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# Development and Validation of Clinical Scoring Tool to Predict Outcomes of Treatment With Vedolizumab in Patients With Ulcerative Colitis



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**BACKGROUND & AIMS:** We created and validated a clinical decision support tool (CDST) to predict outcomes of vedolizumab therapy for ulcerative colitis (UC).

**METHODS:** We performed logistic regression analyses of data from the GEMINI 1 trial, from 620 patients with UC who received vedolizumab induction and maintenance therapy (derivation cohort), to identify factors associated with corticosteroid-free remission (full Mayo score of 2 or less, no subscore above 1). We used these factors to develop a model to predict outcomes of treatment, which we called the vedolizumab CDST. We evaluated the correlation between exposure and efficacy. We validated the CDST in using data from 199 patients treated with vedolizumab in routine practice in the United States from May 2014 through December 2017.

**RESULTS:** Absence of exposure to a tumor necrosis factor (TNF) antagonist (+3 points), disease duration of 2 y or more (+3 points), baseline endoscopic activity (moderate vs severe) (+2 points), and baseline albumin concentration (+0.65 points per 1 g/L) were independently associated with corticosteroid-free remission during vedolizumab therapy. Patients in the derivation and validation cohorts were assigned to groups of low (CDST score, 26 points or less), intermediate (CDST score, 27–32 points), or high (CDST score, 33 points or more) probability of vedolizumab response. We observed a statistically significant linear relationship between probability group and efficacy (area under the receiver operating characteristic curve, 0.65), as well as drug exposure ( $P < .001$ ) in the derivation cohort. In the validation cohort, a cutoff value of 26 points identified patients who did not respond to vedolizumab with high sensitivity (93%); only the

low and intermediate probability groups benefited from reducing intervals of vedolizumab administration due to lack of response ( $P = .02$ ). The vedolizumab CDST did not identify patients with corticosteroid-free remission during TNF antagonist therapy.

## CONCLUSIONS:

We used data from a trial of patients with UC to develop a scoring system, called the CDST, which identified patients most likely to enter corticosteroid-free remission during vedolizumab therapy, but not anti-TNF therapy. We validated the vedolizumab CDST in a separate cohort of patients in clinical practice. The CDST identified patients most likely to benefit from reducing intervals of vedolizumab administration due to lack of initial response. [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00783718) no: NCT00783718

*Keywords:* Prognostic Factor; Response to Treatment; Personalized Medicine; Biologic.

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In phase 3 randomized controlled trials, vedolizumab (VDZ) has been proven efficacious for achieving clinical remission, corticosteroid-free remission (CSFREM), and mucosal healing in ulcerative colitis (UC).<sup>1</sup> In clinical practice, pooled rates for clinical response and remission by week 22 were 51% (95% confidence interval [CI], 43%–61%) and 30% (95% CI, 24%–36%), respectively.<sup>2</sup> Studies have identified predictors of treatment outcomes for VDZ<sup>3</sup>; however, the optimal approach to integrating predictors into routine clinical practice is uncertain.

Waljee et al<sup>4</sup> recently developed a machine learning algorithm for predicting CSFREM with VDZ in UC. This tool was limited by lack of external validation, need for 6 weeks of therapy before determining risk for treatment failure, and difficulty of bedside implementation. There is a need for well-validated, drug-specific, easy-to-use prediction models and clinical decision support tools (CDSTs) to help guide clinicians in the use of VDZ therapy for UC.

We addressed this gap by deriving a prediction model and CDST using the GEMINI 1 VDZ clinical trial dataset for the outcome of CSFREM. We explored correlations between measured VDZ exposure, rapidity in onset of action, and overall efficacy across predicted probability groups in the GEMINI 1 trial, and the CDST was subsequently validated in an external routine practice cohort of UC patients treated with VDZ. To confirm the drug-specific nature of this model, we assessed the performance of the CDST for predicting treatment outcomes in patients with UC treated with tumor necrosis factor (TNF) antagonist therapy in a similar routine clinical practice setting. Our intent was to create a CDST that will help clinicians optimize the use of VDZ therapy specifically for individual patients.

## Materials and Methods

This study is reported according to the TRIPOD (Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis) statement and the STROBE (Strengthening the Reporting of Observational studies in Epidemiology) statement.<sup>5,6</sup> All authors had access to the study results and reviewed and approved the final manuscript.

## Data Sources and Participants

Data from the GEMINI 1 trial were used to derive the prediction model and VDZ-CDST.<sup>1</sup> Patients from GEMINI 1 trial ( $n = 620$ ) were included if they had received VDZ induction therapy and were assigned to receive VDZ during maintenance therapy, irrespective of week 6 response status. Placebo-treated patients were excluded. Data from the Vedolizumab for Health Outcomes in Inflammatory Bowel Diseases (VICTORY) Consortium cohort (VDZ:  $n = 199$ ; TNF antagonist:  $n = 123$ ) were used to externally validate the prediction model and VDZ-CDST ([Supplementary Material](#)).<sup>7</sup>

## Outcome Definitions

The primary objective was to develop and validate a VDZ-specific prediction model and CDST for achieving CSFREM. Secondary objectives were to assess whether the VDZ-CDST was able to predict differences in measured VDZ exposure and onset of action (reductions in partial Mayo score and fecal calprotectin) within the GEMINI 1 trial derivation cohort and differences in colectomy rates and response to VDZ interval shortening within the VICTORY validation cohort. These secondary objectives were designed to explore the exposure-efficacy relationship for VDZ in UC ([Supplementary Material](#)).

CSFREM in the GEMINI 1 trial was defined as a full Mayo score of  $\leq 2$ , with no subscore  $> 1$ , and being off corticosteroids at 52 weeks. CSFREM in the VICTORY cohort was defined as achieving complete resolution of UC-related symptoms (rectal bleeding, urgency, stool frequency), a Mayo endoscopic subscore of 0 or 1, and being off corticosteroids at 26 weeks. Colectomy status was also assessed at 26 weeks. We chose 26 weeks as the time point for validation based on prior clinical observations that patients may need up to 26 weeks to achieve clinical remission and mucosal healing with VDZ. This time point was also judged to be the maximal acceptable duration for clinicians and patients to attempt a therapeutic trial of VDZ.<sup>7,8</sup>

## Statistical Analysis

**VDZ Model and CDST Derivation: GEMINI 1 Trial Cohort.** A multivariable logistic regression prediction model was built from the GEMINI 1 trial cohort data with CSFREM as the dependent variable. Baseline variables with  $P$  value  $<.15$  on univariable analyses were included after assessment for collinearity, clinical importance, and interpretability. A backward model selection approach with a  $P$  value threshold of  $.15$  for inclusion was used. Interaction terms were assessed individually and included in the final model if they had a  $P$  value of  $<.10$  on both the univariable and multivariable analyses. A sensitivity analysis was performed replacing albumin with calculated individual-patient VDZ drug clearance profiles based on measured drug exposure to determine whether this modification better predicted CSFREM ([Supplementary Material](#)).<sup>9,10</sup>

The prediction model was transformed into a CDST, and prognostic scores were calculated by summing the points for all predictors present for each patient.<sup>11</sup> The GEMINI 1 trial cohort subjects were split into quartiles using the VDZ-CDST, and cutoff points were determined for patients with low (lowest quartile of CSFREM rates), intermediate (middle 2 quartiles of CSFREM rates), or high (highest quartile of CSFREM rates) probability of achieving CSFREM with VDZ therapy. We assessed changes in fecal calprotectin, partial Mayo score, and differences in measured VDZ concentrations across probability groups throughout the 52-week GEMINI 1 trial study (exposure-efficacy relationship) ([Supplementary Material](#)).<sup>9,10</sup>

To control for type I error when comparing probability groups, a closed test procedure was used. Each of the pairwise comparisons was conducted at the  $.05$  level, with no  $P$  value adjustments if the hypothesis “all probability groups equal” was first rejected at the  $.05$  level. If the omnibus comparison was not significant at the  $.05$  level, the subsequent comparisons were not made. Finally, the cutoff points were applied to the GEMINI 1 trial intention-to-treat (ITT) population to understand how the probability of achieving CSFREM with VDZ compared with study participants receiving placebo and to understand whether the prediction model was truly predicting outcomes with VDZ or only a patient’s inherent likelihood of responding to any therapy (ie, placebo) ([Supplementary Material](#)).

**VDZ Model and CDST Validation: VDZ-Treated VICTORY Cohort.** External validation of the model and CDST was conducted in the VICTORY cohort. Discriminative ability was assessed by receiver operating characteristic curve analysis. Calibration of the model was evaluated using a calibration curve, a joint hypothesis test using a likelihood ratio, and the Hosmer-Lemeshow goodness-of-fit test. The overall performance of the models was evaluated with the Nagelkerke  $R^2$  and the Brier score ([Supplementary Material](#)).<sup>12</sup>

The sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio of the VDZ-CDST scoring tool

## What You Need to Know

### Background

Studies have identified factors that might be used to predict responses of patients with ulcerative colitis to treatment with vedolizumab, but these have not been systematically analyzed.

