

# Identifying Cancer Patients at High Risk for Chemotherapy-Induced Nausea and Vomiting (CINV): The Development of a Prediction Tool

George Dranitsaris<sup>1</sup>, Alex Molasiotis<sup>2</sup>, Mark Clemons<sup>1</sup>, Eric Roeland<sup>3</sup>, Lee Schwartzberg<sup>4</sup>, David Warr<sup>5</sup>, Karin Jordan<sup>6</sup>, Pascale Dielenseger<sup>7</sup>, Matti Aapro<sup>8</sup>

<sup>1</sup>Ottawa Hospital Regional Cancer Centre, Ottawa, Canada; <sup>2</sup>Hong Kong Polytechnic University, Hong Kong; <sup>3</sup>University of California San Diego Moores Cancer Center, La Jolla, CA, USA; <sup>4</sup>The West Clinic, Memphis, TN, USA; <sup>5</sup>Princess Margaret Cancer Center, Toronto, Canada; <sup>6</sup>University of Halle, Halle, Germany; <sup>7</sup>Gustave Roussy Cancer Campus, Villejuif, France; <sup>8</sup> IMO Clinique de Genolier, Genolier, Switzerland

## BACKGROUND

- Classifying CINV risk by chemotherapy type and corresponding emetogenicity has provided a valuable framework for the development of international prophylactic antiemetic guidelines.<sup>1,2</sup>
- However, antiemetic guideline recommendations based solely on chemotherapy emetogenicity may potentially undertreat patients at higher individual emetic risk, as considerable work has revealed that a number of patient-related variables may also contribute to emetic risk.
- Between 20% to 40% of cancer patients receiving chemotherapy fail to achieve complete control of nausea and vomiting (N&V).
- Recent CINV risk models were developed by Dranitsaris et al<sup>3-5</sup> and Molasiotis et al<sup>6</sup> with the goal of prospectively identifying patient risk factors to support the establishment of personalized CINV management.
- Though valuable, each of these models was developed from a limited sample size. By combining this data, this current study utilizes the largest CINV dataset assembled outside of the clinical trial setting. It encompasses approximately 1200 patients with a variety of cancer types who received up to four cycles of chemotherapy.

## METHODS

### OBJECTIVE

- To identify risk factors associated with grade ≥ 2 CINV in cancer patients receiving outpatient anticancer therapy
- To develop a repeated measures prediction model for grade ≥ 2 CINV that will allow the identification of high-risk patients prior to each cycle of therapy
- To develop a numerical risk algorithm system that can be used for each patient for individualized risk assessment

## DATA SOURCES AND OUTCOMES

- Data was pooled from four non-interventional prospective studies conducted in Canada<sup>3,5,7,8</sup> and one study in the United Kingdom.<sup>6</sup>
- Adult patients with a variety of solid tumors scheduled to receive up to four cycles of chemotherapy of varying levels of emetogenicity (low to high) participated in these studies.
- All study participants completed a daily patient diary or utilized the MASCC Antiemesis Tool (MAT) each chemotherapy cycle, recording episodes of vomiting, severity of nausea, and use of non-prescription rescue antiemetics from time of chemotherapy initiation throughout the following 5 days.
- Patient demographic and baseline clinical characteristics were collected along with additional baseline data such as history of nausea/vomiting, expectation of CINV, pre-chemotherapy anxiety, and hours of sleep the night prior to chemotherapy.
- The dependent variable for the pooled database model was ≥ grade 2 CINV from the first day of chemotherapy through Day 5 according to the National Cancer Institute Common Toxicity Criteria (NCI CTC).<sup>9</sup>
  - Vomiting was defined as ≥ 3 episodes in 24 hours.
  - Nausea was defined as either oral intake decreased without significant weight loss, dehydration or malnutrition (based on NCI CTC) or at least mild nausea (based on a 4-point Likert scale).

## STATISTICAL ANALYSIS

- The databases were combined and predictor variables recoded to ensure consistency.
- To identify the set of factors with the largest potential contribution to presence of CINV, those with a p-value of 0.25 or less in a simple logistic regression were retained for further consideration.
- Generalized estimating equations (GEE) for a repeated measures analysis were then used to develop the final risk model using a backwards elimination process with a preset alpha at < 0.05.
- The goodness of fit of the final model was then assessed with the Hosmer-Lemeshow test.
- Model calibration was evaluated by estimating a smooth calibration line between the observed and predicted outcomes.

