of its beneficial effect on joint disease.[37] We observed an unexpected association between *HLA-C*06:02* and methotrexate cotherapy at the start of biologic treatment ($P = .027$). Cotherapy is common in patients with PsA, and indeed, the association disappears when controlling for PsA status ($P_{adjusted} = .097$). Finally, previous exposure to biologics (biologic naive vs biologic exposed) strongly correlated with drug type ($P = 2.12 \times 10^{-32}$), reflecting the frequent use of adalimumab as a first-line biologic in this patient population[37]; it was not associated with *HLA-C*06:02* genotype ($P = .411$).

The observed rate of PASI90 response to adalimumab (41.9% at 3 months and 49.5% at 6 months) was consistent with that reported in clinical trials (45% at 16 weeks),[9] whereas the observed ustekinumab rate (28.2% at 3 months) was lower than the corresponding trial rate (39% at 12 weeks) (Table II).[10] Observed response rates by *HLA-C*06:02* status and for PASI75 and PASI100 outcomes are presented in Table E1 in this article's Online Repository at www.jacionline.org.

*HLA-C*06:02* is an effective biomarker that could inform treatment selection

We investigated the extent to which *HLA-C*06:02* genotype is predictive of different rates of PASI90 response for adalimumab compared with ustekinumab. Formally, for each time point (3, 6, and 12 months after treatment initiation), we fitted a logistic regression model for PASI90 response that included an interaction term between imputed *HLA-C*06:02* dosage and drug type (adalimumab and ustekinumab, see the main Methods section). These are effectively GxE models in which a statistically significant nonzero interaction term indicates that *HLA-C*06:02* can stratify the response.

A significant interaction term was observed in basic models that considered only *HLA-C*06:02* dosage and drug (see Table E2 in this article's Online Repository at www.jacionline.org). However, we took 2 further steps to ensure that these findings were not primarily driven by the effect of confounding clinical variables reported in Table I. First, we developed multivariable regression models to test for drug × *HLA-C*06:02* interaction that included appropriate main effect and interaction covariate terms (see the Methods section). We observed statistically significant nonzero effects at all time points for the drug × *HLA-C*06:02* interaction term (Table II). The strongest evidence for

TABLE II. *HLA-C*06:02* is a predictive biomarker of PASI90 response to adalimumab or ustekinumab after accounting for potential confounding variables

	PASI90 response		
	3 mo	6 mo	12 mo
Adalimumab (no.)	401	586	514
Adalimumab responders, no. (%)	168 (41.9)	290 (49.5)	257 (50.0)
Ustekinumab (no.)	245	325	298
Ustekinumab responders, no. (%)	69 (28.2)	130 (40.0)	139 (46.6)
Total	646	911	812
Drug × BL PASI interaction			
Effect size (β)	−0.045	0.038	−0.010
95% CI	−0.109 to 0.018	−0.008 to 0.084	−0.062 to 0.043
P value	.162	.108	.724
Drug × age of onset interaction			
Effect size (β)	0.009	−0.003	−0.001
95% CI	−0.026 to 0.044	−0.031 to 0.026	−0.030 to 0.028
P value	.605	.861	.932
Drug × disease duration interaction			
Effect size (β)	0.024	−0.014	0.001
95% CI	−0.009 to 0.058	−0.043 to 0.014	−0.028 to 0.031
P value	.156	.329	.928
Drug × PsA interaction			
Effect size (β)	−0.102	0.491	0.934
95% CI	−1.000 to 0.795	−0.209 to 1.191	0.215 to 1.654
P value	.823	.169	.011
***HLA-C*06:02* × PsA interaction**			
Effect size (β)	−0.926	−0.175	0.327
95% CI	−1.649 to −0.203	−0.725 to 0.374	−0.261 to 0.916
P value	.012	.531	.276
***HLA-C*06:02* × biologic naive interaction**			
Effect size (β)	−0.326	0.101	0.152
95% CI	−1.079 to 0.427	−0.495 to 0.696	−0.464 to 0.768
P value	.396	.741	.629
Drug × *HLA-C*06:02* interaction			
Effect size (β)	−0.901	−1.198	−0.921
95% CI	−1.641 to −0.161	−1.768 to −0.628	−1.503 to −0.340
P value	.017	3.76×10^{-5}	1.90×10^{-3}

