

# Clinical Risk Scores (CRSs) to Predict Resistance to Trimethoprim-Sulfamethoxazole (TMP-SMX), Fluoroquinolone (FQ), Nitrofurantoin (NIT), or Third Generation Cephalosporins (3GC) among Adult Outpatients (OPs) with Complicated Urinary Tract Infections (cUTIs)

T. P. Lodise<sup>1</sup>, PharmD, PhD; L.H. Chen<sup>2</sup>, DrPH, MSPH; K. J. Bruxvoort<sup>2,3</sup>, PhD, MPH; R. Wei<sup>2</sup>, MS; T. M. Im<sup>2</sup>, MPH; R. Contreras<sup>2</sup>, MS; M. Rodriguez<sup>4\*</sup>, PharmD, HS-HEOR, BCPS, BCCCP, BCIDP; L. Friedrich<sup>4\*</sup>, PharmD; J. Reese<sup>4\*</sup>, PharmD; S. Y. Tartof<sup>2</sup>, PhD, MPH

<sup>1</sup>Albany College of Pharmacy Health Sciences, NY, USA; <sup>2</sup>Kaiser Permanente Southern California Department of Research & Evaluation, Pasadena, CA, USA; <sup>3</sup>University of Alabama at Birmingham; <sup>4\*</sup>Spero Therapeutics, Inc. (at the time the study was conducted)

## Background

- Increased resistance rates to available oral antibiotics (ABs) contribute to delays in receipt of appropriate treatment and adverse outcomes among patients with cUTI in the OP setting.
- To optimize empiric AB selection in adult OPs with cUTIs, we developed CRSs using information available at presentation to estimate the risk of having an OP cUTI that was resistant to TMP-SMX, FQ, NIT, or 3GC.

## Methods

- Retrospective cohort study among Kaiser Permanente Southern California members from 2017-2020.
- Inclusion criteria: age ≥18 years; cUTI diagnosis during an OP visit; urine culture with antibiotic susceptibility results; receipt of antibiotic ±3 days of index urine culture, and not hospitalized on day of OP visit.
- Outcome: Resistance to TMP-SMX, FQ, NIT, or 3GC on index urine culture was quantified and based on local laboratory site testing.
- Covariates present on clinical presentation were collected.
- Least absolute shrinkage and selection operator logistic regression (LR) were used to develop separate models to estimate the likelihood of resistance to TMP-SMX, FQ, NIT, or 3GC.
  - The prediction models were developed using training and validation datasets.
  - For all 4 LR models, CRSs were calculated as the weighted sums of regression coefficients.
  - Variables in each of the final LR models were assigned point(s), and an OP's CRS for cUTI resistant to TMP-SMX, FQ, NIT, or 3GC was based on total points in each of the respective models.

## Results

- A total of 30,450 cUTIs among 26,326 OPs met study criteria.
- Resistance to TMP-SMX, FQ, NIT, and 3GC was 37%, 19%, 27%, and 24%, respectively.
- Baseline covariates and associated points for 4 LR models are shown in **Table 1**.
- A CRS of 0, 10, 6, 11 corresponded to a >20% risk of resistance to TMP-SMX, FQ, NIT, or 3GC, respectively (**Figure 1**).