## REFERENCES

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- Internal validation of the final regression coefficients was done using nonparametric bootstrapping.
- A risk scoring algorithm was then derived from final model coefficients.
- The predictive accuracy of the risk algorithm system was determined via a receiver operator characteristic (ROC) curve analysis.

## RESULTS

- A total of 1198 patients receiving a total of 4197 cycles of chemotherapy were included in the analysis.

## PATIENT AND TREATMENT CHARACTERISTICS

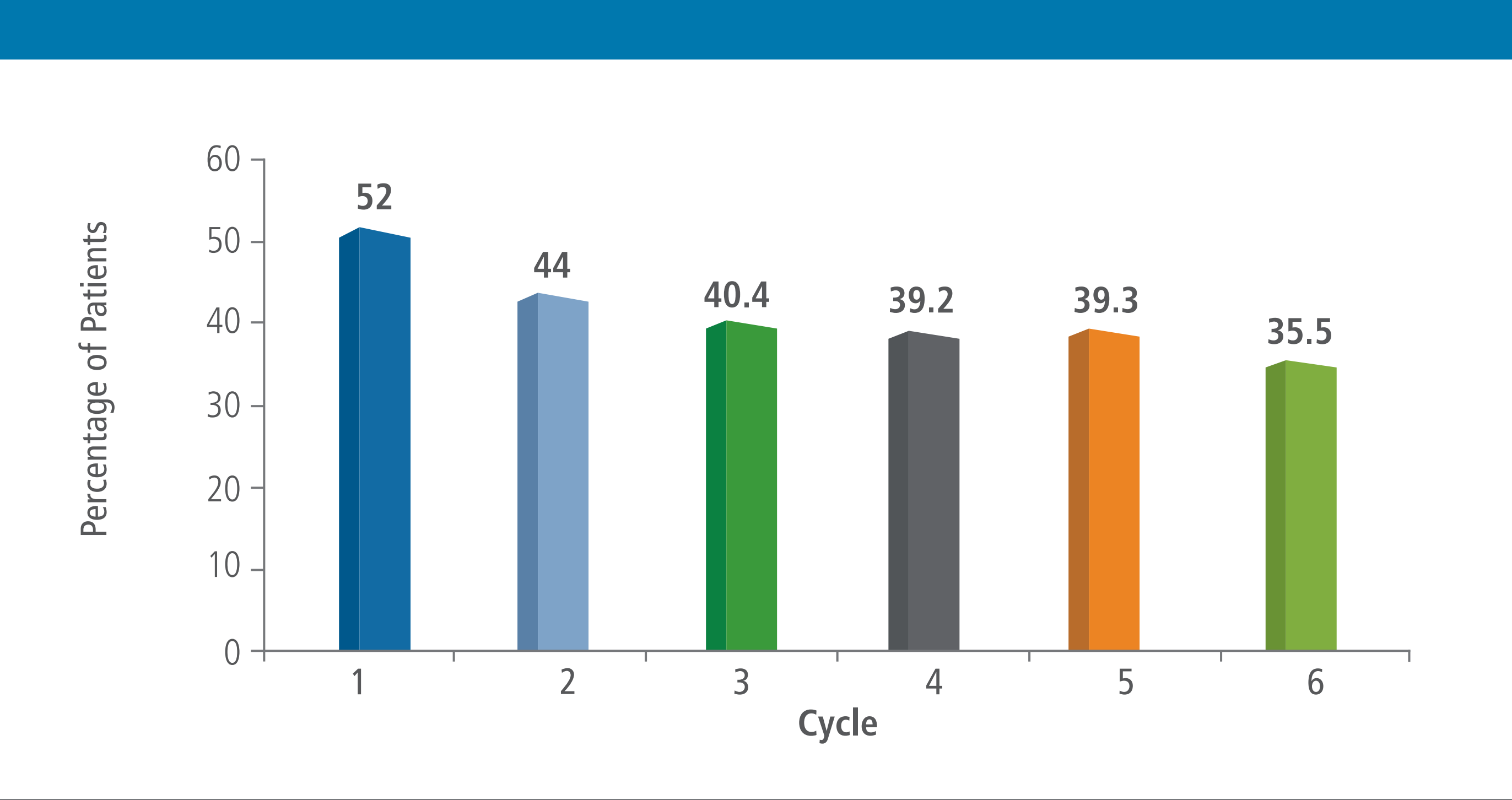
- Patient demographics, clinical characteristics, baseline experiences with potential to influence CINV risk, and chemotherapy/antiemetic specifics are shown in **Table 1**.
- Seventy-five percent of patients in this pooled dataset were females with a median age of 58 years; most had early stage disease with breast cancer being the predominant cancer type in about half of patients (**Table 1**).