Results are presented for model interaction terms only. Results for other model terms are not shown; in particular, main effect terms are not unambiguously interpretable in the presence of an interaction term. See Table III for further elucidation of the effects of *HLA-C*06:02* and PsA status.

interaction was observed at the 6-month time point, at which sample numbers were largest ($P = 3.76 \times 10^{-5}$). A significant interaction effect was also observed for the secondary outcome of PASI75 and for all but the earliest time point (3 months) for PASI100 (see Table E3 in this article's Online Repository at www.jacionline.org).

Second, we used a propensity score–weighted approach to adjust for potential confounding through covariates influencing treatment selection (for full details, see the Methods section in this article's Online Repository). We observed that all covariates were well balanced between the adalimumab and ustekinumab groups after weighting (see Fig E1 and Table E4 in this article's Online Repository at www.jacionline.org). The drug × *HLA-C*06:02* interaction terms remained significant at all time points in the weighted models at very similar levels of significance to the full unweighted multivariable models (see Table E5 in this article's Online Repository at www.jacionline.org). As such, we are confident that our full unweighted model adequately controls for confounding, and all subsequent analyses were based on unweighted models.

To elucidate the observed drug × *HLA-C*06:02* interaction effect, we examined the effect that drug type exerts on probability of response within 2 subgroups of patients: *HLA-C*06:02*–negative (zero copies of the allele) and *HLA-C*06:02*–positive (1 or 2 copies; pooled because of the small number of patients who carry 2 copies) patients. At all time points, drug type was associated with PASI90 response among *HLA-C*06:02*–negative patients (better response to adalimumab; odds ratio $[OR]_{6m} = 2.95$, $P_{6m} = 5.85 \times 10^{-7}$) but not among *HLA-C*06:02*–positive patients (Fig 2, *A*, and Table III). This trend was also observed for the secondary PASI75 and PASI100 outcomes (see Fig E2 and Table E6 in this article's Online Repository at www.jacionline.org).

We performed separate multivariate regression analyses within the adalimumab and ustekinumab groups, including covariate main effects only. These confirmed that although there is some effect size heterogeneity across time points, *HLA-C*06:02* is associated with response to both drugs individually. It is associated with better response to ustekinumab (PASI90 $OR_{6m} = 1.72$, $P_{6m} = .018$), which is consistent with previous reports,[19-21] and poorer response to adalimumab (PASI90 $OR_{6m} = 0.54$, $P_{6m} = 1.67 \times 10^{-4}$), which has not previously been established (see Fig E3 and Table E7 in this article's Online Repository at www.jacionline.org). The opposite effect directions give rise to the observed drug × *HLA-C*06:02* interaction.