### Findings

The authors developed and validated a tool, based on clinical and laboratory values, to identify patients most likely to enter corticosteroid-free remission during vedolizumab therapy. Scores associated with patient drug exposure, time until onset of action, and achievement of corticosteroid-free remission for vedolizumab but not tumor necrosis factor antagonist therapy.

### Implications for patient care

This study has generated and validated an easy to use clinical decision support tool specific to vedolizumab to help clinicians optimize the treatment of individual patients with ulcerative colitis.

to identify patients with a low or high probability of achieving CSFREM or requiring colectomy were calculated after grouping patients into 3 groups according to predicted risk. In UC patients who underwent VDZ interval shortening for insufficient response ( $n = 28$ ), we assessed whether response to VDZ interval shortening varied across VDZ-CDST predicted probability groups. The decision to undergo shortening was made by providers without prior knowledge of the VDZ-CDST scoring tool.

**VDZ-CDST Drug-Specific Assessment: TNF Antagonist-Treated VICTORY Cohort.** The VDZ-CDST cutoff points were applied to patients treated with TNF antagonists in the VICTORY cohort. The proportion of TNF antagonist-treated UC patients who achieved CSFREM or required colectomy by week 26 across the VDZ-CDST-defined probability groups was compared to the proportion of VDZ-treated UC patients who achieved CSFREM or required colectomy by week 26 within defined probability groups.

## Results

### Patient Characteristics

Of the 437 VDZ-treated UC patients within the VICTORY cohort, 85 were excluded for missing baseline albumin values, and 153 were excluded because they had no endoscopic follow-up after starting VDZ. There were no significant differences in the VICTORY cohort patients included or excluded from the current analyses ([Supplementary Table 1](#)). Compared with the VICTORY cohort, participants in the GEMINI 1 trial derivation cohort had shorter disease duration ( $P < .01$ ), were less often exposed to prior TNF



**Table 1.** Comparison of Demographics Between the GEMINI 1 and the VICTORY Cohorts

	GEMINI 1 Trial Cohort	VICTORY Cohort	
	Vedolizumab Derivation Cohort (n = 620)	Vedolizumab Validation Cohort (n = 199)	P value
Female	256 (41)	104 (52)	<.01
Smoker (never)	380 (61)	144 (72)	<.01
Age, y	40.1 ± 13	41.5 ± 17.3	.23
Body mass index, kg/m <sup>2</sup>	25.1 ± 5.6	25.3 ± 5.83	.66
Disease duration, y	5.0 (2.3–9.1)	6.0 (2–12)	<.01
Disease duration <2 y	120 (20)	31 (16)	.25
Prior hospitalization	211 (34)	55 (28)	.10
Prior TNF antagonist exposure	311 (50)	135 (68)	<.01
Prior TNF antagonist failure	266 (43)	117 (59)	<.01
Extensive baseline disease	308 (50)	112 (56)	.12
Baseline moderate endoscopic disease	278 (45)	126 (63)	<.01
Baseline albumin, g/L	37 ± 4.96	39.4 ± 5.41	<.01
Concomitant corticosteroids only	226 (36)	69 (35)	.67
Concomitant IMM only	114 (18)	36 (18)	1.00
Concomitant corticosteroids and IMM	99 (16)	49 (25)	<.01

Values are n (%), mean ± SD, or median (interquartile range).

IMM, immunomodulator; TNF, tumor necrosis factor; VICTORY, Vedolizumab for Health Outcomes in Inflammatory Bowel Diseases.

antagonist therapy ( $P < .01$ ), more often had severe disease on baseline endoscopy ( $P < .01$ ), and had lower baseline albumin concentrations ( $P < .01$ ) (Table 1).

### Variable Selection

Factors significantly ( $P < .05$ ) associated with increased probability of achieving CSFREM with VDZ were disease duration (odds ratio [OR], 1.04 per year), no previous TNF antagonist exposure (OR, 1.84), no previous TNF antagonist failure (OR, 1.88), baseline endoscopic activity (moderate vs severe: OR, 1.57), baseline stool frequency (nonsevere [partial Mayo score 0–2] vs severe [partial Mayo score 3]: OR, 1.70), and baseline albumin (OR, 1.08) (Supplementary Table 2). Disease duration was transformed into a binary categorization ( $\geq 2$  years vs  $< 2$  years), and previous TNF antagonist exposure was used instead of previous TNF antagonist failure for further model building. Baseline endoscopy was used as a metric for disease activity instead of stool frequency because it was considered more objective (Supplementary Material).

### Model Building

Variables identified for potential inclusion were (1) disease duration ( $\geq 2$  years vs  $< 2$  years), (2) previous TNF

antagonist exposure (no vs yes), (3) baseline endoscopy (moderate vs severe), (4) baseline albumin (absolute value), and (5) sex (female vs male). Sex was observed to have a significant relationship to VDZ clearance ( $P < .001$ )<sup>13</sup> and was deemed an indirect predictor of treatment outcomes through correlation with the known covariates of drug clearance: height and weight. Accordingly, sex was dropped from the model. Baseline characteristics for patients with short ( $< 2$  years) or longer ( $\geq 2$  years) disease duration are described in Supplementary Table 3. Patients with longer disease duration were more likely to have been exposed to TNF antagonists before initiation of VDZ therapy (53% vs 38%). Despite this observation, patients with longer disease duration were more likely to respond to VDZ. This finding is of interest because multiple studies have documented a relatively poor prognosis for the use of biologics in patients who have previously had TNF antagonist failure. Therefore, this variable was thought to be a true predictor and was retained in the model. The other 3 variables have been previously identified in the literature and were deemed clinically and biologically relevant.<sup>3</sup>

The final model equation is as follows (Table 2):

$$\begin{aligned}
 Y = & -3.7038 \\
 & + [0.2820 \text{ if no prior TNF antagonist exposure}] \\
 & + [0.2622 \text{ if disease duration } \geq 2 \text{ years}] \\
 & + [0.1847 \text{ if baseline endoscopy activity is moderate}] \\
 & + [0.0647 \times \text{baseline albumin concentration in g/L}]
 \end{aligned}$$

An example calculation is provided in the Supplementary Material.

### Model Performance and Validation

The discrimination ability in the derivation cohort was 0.65 and on external validation it was 0.64 (95% CI, 0.50–0.77). During external validation the model explained approximately 20.8% of variation (Nagelkerke  $R^2 = 0.10$ ; Brier score 0.18, maximum Brier score 0.22). There was poor calibration (likelihood ratio  $\chi^2 = 16.18$ ,  $df = 2$ ,  $P < .001$ ; Hosmer-Lemeshow goodness-of-fit  $\chi^2 = 17.99$ ,  $df = 4$ ,  $P < .01$ ) (Supplementary Figure 1). The calibration slope, however, showed no evidence of overfitting, and the effects of the predictors were therefore similar in the development and validation cohorts.

### Clinical Decision Support Tool

Performance of the CDST in the derivation cohort is described in Supplementary Tables 4–6. Among the ITT population of the GEMINI 1 trial, the difference in clinical remission rates between VDZ and placebo at week 6 was incrementally higher according to stratification into low probability ( $\leq 26$  points; VDZ 8.5% vs placebo 3.3%; difference 5.2%), intermediate probability ( $> 26$  to  $\leq 32$  points; VDZ 16% vs placebo 4.7%; difference 11.3%),

**Table 2.** Final Multivariable Model for Corticosteroid-Free Remission With VDZ After 52 Weeks of Therapy

Variable	Odds ratio	95% CI
Previous TNF antagonist exposure (no vs yes)	1.758	1.194–2.587
Disease duration (≥2 y vs <2 y)	1.689	1.018–2.803
Baseline endoscopy (moderate vs severe)	1.447	0.991–2.114
Baseline albumin	1.067	1.024–1.112

CI, confidence interval; TNF, tumor necrosis factor; VDZ, vedolizumab.

and high probability (>32 points) of response to VDZ (VDZ 25.4% vs placebo 8.8%; difference 16.6%). Using baseline week 0 values for CDST calculation in re-randomized week 6 responders, a similar incremental benefit in treatment effect size was seen for CSFREM at week 52 between the low probability (VDZ 28.2% vs placebo 10.5%; difference 17.7%), intermediate probability (VDZ 35.7% vs placebo 15.2%; difference 20.5%), and high probability (VDZ 55.4% vs placebo 17.1%; difference 38.3%) groups.