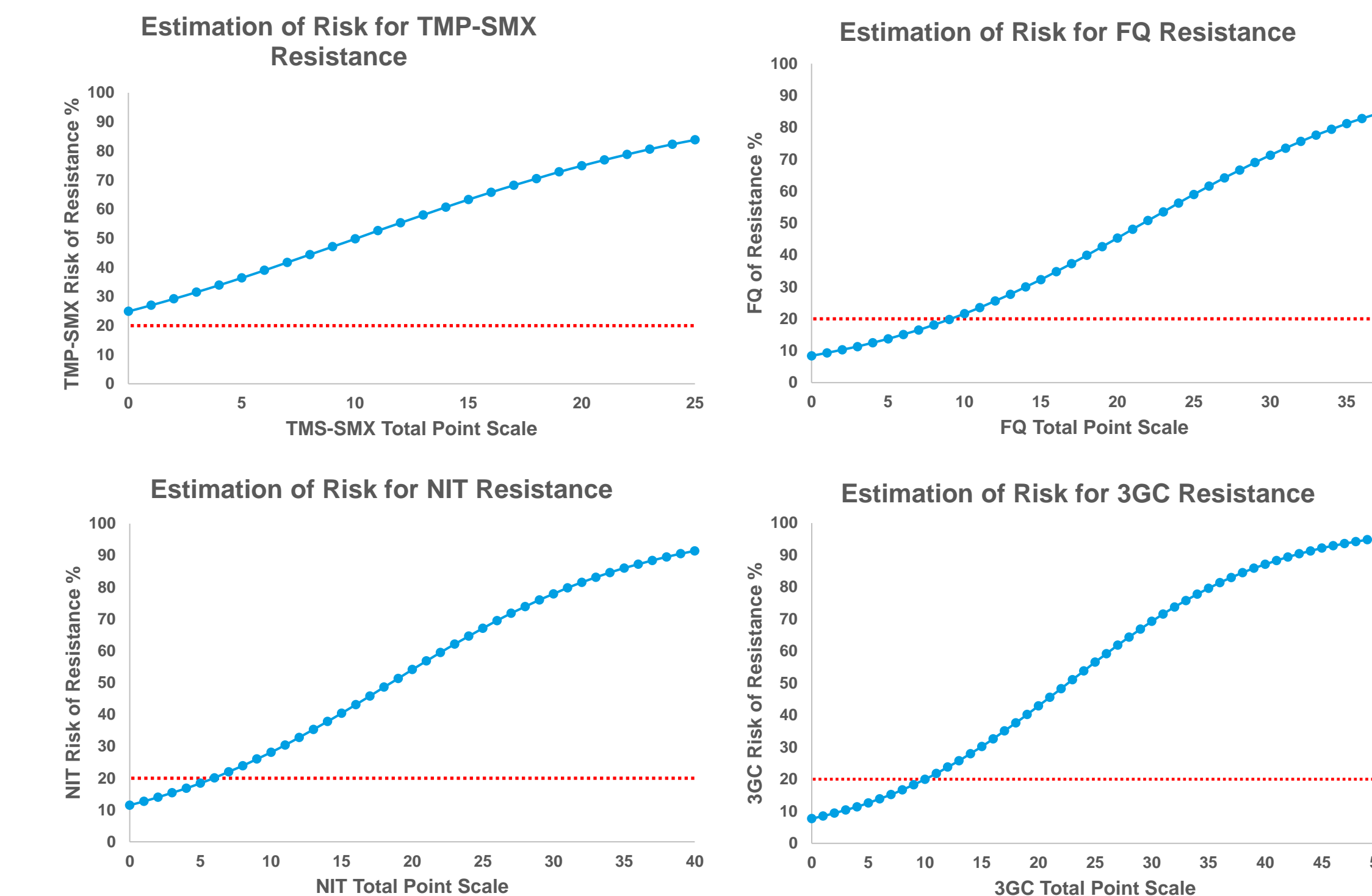
**Conclusions**

**We developed a high-performing parsimonious CRS to aid clinicians in appropriate treatment selection of adult OPs with cUTI.**

**This tool can be used to facilitate empiric antibiotic selection and ensure adult OPs with cUTI have a greater probability of receiving early appropriate therapy.**

**Given its high baseline resistance, TMP/SMX should not be considered for empiric therapy.**

**Figure 1. Predicted Risk of Resistance to TMP-SMX, FQ, NIT, and 3GC by Cumulative Point Scores**



Abbreviations: TMP-SMX = Trimethoprim-Sulfamethoxazole Resistance; FQ = Fluoroquinolone Resistance; NIT = Nitrofurantoin Resistance; 3GC = Third Generation Cephalosporins Resistance