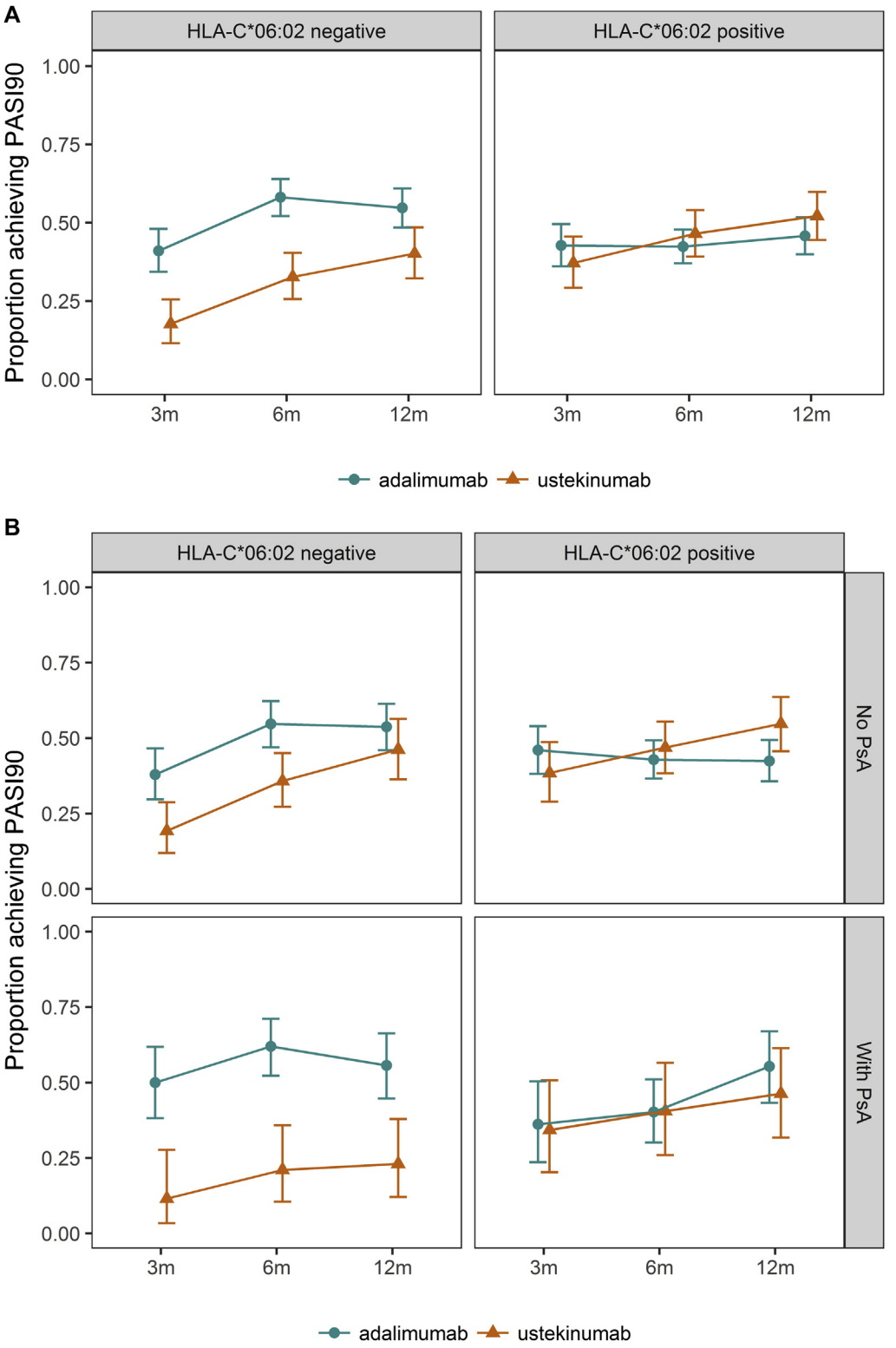

FIG 2. Differential effect of adalimumab and ustekinumab depends on *HLA-C*06:02* status and can be further discriminated by the presence of concomitant PsA. The proportion of patients achieving PASI90 response is shown as follows: **A,** *HLA-C*06:02* status (negative, no copies of the allele; positive, 1 or 2 copies of the allele); **B,** *HLA-C*06:02* and PsA status. Displayed 95% CIs are derived from the Bayesian credible interval by using the Jeffreys prior.