In the VICTORY cohort, a score of 26 had a high sensitivity (93%; 95% CI, 79%–98%) and a good negative likelihood ratio (0.50; 95% CI, 0.16–1.61) for identifying patients less likely to achieve CSFREM with VDZ (Figure 1, Table 3). Poor discriminative performance for the VDZ-CDST was observed in the TNF antagonist-treated patients from the VICTORY cohort (Figure 1, Supplementary Table 7). Rates of CSFREM were higher for VDZ-CDST-predicted high-probability VDZ-treated patients (32%) than for the VDZ-CDST-predicted high-probability TNF antagonist-treated patients (23%). Rates of CSFREM were lower for the VDZ-CDST-predicted low-probability

VDZ-treated patients (12%) than for the VDZ-CDST-predicted low-probability TNF antagonist-treated patients (21%).

### VDZ Drug Exposure-Efficacy Relationships

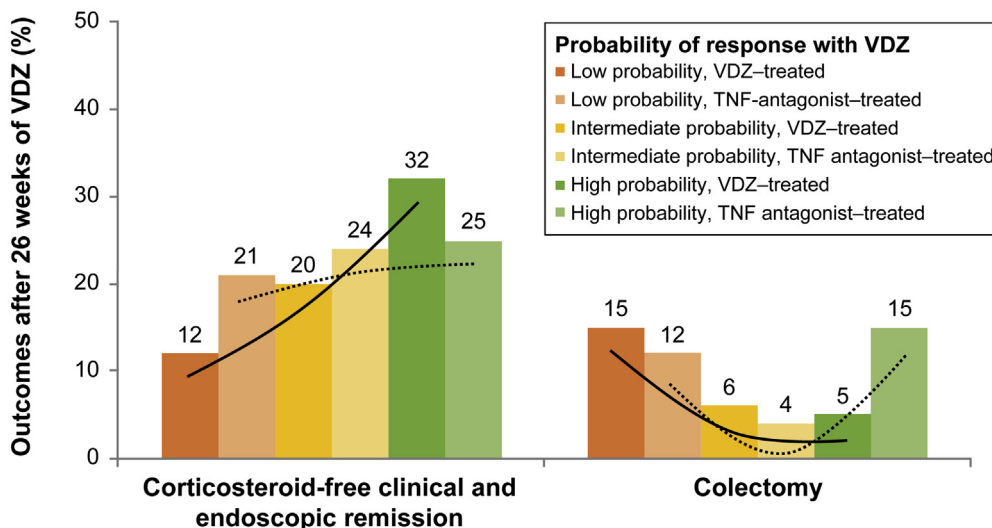
A statistically significant linear trend was observed for VDZ concentrations within the GEMINI 1 trial derivation cohort when stratified by the CDST (Figure 2, Supplementary Table 4). The percent reduction in fecal calprotectin at week 6 was 20% in the low-probability group compared with 49% and 56% in the intermediate- and high-probability groups. By week 30, patients in the low-probability group had achieved a 55% reduction in fecal calprotectin compared with baseline values. There were also statistically significant differences in change from baseline of partial Mayo score across 3 probability groups in the GEMINI 1 trial at all visits from week 2 to week 42, and week 52, based on closed test procedure (Figure 3, Supplementary Table 5).

In the VICTORY cohort, a clinical response (>50% reduction in symptom activity) to VDZ interval shortening was seen in 46% (n = 10 of 22) of patients classified as low or intermediate probability of response using the CDST. However, among patients undergoing VDZ interval shortening classified as high probability using the CDST (n = 6), none achieved a clinical response to VDZ interval shortening (P = .024).

### Discussion

We derived and validated a VDZ-specific multivariable prediction model and CDST capable of predicting differences in measured VDZ drug exposure, onset of

Disease duration ≥2 years	No prior TNF antagonist	Baseline endoscopy moderate activity	Baseline albumin concentration
+3 points	+3 points	+2 points	+0.65 points per unit (g/L)



**Figure 1.** Prognostic CDST with stratified treatment outcomes in the VICTORY cohort.

**Table 3.** Diagnostic Performance of Clinical Decision Support Tool in the VICTORY Cohort Among Vedolizumab-Treated Patients

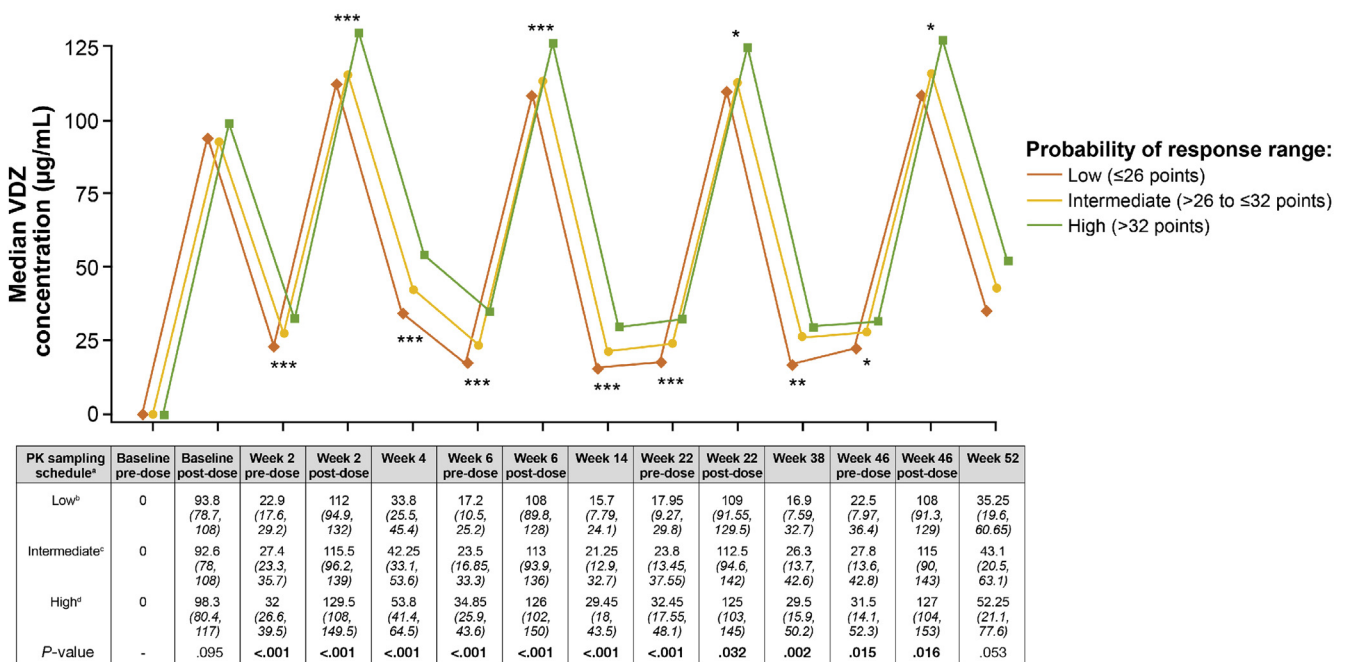
	Sensitivity (95% CI) (%)	Specificity (95% CI) (%)	Positive likelihood ratio (95% CI)	Negative likelihood ratio (95% CI)
26 points				
Corticosteroid-free remission <sup>a</sup> at 26 wk	93 (79–98)	15 (10–21)	1.08 (0.97–1.21)	0.50 (0.16–1.61)
Colectomy-free at 26 wk	88 (83–92)	29 (8–58)	1.23 (0.88–1.73)	0.42 (0.17–1.04)
32 points				
Corticosteroid-free remission <sup>a</sup> at 26 wk	51 (35–67)	68 (60–75)	1.59 (1.09–2.31)	0.72 (0.52–1.00)
Colectomy-free at 26 wk	37 (30–44)	71 (42–92)	1.29 (0.55–3.01)	0.89 (0.62–1.26)

CI, confidence interval; VICTORY, Vedolizumab for Health Outcomes in Inflammatory Bowel Diseases.  
<sup>a</sup>Remission defined as full Mayo score of ≤2 points with no subscore >1 point and being off steroids.

action, and VDZ treatment effectiveness, as well as identifying patients potentially most likely to benefit from VDZ interval shortening to optimize response. At a cutoff of 26 points the tool is sensitive for identifying patients who will not respond to VDZ. With increasing score there is increased confidence in expectation of achieving remission with VDZ in UC, with the greatest confidence achieved at a cutoff of 32 points. When applied to a TNF antagonist-treated observational cohort in a routine clinical practice setting, the VDZ-CDST was not able to predict differences in treatment effectiveness, confirming the drug-specific prediction of this VDZ-CDST.