**Table 1. Baseline Clinical Covariates and Associated Point Values in Each of the 4 Clinical Risk Scores**

	TMP-SMX		Fluroquinolone		Nitrofurantoin		3GC	
	OR (95% CI)	Points = $\beta_i(W_{ij} - W_{ref})/B^*$	OR (95% CI)	Points = $\beta_i(W_{ij} - W_{ref})/B^*$	OR (95% CI)	Points = $\beta_i(W_{ij} - W_{ref})/B^*$	OR (95% CI)	Points = $\beta_i(W_{ij} - W_{ref})/B^*$
Age ≥65					1.11 (1.06-1.17)	1	1.14 (1.09-1.19)	1
Male Sec	1.21 (1.14-1.29)	2	1.24 (1.15-1.34)	2	1.72 (1.59-1.86)	5	1.87 (1.72-2.03)	6
<i>Chronic Comorbidities in 12 months prior to index date</i>								
Peripheral Vascular Disease					1.11 (1.02-1.22)	1		
Dementia					1.46 (1.29-1.66)	4	1.49 (1.31-1.70)	4
Diabetes			1.30 (1.20-1.41)	2	1.10 (1.02-1.19)	1		
Renal Disease					1.09 (1.00-1.19)	1		
Chronic Pulmonary Disease							1.14 (1.05-1.25)	1
Urinary tract devices in 30 days prior to index date	1.16 (1.05-1.28)	1			1.60 (1.45-1.77)	4	1.53 (1.38-1.69)	4
<i>Cumulative number of antibiotic dispenses ≤ 90 days prior to index date</i>								
1	1.49 (1.37-1.62)	4	1.38 (1.23-1.53)	3	1.44 (1.31-1.58)	3	1.64 (1.47-1.82)	5
2-3	1.85 (1.68-2.03)	6	1.86 (1.67-2.07)	6	1.48 (1.33-1.63)	4	2.14 (1.93-2.39)	7
4+	2.56 (2.29-2.87)	9	2.97 (2.64-3.35)	10	1.56 (1.38-1.76)	4	3.66 (3.23-4.15)	12
Prior UTI in 12 months prior to index date	1.17 (1.09-1.26)	1	1.86 (1.69-2.04)	6	1.24 (1.14-1.35)	2	1.29 (1.18-1.41)	2
<i>Prior utilization in 12 months prior to index date</i>								
Hospitalizations	1.14 (1.05-1.23)	1			1.21 (1.11-1.33)	2	1.29 (1.18-1.42)	2
ED Visits	1.11 (1.04-1.19)	1			1.24 (1.14-1.34)	2	1.27 (1.17-1.38)	2
Recurrence			1.54 (1.40-1.70)	4	1.19 (1.08-1.31)	2	1.11 (1.00-1.23)	1
Long term care (nursing home/SNF) in 12 months prior to index date			1.61 (1.39-1.85)	4	1.48 (1.28-1.71)	4	1.25 (1.08-1.45)	2
Total possible points		25		37		40		49

TMP-SMX: Trimethoprim-Sulfamethoxazole, 3GC: Third-Generation Cephalosporins, OR: Odds Ratio, CI: confidence interval, UTI: Urinary Tract Infection, ED: Emergency Department, SNF: Skilled Nursing Facility

## Limitations

- Risk factors not readily available at presentation (prior colonization or prior infections with a resistant pathogen) were omitted and this may have affected the predictive performance of the CRSs.
- Use of NIT is limited to cUTIs that only involves the lower genitourinary tract and it may not be an appropriate agent for all cUTI OPs.
- Amoxicillin-clavulanate and Fosfomycin were not included given their limited use relative to the agents assessed.

This study was funded by Spero Therapeutics, Inc., Cambridge, MA, USA.