TABLE III. Association of drug type with PASI90 response by *HLA-C*06:02* status and presence of concomitant PsA

	All			Subgroup without PsA			Subgroup with PsA		
	3 mo	6 mo	12 mo	3 mo	6 mo	12 mo	3 mo	6 mo	12 mo
***HLA-C*06:02* negative**									
Adalimumab (no.)	195	265	243	124	159	160	66	100	79
Adalimumab responders, no. (%)	80 (41.0)	154 (58.1)	133 (54.7)	47 (37.9)	87 (54.7)	86 (53.8)	33 (50.0)	62 (62.0)	44 (55.7)
Ustekinumab (no.)	113	153	137	83	109	93	26	38	39
Ustekinumab responders, no. (%)	20 (17.7)	50 (32.7)	55 (40.1)	16 (19.3)	39 (35.8)	43 (46.2)	3 (11.5)	8 (21.1)	9 (23.1)
Total (no.)	308	418	380	207	268	253	92	138	118
Drug: adalimumab vs ustekinumab									
OR	3.271	2.950	1.860	2.586	2.316	1.430	7.423	5.977	4.076
95% CI	1.846-5.795	1.930-4.510	1.207-2.867	1.330-5.027	1.383-3.878	0.845-2.420	1.984-27.769	2.478-14.417	1.707-9.733
P value	4.91×10^{-5}	5.85×10^{-7}	4.94×10^{-3}	5.10×10^{-3}	1.41×10^{-3}	.182	2.90×10^{-3}	6.89×10^{-5}	1.55×10^{-3}
***HLA-C*06:02* positive**									
Adalimumab (no.)	206	321	271	150	231	198	47	82	65
Adalimumab responders, no. (%)	88 (42.7)	136 (42.4)	124 (45.8)	69 (46.0)	99 (42.9)	84 (42.4)	17 (36.2)	33 (40.2)	36 (55.4)
Ustekinumab (no.)	132	172	161	91	128	115	35	37	41
Ustekinumab responders, no. (%)	49 (37.1)	80 (46.5)	84 (52.2)	35 (38.5)	60 (46.9)	63 (54.8)	12 (34.3)	15 (40.5)	19 (46.3)
Total (no.)	338	493	432	241	359	313	82	119	106
Drug: adalimumab vs ustekinumab									
OR	1.266	0.841	0.738	1.366	0.846	0.565	1.057	0.978	1.461
95% CI	0.806-1.987	0.579-1.221	0.495-1.102	0.801-2.329	0.548-1.307	0.351-0.907	0.417-2.680	0.442-2.166	0.657-3.251
P value	.306	.362	.137	.252	.451	.018	.907	.957	.353

Note that PsA subgroup numbers sum to less than total numbers because of a minority of patients without PsA status recorded.

Nominally significant interactions are observed between PsA and drug type at 12 months and between PsA and *HLA-C*06:02* genotype at 3 months (Table II). We tested the effect of drug type on PASI90 response within patient subgroups characterized by both *HLA-C*06:02* status (positive/negative) and PsA status (presence/absence; Fig 2, *B*, and Table III). In *HLA-C*06:02*–negative patients the effect of drug type on the likelihood of PASI90 response was stronger at all time points among patients with PsA ($OR_{6m} = 5.98$, $P_{6m} = 6.89 \times 10^{-5}$) than among patients without PsA ($OR_{6m} = 2.32$, $P_{6m} = 1.41 \times 10^{-3}$; not significant at 12 months). Conversely, among *HLA-C*06:02*–positive patients, the only significant difference in PASI90 response by drug comprised a weak association in the *HLA-C*06:02*–positive and PsA-negative group at 12 months, when adalimumab demonstrated poorer rates of response than ustekinumab (OR = 0.56, $P = .018$). The same trends held true in general for PASI75 and PASI100 outcomes (see Table E8 in this article's Online Repository at www.jacionline.org).