Four predictors for CSFREM with VDZ were identified (1) previous TNF antagonist exposure, (2) baseline endoscopic activity, (3) baseline albumin, and (4) disease duration. Previous TNF antagonist exposure and severe disease have been shown to be consistent predictors of reduced effectiveness for VDZ in clinical practice across multiple cohorts.<sup>3</sup> Albumin is the main determinant of VDZ clearance, and a correlation between VDZ exposure and efficacy has been observed in post hoc analyses of the GEMINI 1 trial.<sup>9,10</sup> A novel observation was that longer disease duration was associated with improved effectiveness of VDZ. In the GEMINI 1 trial derivation

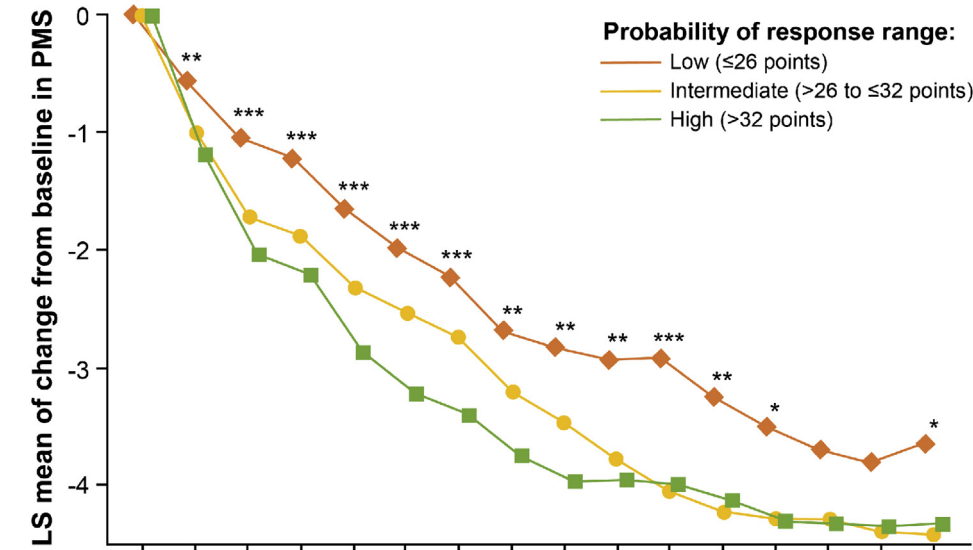
**VDZ concentrations stratified by probability of response**



**Figure 2.** Prognostic CDST with stratified VDZ concentrations in the GEMINI 1 trial. Three-group statistical comparisons at each time point done using nonparametric testing (Kruskal-Wallis). \**P* < .05, \*\**P* < .01, \*\*\**P* < .001. <sup>a</sup>All values in the table are median VDZ concentration (interquartile range) (µg/mL); postdose concentration was measured 2 hours after dosing. <sup>b</sup>Low probability; ≤26 points in the CDST model at baseline. <sup>c</sup>Intermediate probability; >26 to ≤32 points in the CDST model at baseline. <sup>d</sup>High probability; >32 points in the CDST model at baseline. PK, pharmacokinetics.

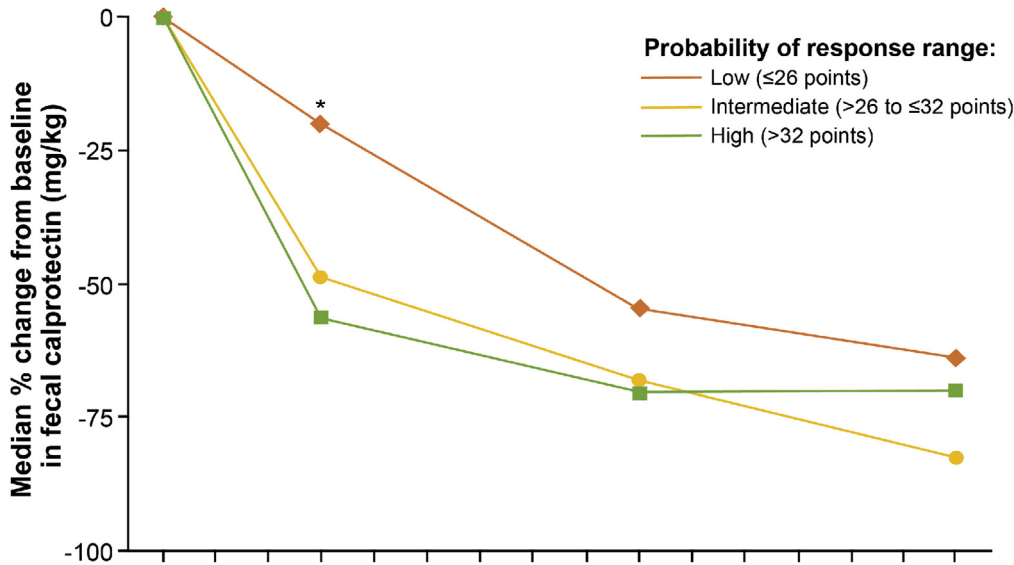


**A** Partial Mayo score stratified by probability of response



Time point <sup>a</sup>	Baseline	Wk 2	Wk 4	Wk 6	Wk 10	Wk 14	Wk 18	Wk 22	Wk 26	Wk 30	Wk 34	Wk 38	Wk 42	Wk 46	Wk 50	Wk 52
Low <sup>b</sup>	0	-0.55 (0.138)	-1.04 (0.175)	-1.22 (0.183)	-1.65 (0.205)	-1.97 (0.212)	-2.23 (0.222)	-2.68 (0.238)	-2.83 (0.249)	-2.94 (0.243)	-2.92 (0.246)	-3.24 (0.240)	-3.50 (0.245)	-3.68 (0.244)	-3.80 (0.265)	-3.64 (0.254)
Intermediate <sup>c</sup>	0	-1.00 (0.089)	-1.72 (0.111)	-1.89 (0.117)	-2.31 (0.130)	-2.52 (0.129)	-2.74 (0.134)	-3.20 (0.145)	-3.47 (0.155)	-3.78 (0.154)	-4.06 (0.152)	-4.21 (0.149)	-4.29 (0.149)	-4.27 (0.144)	-4.39 (0.157)	-4.42 (0.151)
High <sup>d</sup>	0	-1.20 (0.139)	-2.03 (0.173)	-2.21 (0.182)	-2.87 (0.200)	-3.23 (0.196)	-3.41 (0.200)	-3.75 (0.202)	-3.97 (0.209)	-3.95 (0.203)	-4.00 (0.197)	-4.13 (0.190)	-4.31 (0.192)	-4.33 (0.182)	-4.34 (0.193)	-4.33 (0.188)
P-value	-	.003	<.001	<.001	<.001	<.001	<.001	.003	.002	.004	<.001	.002	.015	.074	.145	.029

**B** Fecal calprotectin stratified by probability of response



Time point <sup>a</sup>	Baseline	Wk 6	Wk 30	Wk 52
Low <sup>b</sup>	0	-20.05 (-71.79, 74.86)	-54.56 (-91.08, 80.01)	-63.91 (-93.70, 11.07)
Intermediate <sup>c</sup>	0	-48.79 (-82.42, 37.82)	-68.35 (-95.07, 3.16)	-82.74 (-96.05, -11.16)
High <sup>d</sup>	0	-56.25 (-86.22, 14.10)	-70.23 (-93.55, -8.81)	-69.95 (-93.15, 8.91)
P-value	-	.0135	.2462	.2108

**Figure 3.** Changes in (A) partial Mayo score and (B) fecal calprotectin in the GEMINI 1 trial cohort stratified by CDST. Statistical comparisons at each time point for partial Mayo score was done by ANOVA with type I error controlled based on a closed test procedure; fecal calprotectin statistical analysis was done using nonparametric testing (Kruskal-Wallis). \* $P < .05$ , \*\* $P < .01$ , \*\*\* $P < .001$  for both. <sup>a</sup>All values in the table are least-squares (LS) mean partial Mayo score (PMS) (with standard error in parentheses). <sup>b</sup>Low probability;  $\leq 26$  points in the CDST model at baseline. <sup>c</sup>Intermediate probability;  $>26$  to  $\leq 32$  points in the CDST model at baseline. <sup>d</sup>High probability;  $>32$  points in the CDST model at baseline. <sup>e</sup>All values in the table are median percent change in fecal calprotectin (interquartile range).

cohort, patients with longer disease duration more often had prior exposure to TNF antagonists. It may have been anticipated that patients with longer disease duration would therefore be less likely to respond to VDZ; however, the opposite was seen. The biological rationale for this is unclear, although it could be speculated that chronic inflammation in those with longer disease duration results in continuous inflammatory signaling causing cytokine-based signaling pathways to become refractory to further stimuli, or that resident proinflammatory T cells are exhausted from chronic stimuli. In other chronic autoimmune conditions, T cell exhaustion has been associated with a good prognosis.<sup>14</sup> This finding does not imply that clinicians should wait until a patient has longer disease duration to start VDZ, but rather that among patients with a chronic course, VDZ may have improved effectiveness.