Table 1. Patient and Treatment Characteristics from Pooled CINV Studies	
Patient Characteristic	Total Number of Patients = 1198 % of patients (no. of patients)
Female gender	74.6% (894)
Median patient age (range)	58 (19 -100)
<b>Type of cancer</b>	
Breast	55.5% (665)
Gastrointestinal	14.4% (172)
Genitourinary	1.8% (21)
Gynecological	5.7% (68)
Lung	8.1% (97)
Other	13.2% (158)
Missing	1.4% (17)
Early stage (vs. metastatic)	73.4% (879)
History of motion sickness	26.7% (320)
History of morning sickness during a pregnancy	37.5% (449)
Daily alcohol intake	24.5% (294)
Patient/Treatment Characteristic	Total Number of Cycles = 4197 % of cycles (no. of cycles)
<b>Median number of cycles (range)</b>	2 (1 to 11)
<b>Anticipatory nausea and vomiting</b>	27.9% (1174)
<b>Sleep the night before chemotherapy</b>	
Less than 5 hours	12.8% (538)
Five to seven hours	56.0% (2351)
Eight to nine hours	26.8% (1125)
Ten hours or more	2.9% (123)
Missing	1.4% (60)
<b>Anxiety before chemotherapy</b>	
None	29.5% (1237)
Mild	21.8% (916)
Moderate	18.1% (760)
High	4.9% (205)
Missing	25.7% (1079)
<b>Type of Chemotherapy</b>	
Platinum-based	27.4% (1151)
Anthracycline-based	52.8% (2217)
Single agent taxanes	7.4% (310)
Other	12.4% (519)

## CINV OUTCOMES DATA

- Considering all cycles, more than half of patients (61.1%) experienced either nausea and/or vomiting during the 5 days following chemotherapy, with 42.2% of patients with ≥ grade 2 CINV.
- **Figure 1** show the proportions of patients experiencing ≥ grade 2 CINV by cycle.

Figure 1. Prevalence of CINV (0-120 h) by Cycle of Chemotherapy



## ASSESSMENT OF CINV RISK FACTORS

- A number of variables were shown to have a significant association with CINV (**Table 2**).

Table 2. Predictive Factors for Nausea and Vomiting from Day 0 to Day 5

Predictive Factor <sup>1</sup>	Odds Ratio <sup>2</sup>	Impact on Risk
Age less than 60	1.41	↑ by 41%
Patient expects to develop CINV	1.41	↑ by 41%
Sleep less than 7 hours	1.34	↑ by 34%
History of morning sickness	1.30	↑ by 30%
Platinum- or anthracycline-based chemotherapy	1.94	↑ by 94%
N or V in prior cycle	5.17	↑ by 5.17 times
Use of non-prescribed antiemetics at home	2.70	↑ by 2.7 times
<b>Cycle number (vs. cycle 1)</b>		
Cycle 2	0.17	↓ by 83%
≥ Cycle 3	0.15	↓ by 85%

Dependent variable: ≥ grade 2 CINV from day 0 to 5

<sup>1</sup>These variables were retained in the final model using a backwards elimination process with p < 0.05 as the cut off to retain.  
<sup>2</sup>An odds ratio of less than one means lower risk and greater than one means increased risk.