We note that biologic-naive status has a stronger direct effect than drug type on the likelihood of achieving PASI90 response (see Table E9 in this article's Online Repository at www.jacionline.org). However, Table II shows clearly that in the full model *HLA-C*06:02* has a significant GxE interaction with drug and not with biologic-naive status. Therefore the different relative response rates to adalimumab and ustekinumab among *HLA-C*06:02*–positive and *HLA-C*06:02*–negative patients are likely to be drug specific and not explained by these 2 groups having different propensities to respond to biologic therapy when accounting for previous biologic exposure. Fitting the multivariable GxE models in biologic-naive patients only (925/1326 patients) confirmed a drug × *HLA-C*06:02* interaction effect of similar magnitude to the main analysis (see Fig E4, *A*, and Tables E10 and E11 in this article's Online Repository at www.jacionline.org). Interestingly, the aforementioned poorer response to adalimumab than ustekinumab at 12 months in *HLA-C*06:02*–positive and PsA-negative patients is much more striking in this biologic-naive group ($OR_{12m} = 0.31$, $P_{12m} = 3.42 \times 10^{-4}$; see Fig E4, *B*, and Table E11). When considering biologic-experienced patients only, the drug × *HLA-C*06:02* interaction effect does not achieve statistical significance at any time point, potentially because of much smaller sample sizes (see Tables E10 and E11). Nevertheless, the same general trend is observed: the subgroup with the biggest difference in response rates are *HLA-C*06:02*–negative and PsA-positive patients (better response to adalimumab), whereas *HLA-C*06:02*–positive and PsA-negative patients see marginally better response to ustekinumab (see Fig E5 in this article's Online Repository at www.jacionline.org).

Finally, our data show a trend suggesting that ustekinumab might be more effective than adalimumab at inducing a PASI90 response among the subgroup of *HLA-C*06:02*–positive patients homozygous for the allele, regardless of PsA status (see Fig E6 in this article's Online Repository at www.jacionline.org). This suggests an additive genetic effect of *HLA-C*06:02* on differential treatment response. Larger sample sizes are required to fully investigate the significance of this observation and its implications for clinical practice.

Among all HLA alleles, *HLA-C*06:02* displays the strongest evidence for being a predictive biomarker

Although *HLA-C*06:02* has been established as the allele most highly associated with psoriasis susceptibility, it is possible that