We observed an exposure-efficacy relationship across model-derived prognostic groupings that may be related to differences in drug disposition. An exposure-efficacy relationship for VDZ induction has been observed in UC,<sup>10</sup> and post hoc analyses of the GEMINI 1 trial have indicated that patients with higher VDZ trough concentrations had higher deep remission rates at 52 weeks.<sup>15</sup> Despite these associations, clinicians are unable to predict at baseline who may benefit from early therapeutic drug monitoring with attempts at dose optimization through interval shortening. We observed a significant trend in increasing exposure-efficacy relationships across the low-, intermediate-, and high-probability groups with the VDZ-CDST. Furthermore, a clinical response to VDZ interval shortening was only observed in the low- to intermediate-probability group within the VICTORY cohort, presumably because these patients had lower trough concentrations than patients in the high-probability group. Although trough VDZ concentration testing was not routinely performed in the VICTORY cohort, these data help support the potential use of the VDZ-CDST to identify at baseline which patients are likely to have lower VDZ trough concentrations and are thus potentially most likely to benefit from early proactive therapeutic drug monitoring with VDZ interval shortening or upfront dose optimization strategies. The ongoing Vedolizumab Intravenous (IV) Dose Optimization in Ulcerative Colitis (ENTERPRET) trial (NCT03029143) will evaluate higher doses vs standard doses of VDZ and will help inform our understanding of the role of dose optimization in UC.

One of the main limitations with prior prediction model work is that it remains unclear whether identified predictors in those models are specific to the drug being assessed or are global markers of improved responsiveness to all biologics. In our study, we addressed this gap and observed that the VDZ-CDST was not able to predict treatment effectiveness with TNF antagonist therapy for UC patients in routine clinical practice. Among patients deemed to have low probability of response based on the VDZ-CDST, we observed a

CSFREM rate of 21% among those treated with TNF antagonist therapy, compared with 12% for patients treated with VDZ therapy. In contrast, among patients deemed to have high probability of response based on the VDZ-CDST, we observed a CSFREM rate of 25% among those treated with TNF antagonist therapy, compared with 32% for patients treated with VDZ therapy. This would suggest that patients with a low probability of response might be more appropriately treated with TNF antagonist therapy, and those with a high probability are the best candidates for VDZ therapy. Among patients classified as having intermediate probability of response, the rates of CSFREM and colectomy were comparable between those who received TNF antagonist or VDZ therapy. For these patients, a careful discussion is warranted that should take into consideration the broader literature for comparative effectiveness and comparative safety when determining optimal treatment selection.

Our study has several strengths, including external validation in an independent, real-world dataset derived from multiple sites, ease of use in routine clinical practice, the ability to screen for patients who are less likely to achieve key outcomes (CSFREM) and more likely to require colectomy, and the drug-specific prediction of our CDST. There also are several limitations to our study. The lower bound of the confidence interval for the performance reached 0.5, suggesting that model discrimination may not be ideal. Further validation will therefore be needed to understand external validity on additional cohorts. Prospective validation will also be needed for the observation regarding interval-shortening benefits being limited to the low-probability cohort, ideally in a randomized, controlled trial setting. Caution should be taken when interpreting comparisons of subgroups to placebo recipients within the ITT population. The negative likelihood ratio of the VDZ-CDST predicts an approximate 15% reduction in effectiveness and posttest odds of achieving the outcome (CSFREM) in the low-probability group,<sup>16</sup> but this is likely to be further modified by the ability of clinicians to achieve these outcomes (through enhanced monitoring and care pathways), irrespective of treatment assignment. Further work will need to be done to understand how care pathways integrated with therapeutic CDSTs affect overall probabilities of achieving key outcomes.

In conclusion, we have derived and externally validated a prediction model and CDST for achieving CSFREM with VDZ in UC. The VDZ-CDST was observed to have a high sensitivity for identifying patients with a latency of onset for response, who were less likely to achieve CSFREM with VDZ and were more likely to require colectomy while on VDZ. Furthermore, the CDST was observed to predict treatment effectiveness with VDZ but not TNF antagonist therapy, confirming its drug-specific use. We have made several key novel observations regarding VDZ exposure-efficacy relationships, and the use of this VDZ-CDST in the clinical setting will likely help

to better guide the decision-making process for choosing VDZ as a therapeutic option and monitoring or adjusting therapy over time. To aid in the integration of this tool in clinical practice, an online tool is available to providers at: <https://rme.arche.services/curriculum/a26dcdf0-00c3-4209-a67c-b4d4abe02f32>. This learning health platform will allow the user to gain Continuing Medical Education credits for navigating through a search and learn educational platform which includes the CDST presented here. We anticipate this educational platform will help to streamline the integration of guidelines, evidence-based best practices, and all decision support tools as they become available over time.

## Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at [www.cghjournal.org](http://www.cghjournal.org), and at <https://doi.org/10.1016/j.cgh.2020.02.010>.

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## Reprint requests

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## Conflicts of interest

These authors disclose the following: Parambir S. Dulai and the University of California, San Diego hold a provisional patent for the prediction modeling outlined herein. Parambir S. Dulai reports consulting for Takeda, Janssen, Pfizer, and AbbVie; travel support from Takeda and Janssen; and grant support from Takeda, Pfizer, Janssen, and AbbVie. Siddharth Singh reports research support from AbbVie and Pfizer; consulting for Pfizer, AbbVie, Takeda, and AMAG Pharmaceuticals; and career development awards from the American College of Gastroenterology and Crohn's and Colitis Foundation. Niels Vande Castele reports consulting for Takeda and Janssen. Joseph Meserve reports travel support from Takeda. Jenna L. Koliari-Pace reports travel support from Takeda. Brigid S. Boland reports research support from Takeda and Janssen; and consulting for AbbVie and Prometheus. John T. Chang reports grant support from Takeda. David Faleck reports travel support from Takeda. Robert Hirten reports speaking or advisory boards for Takeda and Janssen. Ryan Ungaro reports service as a consultant or advisory board member for Takeda, Pfizer, and Janssen. Dana Lukin reports consulting for AbbVie, Janssen, and Salix. Keith Sultan reports speaking engagement for AbbVie; research support for Takeda, Celgene, Hoffmann-La Roche, Gilead, and Pfizer. David Hudesman reports consulting for AbbVie, Takeda, Janssen, and Pfizer. Shannon Chang reports consulting for Oshi. Eugenia Schmidt reports travel support from Takeda. Arun Swaminath reports fellowship support from Janssen, AbbVie, and Pfizer; and grant support from Pfizer. Maria Rosario reports being an employee of Takeda Pharmaceuticals U.S.A., Inc. Vipul Jairath reports consulting fees from AbbVie, Janssen, Takeda, Sandoz, Ferring, Pfizer, GlaxoSmithKline, Robarts Clinical Trials, Eli Lilly, and Arena; and speaker fees from Takeda, Ferring, Janssen, and Shire. Leonardo Guizzetti reports being an employee of Robarts Clinical Trials. Brian G. Feagan reports grant support from AbbVie, Amgen, AstraZeneca, Bristol-Myers Squibb, Roche, Genentech, Johnson & Johnson, Janssen, Millennium, Pfizer, Receptos, Tillotts, and UCB; service as a consultant or advisory board member for AbbVie, ActoGenix, Akros, Albireo, Amgen, AstraZeneca, Avaxia Biologics, Avir Pharma, Baxter Healthcare Corp, Biogen Idec, Boehringer Ingelheim, Bristol-Myers Squibb, Calypso Biotech, Celgene, Elan/Biogen, enGene, Ferring Pharmaceuticals, Galapagos, Genentech/Roche, GiCare Pharma, Gilead, Given Imaging, GlaxoSmithKline, Inception IBD Inc, Ironwood Pharmaceuticals, Johnson & Johnson, Janssen, Japan Tobacco, Kyowa Hakko Kirin Co Ltd, Lexicon, Lilly, Lycera Biotech, Merck, Mesoblast Ltd, Millennium, Nektar, Nestlé, Novartis, Novo Nordisk, Pfizer, Prometheus Therapeutics & Diagnostics, Protagonist, Receptos, Salix, Shire, Sigmoid Pharma, Synergy Pharmaceuticals Inc, Takeda, Teva Pharmaceutical Industries Ltd, TiGenix, Tillotts, UCB, Vertex Pharmaceuticals, VHSquared Ltd, Warner Chilcott, Wyeth, Zealand Pharma, and Zyngenia. Corey A. Siegel reports service as a consultant or advisory board member for AbbVie, Amgen, Celgene, Lilly, Janssen, Sandoz, Pfizer, Prometheus, Sebel, and Takeda; speaker for AbbVie, Janssen, Pfizer, and Takeda; grant support from the Crohn's and Colitis Foundation, AHRQ (1R01HS021747-01), AbbVie, Janssen, Pfizer, and Takeda; intellectual property for MiTest Health, LLC, and ColonyConcepts, LLC; and equity interest for MiTest Health and ColonyConcepts. Bo Shen reports consulting for Janssen, Salix, AbbVie, Takeda, Theravance, and Robarts Clinical Trials. Sunanda Kane reports consulting for AbbVie, Merck, Spherix Health, Seres Pharmaceuticals, and Samsung Bioepis. Edward V. Loftus Jr reports consulting for Janssen, Takeda, AbbVie, UCB, Amgen, Pfizer, Salix, Mesoblast, Eli Lilly, Celgene, and CVS Caremark; and research support from Janssen, Takeda, AbbVie, UCB, Amgen, Pfizer, Genentech, Gilead, Receptos, Celgene, MedImmune, Seres Therapeutics,

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## Supplementary Material and Methods

### Data Source

GEMINI 1 trial data were collected as part of the phase 3 clinical trial (NCT00783718) with corresponding ethics/institutional review board approval. The VICTORY consortium dataset was collected after ethics/institutional review board approval at all participating sites.