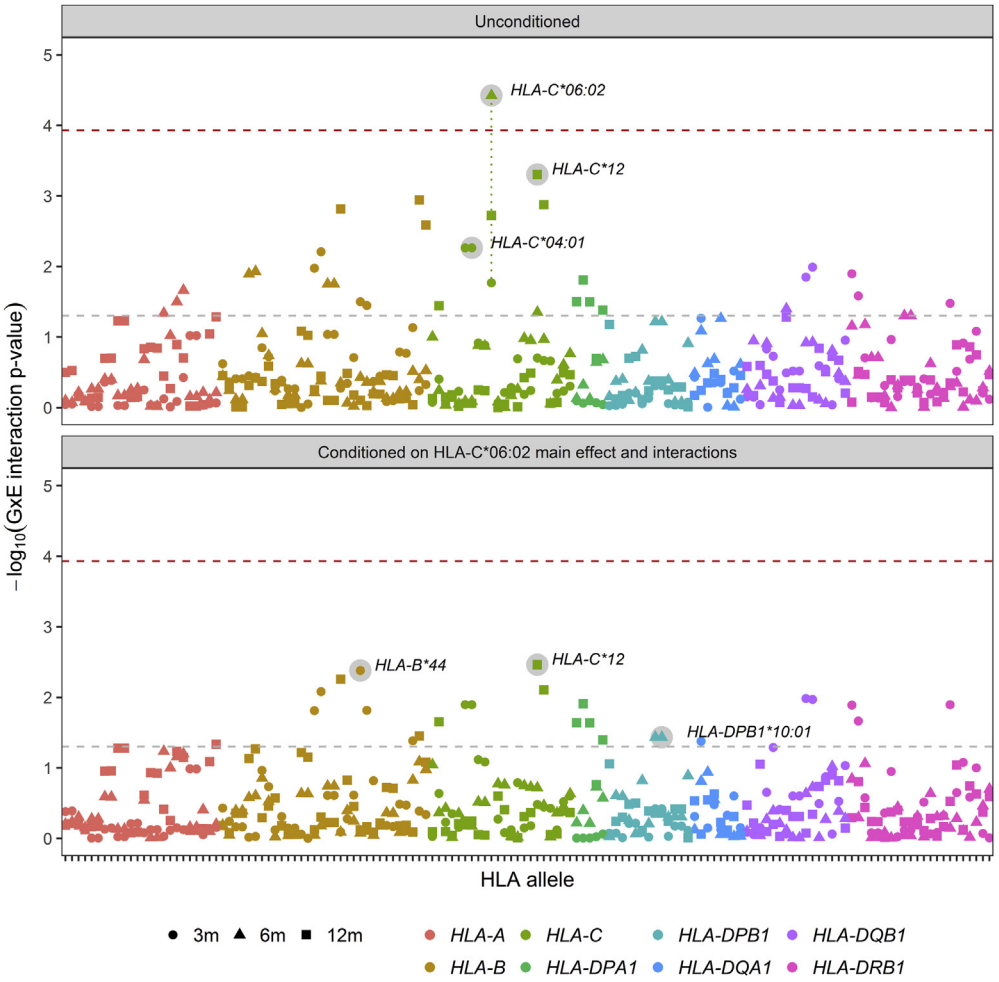

FIG 3. GxE interaction *P* values for PASI90 response across common 2- and 4-digit HLA alleles. *Top panel*, GxE interaction *P* value by HLA allele; *bottom panel*, GxE interaction *P* value by HLA allele after conditioning on *HLA-C*06:02* main effect and interaction terms; *y-axis*, $-\log_{10}$(*P* value); *dark red dashed line*, Bonferroni-corrected significance threshold of 1.17×10^{-4}; *gray dashed line*, nominal significance threshold of 0.05. Time points are represented by different shaped points. Note that the *x-axis* represents the HLA allele as a categorical variable ordered lexicographically and does not represent the scaled chromosome position. In each panel the most significantly associated allele at each time point is labeled and highlighted by a *gray circle*. For ease of identification, *HLA-C*06:02 P* values for the 3 time points are joined by a *dotted green line*; there are no *HLA-C*06:02 P* values for the conditional tests.

distinct *HLA-C* alleles or alleles of other class I or class II MHC genes might elicit an enhanced antidrug immune response to one of the drugs and consequently better predict differential treatment response. Therefore we repeated our analysis for all 142 2- and 4-digit HLA alleles that were imputed with high confidence (Methods section) by using the same full GxE model as for *HLA-C*06:02* (see Table E12 in this article's Online Repository at www.jacionline.org). We confirmed that *HLA-C*06:02* displays the strongest evidence for a drug × HLA allele interaction for 6-month PASI90 response, demonstrating statistical significance at a Bonferroni-corrected *P* value threshold of 1.17×10^{-4} (based on 426 tests: 142 alleles × 3 time points; Fig 3). Results at other time points were not inconsistent with this, with no HLA alleles achieved significance at the Bonferroni-corrected threshold (see Table E12). A similar pattern was also observed for the secondary PASI75 and PASI100 outcomes (see Fig E7 and Table E12 in this article's Online Repository at www.jacionline.org). These findings suggest that *HLA-C*06:02* is likely to be the primary effect allele contributing to biologic response, but because of the extensive linkage disequilibrium across this region, larger samples will be necessary to fully investigate the role of other HLA alleles.

To identify potential independent secondary predictive biomarkers in the HLA region, we also report the most associated 2- and 4-digit HLA alleles after conditioning on *HLA-C*06:02* (main and interaction terms, see Table E13 in this article's Online Repository at www.jacionline.org). No alleles achieved *P* values of less than the Bonferroni-corrected significance threshold of 1.17×10^{-4}. The smallest *P* values were observed for other *HLA-C* alleles and for *HLA-B* alleles; we found little evidence to support independent secondary predictive biomarkers at MHC class II genes. Note that full results for all HLA alleles are provided in Table E14 in this article's Online Repository at www.jacionline.org.