### Data Source: VICTORY Consortium

The VICTORY Consortium is a multicenter collaborative research group in which patient demographics, disease characteristics, and treatment outcomes are pooled for inflammatory bowel disease (IBD) patients treated with biologics. Institutional review board approval was obtained from each site for ongoing retrospective data collection and transfer. Data were collected individually by sites using a standardized data collection form and transferred (after de-identification) to the coordinating site (University of California, San Diego) for data compilation and analysis.

### Model and Clinical Decision Support Tool Sensitivity Analyses in GEMINI 1 Trial for VDZ Exposure-Efficacy Relationships

Albumin has previously been shown to be the strongest predictor of exposure-efficacy relationships for vedolizumab (VDZ) in ulcerative colitis (UC); however, albumin does not explain the entirety of VDZ exposure variability.<sup>8,9</sup> Before finalizing the model for external validation, a sensitivity analysis was performed by replacing albumin with calculated VDZ clearance profiles for GEMINI 1 trial participants.<sup>8,9</sup> Performance of this model within the GEMINI 1 trial derivation cohort was slightly better than the original model that included albumin (area under the receiver-operating characteristic curve [AUC] 0.69 vs 0.65). A baseline prediction model is not currently available for predicting VDZ exposure over time, and therefore clearance could not be readily substituted for albumin in the final prediction model. Albumin was therefore retained for external validation of the model in the VICTORY Consortium dataset.

### GEMINI 1 Trial VDZ Concentration Assessments

VDZ concentrations were assessed in the GEMINI 1 trial using serum samples with a direct VDZ capture pharmacokinetic assay. A sandwich enzyme-linked immunosorbent assay was used for quantifying VDZ in human serum. Serum concentrations of VDZ were determined by QPS in accordance with Good Laboratory Practice. The lower limit of detection was 0.125  $\mu\text{g/mL}$ .

Time points for trough concentration assessments taken 30 minutes before VDZ infusions were weeks 0, 2, 6, 22, and 46. Additional concentration assessments were taken at weeks 4, 14, 38, and 52. Time points for peak concentration assessments taken 2 hours postinfusion were weeks 0, 2, 6, 22, and 46. Differences in median concentrations at each time point across the 3 probability groups were first assessed using non-parametric testing (Kruskal-Wallis), and then pairwise comparisons were done for each group at each time point.

### GEMINI 1 Trial Fecal Calprotectin Assessments

Fecal calprotectin was assessed in the GEMINI 1 trial using the CAL0100 test kit. Time points for assessments were weeks 0, 6, 30, and 52. Differences in median concentrations at each time point across the three probability groups were first assessed using nonparametric testing (Kruskal-Wallis), and then pairwise comparisons were done for each group at each time point.

### GEMINI 1 Intention-to-Treat Sensitivity Analyses

**Intention-to-Treat Induction Analysis.** In accordance with an intent-to-treat approach, the intention-to-treat (ITT) population for the induction study consisted of all randomized patients in the GEMINI 1 trial cohort who received any amount of blinded study drug during induction treatment.

**ITT Maintenance Analysis.** In accordance with an intent-to-treat approach, the ITT population for the maintenance treatment consisted of all rerandomized patients randomized as week 6 responders who received VDZ during induction treatment and then received any amount of study drug in the maintenance phase.

### Model Validation VICTORY Consortium

External validation of the model was conducted in the VICTORY Consortium cohort. Discriminative ability was assessed by receiver-operating characteristic curve analysis and is presented as AUC. An AUC value of 0.5 denotes that the model does not discriminate any better than random guessing and 1 denotes perfect discrimination. Calibration of the model applied to the external validation cohort was evaluated in multiple ways. The observed event rates and predicted risk were graphically assessed by a calibration curve. The intercept (calibration-in-the-large) assessed whether the overall predicted event rate matches the observed rate, and should ideally be zero, indicating no systematic difference in observed predicted rates. The calibration slope gives an indication of how over- or under-fit the model is, and should ideally be 1, indicating no overfitting. A joint hypothesis test of perfect calibration using a likelihood ratio test was evaluated as an overall test of calibration. This test is



more sensitive to potential miscalibration than the Hosmer-Lemeshow goodness-of-fit test, which is also shown for comparison after splitting the sample into quintiles. This test assesses whether or not the observed event rates match expected event rates in subgroups of the model population, with  $P$  values  $<.05$  indicating evidence of poor fit for both calibration tests. The overall performance of the models was evaluated with the Nagelkerke  $R^2$  and the Brier score. Nagelkerke  $R^2$  is a measure between 0 and 1, with 0 denoting that the model does not explain any variation and 1 denoting that it perfectly explains the observed variation in outcomes. The Brier score is a measure of prediction error with the mean squared difference between the predicted probability and the actual outcome, and values range from 0 (perfect prediction) to 0.25 (a noninformative model).<sup>10</sup>

## Results

### *Variable Selection*

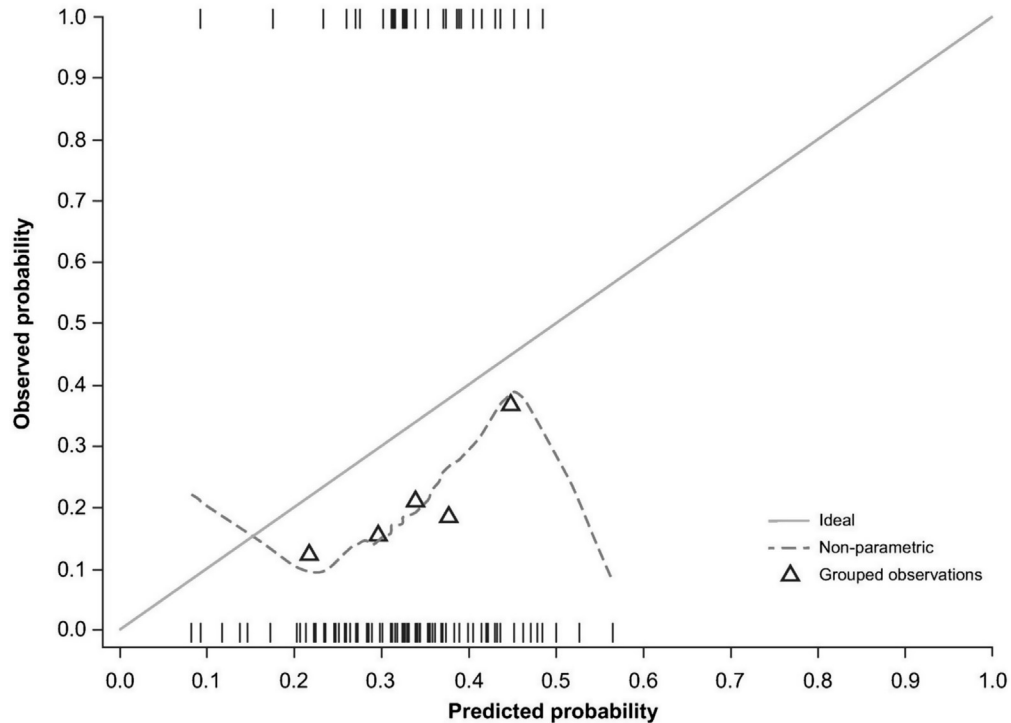
A binary categorization was chosen for disease duration ( $\geq 2$  years vs  $< 2$  years) because nonlinearity was observed for the association between disease duration and corticosteroid-free remission, and a binary categorization was thought to be easier to interpret and apply clinically. Previous tumor necrosis factor (TNF) antagonist exposure was used instead of previous TNF antagonist failure, given the inability to accurately classify failure subtypes in routine practice and similarity in significance between these variables. Baseline endoscopy

was used as a metric for disease activity instead of baseline stool frequency, given the subjectivity in stool frequency assessment in routine practice, the observation that the significance for stool frequency was being driven by the comparison of severe (Mayo score stool frequency 3) vs inactive (Mayo score stool frequency 0) disease, the inclusion of endoscopic disease activity as an endpoint for the model, and observed collinearity between baseline endoscopy and baseline stool frequency ( $P < .01$ ). Current or prior smoking was further investigated as individual variables instead of as a composite variable, when separating this into current smokers vs nonsmokers and prior smokers vs nonsmokers, it was found to not meet the thresholds for inclusion and was therefore excluded before the second step of model building.

### *Model Equation Example*

A 35-year-old man with UC is being considered for VDZ therapy. His UC was diagnosed 15 months prior, and he had no prior TNF antagonist exposure. Baseline endoscopy is performed and is notable for the absence of vascular pattern, marked erythema, and friability, without ulcers or spontaneous bleeding (Mayo endoscopic subscore 2). Baseline lab results are notable for an albumin of 40 g/L (4 g/dL).

$$\begin{aligned} \text{This patient's model calculation} &= \\ &- 3.7038 + [0.2820] + [0.1847] \\ &+ [0.0647 \times 40] = - 0.7464 \end{aligned}$$



**Supplementary Figure 1.** The calibration plot compares the predicted risk for all patients to their expected risk. The ideal line (gray) shows perfect calibration (ie, predicted risk is equal to observed risk). The nonparametric line (dashed, gray) shows the risk for patients over the entire range of risks predicted by the model. The grouped observations (triangles) are the average risks within each quintile group. The calibration intercept (calibration-in-the-large) and slope were estimated from the calibration curve. The calibration-in-the-large compares the systematic difference between the average observed risk and predicted risk and should ideally be equal to 0, indicating no systematic difference. The calibration-in-the-large estimate is  $-0.674$  (95% confidence interval,  $-1.379$  to  $0.031$ ) for the current model. The calibration slope gives an indication of overfitting and should ideally be equal to 1, indicating no overfitting or underfitting. Its estimate is  $0.999$  (95% confidence interval,  $0.029$  to  $1.968$ ) for the current model. A format test of calibration can be done by a likelihood ratio test so that the intercept is 0 and slope is 1. This test confirms that the model predicts risks approximately twice as large as observed on the odds scale ( $\exp(0.674) = 1.96$ ) (likelihood ratio  $\chi^2 = 16.18$ ,  $df = 2$ ,  $P = .00031$ ), confirming model miscalibration.

**Supplementary Table 1.** Comparison of Demographics Between the VICTORY Cohorts Included in Validation

	VICTORY Consortium		<i>P</i> value
	Entire Vedolizumab-Treated Cohort (N = 352) <sup>a</sup>	Vedolizumab-Treated Validation Cohort (n = 199)	
Female	184 (52)	104 (52)	1.00
Smoker (never)	256 (73)	144 (72)	.92
Age, y	41.6 ± 17.3	41.5 ± 17.3	.95
BMI, kg/m <sup>2</sup>	25.6 ± 5.77	25.3 ± 5.83	.56
Disease duration, y	6.0 (2–12)	6.0 (2–12)	1.00
Disease duration <2 y	54 (16)	31 (16)	1.00
No prior hospitalization	93 (26)	55 (28)	.77
Prior TNF antagonist exposure	231 (66)	135 (68)	.64
Prior TNF antagonist failure	194 (55)	117 (59)	.42
Extensive baseline disease	210 (60)	112 (56)	.47
Baseline moderate endoscopic disease	237 (67)	126 (63)	.35
Baseline albumin, g/L	39.1 ± 5.54	39.4 ± 5.41	.54
Concomitant CS only	118 (34)	69 (35)	.78
Concomitant IMM only	50 (14)	36 (18)	.27
Concomitant CS and IMMs	73 (21)	49 (25)	.37

Values are n (%), mean ± SD, or median (interquartile range).

BMI, body mass index; CS, corticosteroid; IMM, immunomodulator; TNF, tumor necrosis factor; VICTORY, Vedolizumab for Health Outcomes in Inflammatory Bowel Diseases.

<sup>a</sup>Includes patients who were ultimately excluded for lack of endoscopic follow-up.

**Supplementary Table 2.** Univariable Analyses for Corticosteroid-Free Remission After 52 Weeks of Vedolizumab in the GEMINI 1 Trial Cohort

Baseline variable	Univariable	
	Odds ratio	<i>P</i> value
Age	1.00	.958
Sex (female vs male)	1.34	.119
Ethnicity (other vs non-Hispanic/Latino)	0.78	.549
Race (non-white vs white)	0.82	.450
Smoker (current/previous vs nonsmoker)	0.72	.091
Smoker (current vs nonsmoker)	0.78	.854
Smoker (previous vs nonsmoker)	0.71	.413
BMI	1.03	.046
Disease duration (continuous)	1.04	.017
Disease duration (≥5 y vs <5 y)	1.28	.192
Disease duration (≥2 y vs <2 y)	1.49	.107
EIM (no vs yes)	1.03	.890
Prior hospitalization (no vs yes)	1.21	.352
Previous TNF antagonist exposure (no vs yes)	1.84	.001
Previous TNF antagonist failure (no vs yes)	1.88	.001
Concomitant corticosteroids (no vs yes)	0.99	.952
Concomitant immunomodulator (no vs yes)	0.72	.085
Baseline severe disease, full Mayo score (<10 vs ≥10)	1.62	.023
Baseline full Mayo score	0.91	.079
Baseline partial Mayo score	0.94	.246
Baseline rectal bleeding Mayo score (1 vs 0)	1.37	.717
Baseline rectal bleeding Mayo score (2 vs 0)	1.70	.292
Baseline rectal bleeding Mayo score (3 vs 0)	1.92	.209
Baseline stool frequency Mayo score (0–2 vs 3)	1.70	.005
Baseline stool frequency Mayo score (1 vs 0)	1.52	.010
Baseline stool frequency Mayo score (2 vs 0)	1.25	.409
Baseline stool frequency Mayo score (3 vs 0)	0.75	.015
Baseline endoscopy (moderate vs severe)	1.57	.016
Baseline albumin	1.08	<.001
Baseline albumin (>35 g/L vs ≤35 g/L)	1.88	.002
Baseline fecal calprotectin	1.00	.939

BMI, body mass index; EIM, extraintestinal manifestation; TNF, tumor necrosis factor.

**Supplementary Table 3.** Baseline Differences in Demographics Between Longer Disease Duration ( $\geq 2$  y) and Shorter Disease Duration ( $< 2$  y) Patients in the GEMINI 1 Cohort

Variable	Short disease duration ( $< 2$ y) (n = 126)	Long disease duration ( $\geq 2$ y) (n = 492)
Age, y	33 (25–51)	40 (31–49)
Female	50 (40)	205 (42)
BMI, kg/m <sup>2</sup>	23 (21–27)	24 (22–28)
Disease duration, y <sup>a</sup>	1.2 (0.7–1.5)	6.2 (3.7–10.5)
Prior hospitalization	65 (52)	145 (29)
Baseline EIM	37 (29)	177 (36)
Previous TNF antagonist exposure	48 (38)	263 (53)
Previous TNF antagonist failure	44 (35)	222 (45)
Concomitant CS only	73 (58)	252 (51)
Concomitant IMMs only	41 (33)	171 (35)
Baseline endoscopy moderate	63 (50)	214 (44)
Baseline partial Mayo score	6 (5–7)	6 (5–7)
Baseline calprotectin, mg/kg	952 (305–1800)	832 (355–1727)
Baseline albumin, g/L	36 (33–41)	37 (34–40)
VDZ maintenance q4	105 (83)	391 (79)

BMI, body mass index; CS, corticosteroid; EIM, extraintestinal manifestation; IMM, immunomodulator; q, quartile; TNF, tumor necrosis factor.

<sup>a</sup>2 patients had missing data for disease duration.