No evidence observed for an interaction with *ERAP1* genotype

Variants such as rs27524 in *ERAP1* exhibit an epistatic effect on psoriasis susceptibility through interaction with *HLA-C*06:02*, with each copy of the risk allele amplifying the increase in disease risk that positive *HLA-C*06:02* status confers.[15] Case-only analysis in our full cohort of 3320 patients supports this interaction: rs27524 is strongly associated with *HLA-C*06:02* status (OR = 1.35, $P = 5.91 \times 10^{-9}$).

We sought to establish whether a similar effect is observed for differential response to adalimumab versus ustekinumab. We found no evidence for epistasis based on 2 complementary approaches: a full model including the second-order interaction term rs27524 genotype × *HLA-C*06:02* dosage × drug (effectively a gene-gene-environment model, see Table E15 in this article's Online Repository at www.jacionline.org) and a simple GxE model within the subgroup of 622 *HLA-C*06:02*–negative patients (in which differential response by drug was previously observed) that included the interaction term rs27524 genotype × drug (see Table E16 in this article's Online Repository at www.jacionline.org). When removing the (nonsignificant) second-order interaction term from the gene-gene-environment model, significant *P* values are observed for *HLA-C*06:02* dosage × drug, as expected, but for neither interaction term involving the *ERAP1* variant (see Table E17 in this article's Online Repository at www.jacionline.org).

We estimate that our sample sizes provide 80% power to detect interactions between *ERAP1* and drug in the *HLA-C*06:02*–negative subgroup when interaction effect sizes (β regression parameters) are larger than 1.62, 1.28, and 1.37 at 3, 6, and 12 months, respectively. Because such effects were not observed, we find no evidence to suggest that an interaction between *ERAP1* and *HLA-C*06:02* could provide a more effective predictive biomarker than *HLA-C*06:02* alone. A similar conclusion holds when considering the secondary outcomes PASI75 and PASI100 (see Tables E15-E17).

DISCUSSION

This study constitutes the largest investigation to date into the pharmacogenetics of biologic response in patients with psoriasis and is the first to use jointly generated clinical and genetic data on different drugs to identify a predictive biomarker with potential clinical utility. We report that the *HLA-C*06:02* allele effectively stratifies patients with psoriasis into groups with different profiles of response to the 2 most frequently prescribed biologics: adalimumab and ustekinumab.

Although the scale of our clinical data resource makes it highly representative of the UK psoriasis population,[38,39] limitations include the heterogeneous nature of the response data, which lack a structured series of PASI observations at fixed time points. This limits more formal longitudinal analyses. Similarly, baseline PASI scores are defined pragmatically. They can precede treatment by up to 6 months and might have been recorded during alternative treatment, although we took steps to minimize any resulting bias (see the Methods). Adverse drug reactions, which were not investigated here, represent another important consideration when selecting treatment. Independent replication will be important, although our findings concord with those of previous studies that consider adalimumab and ustekinumab separately.[19-22]

Our results demonstrate that *HLA-C*06:02*–negative patients with psoriasis are significantly more likely to respond to adalimumab than to ustekinumab but that there is no significant benefit to adalimumab over ustekinumab in *HLA-C*06:02*–positive patients.

We also find that the effect of *HLA-C*06:02* is modulated by the presence or absence of comorbid PsA, with adalimumab conferring the greatest benefit over ustekinumab in patients who are *HLA-C*06:02* negative and PsA positive (31.9% of all patients with PsA status available). Interestingly, these findings demonstrate the effectiveness of adalimumab at treating psoriatic skin disease only. Therefore further investigation of the ability of HLA genes to predict combined skin and joint response for PsA-positive patients with psoriasis is warranted, ideally through longitudinal studies that collect separate validated objective measurements for both skin and joint involvement.

Through HLA imputation, we estimated that 46.6% of patients with severe psoriasis are *HLA-C*06:02* negative. Although treatment selection should always be considered on a case-by-case basis,[11] our results suggest that a default strategy of ascertaining *HLA-C*06:02* status and administering adalimumab as a first-line biologic to *HLA-C*06:02*–negative patients might be an effective approach. Of the 53.4% of patients who are *HLA-C*06:02* positive, Table I suggests that more than three quarters will not have active PsA. This group can benefit from ustekinumab as a default first-line treatment over the longer term (see Fig E4), particularly in light of its longer dosing intervals and better persistence relative to adalimumab.[40] Our findings are not conclusive for patients who are *HLA-C*06:02* and PsA positive. Because adalimumab is already the recommended first-line biologic in the United Kingdom when PsA is present,[11] our recommendations primarily affect the 71.8% of patients without active PsA (Table I). Therefore *HLA-C*06:02*–informed treatment selection could offer improved likelihood of PASI90 response through the first 12 months of treatment for 35.9% of all patients with severe psoriasis compared with random assignment to adalimumab or ustekinumab. We acknowledge that random assignment does not reflect current clinical practice in this patient population.[37] However, current UK guidelines do not favor either adalimumab or ustekinumab in the absence of PsA,[11] and prescribing practices evolve over time and vary by region. We also note that our recommendations will have health economic implications as adalimumab biosimilars emerge.

The results presented here support the notion that *HLA-C*06:02*–positive and *HLA-C*06:02*–negative plaque psoriasis represent biologically distinct pathologies or endotypes. Differences in presentation have long been recognized.[16] However, we suggest that with the implications for clinical decision making raised by our findings, *HLA-C*06:02* status represents a more relevant stratification of patients with psoriasis than the primarily age-of-onset–delimited type I/type II distinction.[41]

It is widely accepted that *HLA-C*06:02* is the genetic allele that makes by far the largest individual contribution to the risk of psoriasis.[42-44] Intriguingly, our HLA-wide analysis suggests that this allele is also mechanistically relevant to biologic response among patients (Fig 3 and see Table E12). As such, it is unlikely that *HLA-C*06:02* should generalize as a predictive biomarker for biologic response in other immune-mediated inflammatory diseases. Conversely, these findings might shed important light on the complex pathogenic mechanisms underlying psoriasis. The difference in response to the 2 drugs among

*HLA-C*06:02*–negative patients suggests that aberrant signaling of immune pathways downstream of TNF-α, adalimumab's target molecule, might play a more prominent role in the development and maintenance of psoriatic lesions for these patients than for *HLA-C*06:02*–positive patients.

Further investigation of the genetic, transcriptomic, and immunologic differences between *HLA-C*06:02*–positive and *HLA-C*06:02*–negative patients could offer vital insights into the pathophysiology of psoriasis and mechanisms of treatment response. Much larger sample sizes will be required to provide sufficient statistical power to accurately quantify the effect of *HLA-C*06:02* and refine the contributions of other HLA alleles. More generally, genome-wide analyses have the potential to uncover genetic contributions to treatment response beyond the HLA region. The genotype data used in this study will contribute to such efforts, and results are eagerly anticipated. With respect to clinical application, the potential effect of our findings on patient outcomes is substantial, but it will be important to validate our findings more formally in an appropriately structured prospective clinical trial setting. The design of such a trial should also formally account for PsA status and the clinical factors most likely to confound observational studies, such as previous biologic exposure.

In summary, we show that *HLA-C*06:02* status is a predictive biomarker that influences response to adalimumab and ustekinumab. Ascertainment of *HLA-C*06:02* genotype is straightforward, and our results could have substantial clinical relevance when selecting between 2 of the most commonly used biologic treatments for psoriasis.

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Clinical implications: *HLA-C*06:02* is associated with differential response to adalimumab and ustekinumab in patients with psoriasis. Together with PsA status, *HLA-C*06:02* status could inform optimal selection of first-line biologic therapy.

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