**Supplementary Table 4.** Differences in Median Measured VDZ Concentrations Over 52 Weeks in GEMINI 1 Trial Derivation Cohort

Time point	Low probability ( $\mu\text{g/mL}$ )	Intermediate probability ( $\mu\text{g/mL}$ )	High probability ( $\mu\text{g/mL}$ )	<i>P</i> value (overall)	<i>P</i> value (low vs intermediate)	<i>P</i> Value (Low vs High)	<i>P</i> Value (Intermediate vs High)
Baseline predose	0	0	0	—	—	—	—
Baseline postdose	93.8 (78.7–108)	92.6 (78–108)	98.3 (80.4–117)	.095	.842	.103	.034 <sup>a</sup>
Week 2 predose	22.9 (17.6–29.2)	27.4 (23.3–35.7)	32 (26.6–39.5)	<.001 <sup>a</sup>	<.001 <sup>a</sup>	<.001 <sup>a</sup>	<.001 <sup>a</sup>
Week 2 postdose	112 (94.9–132)	115.5 (96.2–139)	129.5 (108–149.5)	<.001 <sup>a</sup>	.593	<.001 <sup>a</sup>	<.001 <sup>a</sup>
Week 4	33.8 (25.5–45.4)	42.25 (33.1–53.6)	53.8 (41.4–64.5)	<.001 <sup>a</sup>	<.001 <sup>a</sup>	<.001 <sup>a</sup>	<.001 <sup>a</sup>
Week 6 predose	17.2 (10.5–25.2)	23.5 (16.85–33.3)	34.85 (25.9–43.6)	<.001 <sup>a</sup>	<.001 <sup>a</sup>	<.001 <sup>a</sup>	<.001 <sup>a</sup>
Week 6 postdose	108 (89.8–128)	113 (93.9–136)	126 (102–150)	<.001 <sup>a</sup>	.062	<.001 <sup>a</sup>	<.001 <sup>a</sup>
Week 14	15.7 (7.79–24.1)	21.25 (12.9–32.7)	29.45 (18–43.5)	<.001 <sup>a</sup>	<.001 <sup>a</sup>	<.001 <sup>a</sup>	<.001 <sup>a</sup>
Week 22 predose	17.95 (9.27–29.8)	23.8 (13.5–37.55)	32.45 (17.55–48.1)	<.001 <sup>a</sup>	.007 <sup>a</sup>	<.001 <sup>a</sup>	.004 <sup>a</sup>
Week 22 postdose	109 (91.55–129.5)	112.5 (94.6–142)	125 (103–145)	.032 <sup>a</sup>	.285	.009 <sup>a</sup>	.059
Week 38	16.9 (7.59–32.7)	26.3 (13.7–42.6)	29.5 (15.9–50.2)	.002 <sup>a</sup>	.010 <sup>a</sup>	<.001 <sup>a</sup>	.154
Week 46 predose	22.5 (7.97–36.4)	27.8 (13.6–42.8)	31.5 (14.1–52.3)	.015 <sup>a</sup>	.069	.005 <sup>a</sup>	.104
Week 46 postdose	108 (91.3–129)	115 (90–143)	127 (104–153)	.016 <sup>a</sup>	.368	.008 <sup>a</sup>	.023 <sup>a</sup>
Week 52	35.25 (19.6–60.65)	43.1 (20.5–63.1)	52.25 (21.1–77.6)	.053	.498	.028 <sup>a</sup>	.050

Values are median (interquartile range). All postdose assessments were done 2 hours postdose.

VDZ, vedolizumab.

<sup>a</sup>Closed test procedure used to control for type I error.



**Supplementary Table 5.** Differences in Partial Mayo Score Over 52 Weeks in GEMINI 1 Trial Derivation Cohort

Time point	Low probability; mean change from baseline (interquartile range)	Intermediate probability; mean change from baseline (interquartile range)	High probability; mean change from baseline (interquartile range)	P value			
				P value (overall)	P value (low vs intermediate)	P value (low vs high)	
Baseline	0	0	0	—	—	—	
Week 2	-0.67 (-1.0 to 0.0)	-0.98 (-2.0 to 0.0)	-1.11 (-2.0 to 0.0)	.003 <sup>a</sup>	.007 <sup>a</sup>	.001 <sup>a</sup>	.230
Week 4	-1.18 (-2.0 to 0.0)	-1.71 (-3.0 to 0.0)	-1.91 (-3.0 to 0.0)	<.001 <sup>a</sup>	.001 <sup>a</sup>	<.001 <sup>a</sup>	.134
Week 6	-1.38 (-2.0 to 0.0)	-1.88 (-3.0 to 0.0)	-2.08 (-3.0 to -1.0)	<.001 <sup>a</sup>	.002 <sup>a</sup>	<.001 <sup>a</sup>	.135
Week 10	-1.81 (-3.0 to 0.0)	-2.31 (-4.0 to 0.0)	-2.73 (-4.0 to -1.0)	<.001 <sup>a</sup>	.007 <sup>a</sup>	<.001 <sup>a</sup>	.021 <sup>a</sup>
Week 14	-2.19 (-4.0 to -1.0)	-2.51 (-4.0 to -1.0)	-3.06 (-4.0 to -2.0)	<.001 <sup>a</sup>	.027 <sup>a</sup>	<.001 <sup>a</sup>	.003 <sup>a</sup>
Week 18	-2.44 (-4.0 to -1.0)	-2.74 (-4.0 to -1.0)	-3.23 (-5.0 to -2.0)	<.001 <sup>a</sup>	.050	<.001 <sup>a</sup>	.005 <sup>a</sup>
Week 22	-3.04 (-4.0 to -1.0)	-3.16 (-5.0 to -1.0)	-3.55 (-5.0 to -2.0)	.003 <sup>a</sup>	.064	<.001 <sup>a</sup>	.028 <sup>a</sup>
Week 26	-3.15 (-5.0 to -2.0)	-3.45 (-5.0 to -2.0)	-3.77 (-5.0 to -2.0)	.002 <sup>a</sup>	.030 <sup>a</sup>	<.001 <sup>a</sup>	.055
Week 30	-3.29 (-5.0 to -1.0)	-3.75 (-6.0 to -2.0)	-3.75 (-5.0 to -3.0)	.004 <sup>a</sup>	.004 <sup>a</sup>	.002 <sup>a</sup>	.509
Week 34	-3.26 (-5.0 to -1.0)	-4.06 (-6.0 to -2.0)	-3.77 (-5.0 to -2.0)	<.001 <sup>a</sup>	<.001 <sup>a</sup>	<.001 <sup>a</sup>	.805
Week 38	-3.52 (-5.0 to -2.0)	-4.22 (-6.0 to -3.0)	-3.95 (-6.0 to -3.0)	.002 <sup>a</sup>	<.001 <sup>a</sup>	.004 <sup>a</sup>	.732
Week 42	-3.74 (-5.0 to -2.0)	-4.28 (-6.0 to -3.0)	-4.16 (-6.0 to -3.0)	.015 <sup>a</sup>	.006 <sup>a</sup>	.010 <sup>a</sup>	.937
Week 46	-3.92 (-5.0 to -2.0)	-4.30 (-6.0 to -3.0)	-4.14 (-6.0 to -3.0)	.074	.037 <sup>a</sup>	.035 <sup>a</sup>	.812
Week 50	-3.94 (-5.0 to -2.0)	-4.45 (-6.0 to -3.0)	-4.18 (-6.0 to -3.0)	.145	.056	.098	.853
Week 52	-3.88 (-6.0 to -2.0)	-4.44 (-6.0 to -3.0)	-4.17 (-6.0 to -3.0)	.029 <sup>a</sup>	.009 <sup>a</sup>	.031 <sup>a</sup>	.702

<sup>a</sup>Closed test procedure used to control for type I error.

**Supplementary Table 6.** Model Performance in GEMINI 1 Trial Derivation Cohort

Cutoff	Sensitivity (95% CI) (%)	Specificity (95% CI) (%)	PPV (95% CI)	NPV (95% CI)	Positive LR (95% CI)	Negative LR (95% CI)
26 points	87.5 (81.8–91.9)	28.1 (23.9–32.6)	34.0 (29.8–38.5)	84.1 (77.2–89.7)	1.22 (1.12–1.32)	0.44 (0.29–0.67)
32 points	34.2 (27.4–41.6)	82.5 (78.6–85.9)	45.3 (36.9–54.0)	74.7 (70.6–78.6)	1.96 (1.47–2.60)	0.80 (0.71–0.89)

Area under the receiver-operating characteristic curve 0.65, Brier score 0.18, Nagelkerke R-square 0.07, Hosmer-Lemeshow goodness-of-fit P value = .46. CI, confidence interval; LR, likelihood ratio; NPV, negative predictive value; PPV, positive predictive value.

**Supplementary Table 7.** Anti-TNF–Treated UC Patients

	Anti-TNF Cohort (n = 123)
Female	57 (46)
Smoker (never)	85 (69)
Age, y	37.7 ± 15.7
Body mass index, kg/m <sup>2</sup>	25.4 ± 7.8
Disease duration, y	3 (1–9)
Disease duration <2 y	84 (68)
Prior hospitalization	72 (58)
Prior TNF antagonist exposure	41 (33)
Prior TNF antagonist failure	27 (22)
Extensive baseline disease	83 (68)
Baseline moderate endoscopic disease	54 (44)
Baseline albumin, g/L	3.6 ± 0.6

Values are n (%), mean ± SD, or median (interquartile range).  
TNF, tumor necrosis factor; UC, ulcerative colitis.