## RISK PREDICTION ALGORITHM

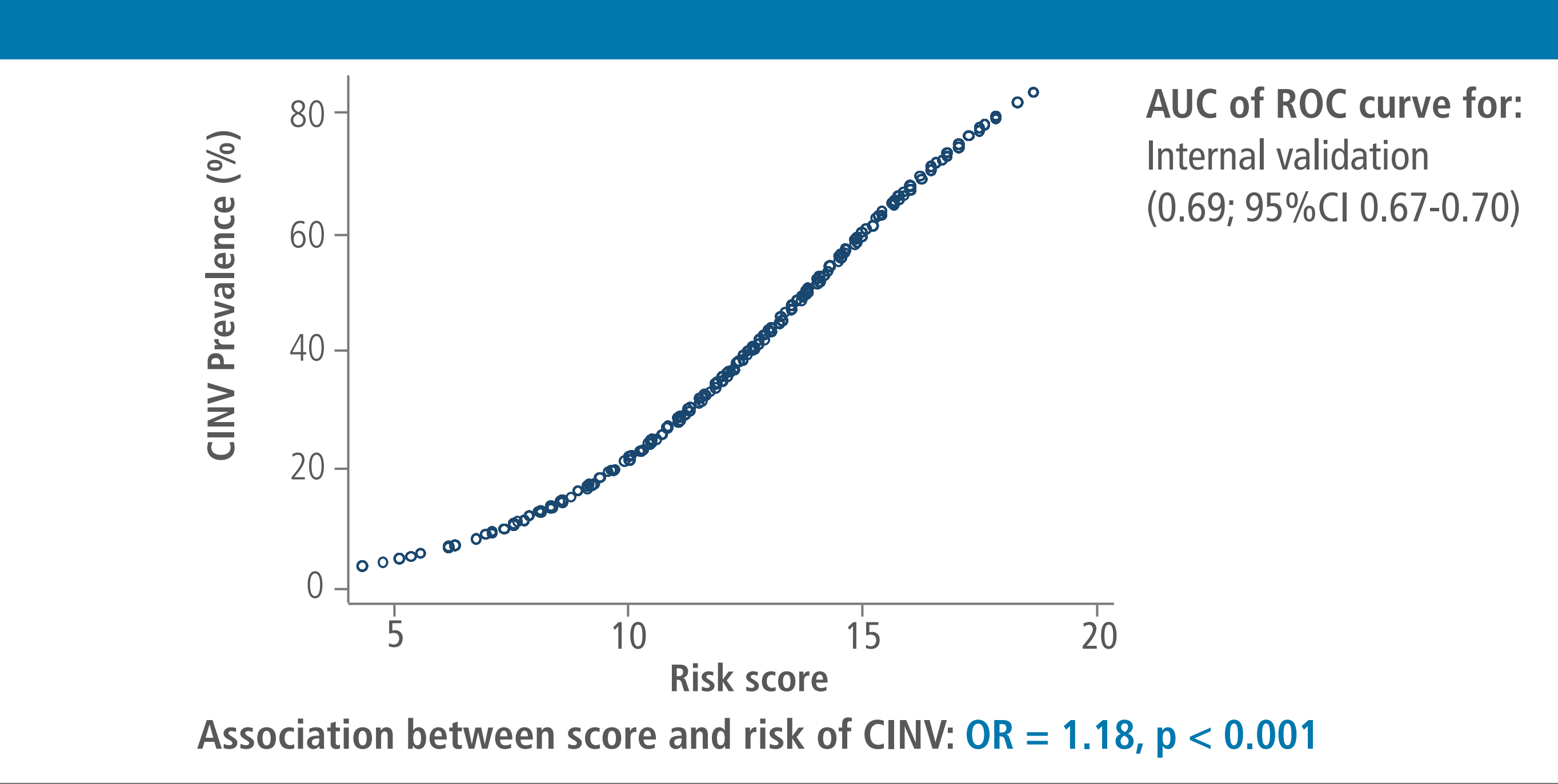
- A risk scoring algorithm was derived from the final model coefficients (**Table 3**).

Table 3. CINV Prediction Tool

	Start at base score of 10	
Patient age	If patient age < 60	+1
Expectation	If patient expects to have CINV	+1
Sleep	If patient slept < 7 hours the night before chemotherapy	+1
Morning sickness	If patient has a history of morning sickness	+1
Chemotherapy	If patient is about to receive platinum or anthracycline chemotherapy	+2
Prior CINV	If patient had nausea or vomiting in the prior cycle	+5
Antiemetic use at home	If non-prescription antiemetics are used at home	+3
Cycle	If 2 <sup>nd</sup> cycle of chemotherapy	-5
	If ≥ 3 <sup>rd</sup> cycle	-6

- The ROC analysis indicated good predictive accuracy with an area under the curve of 0.71 (95% CI: 0.69 – 0.73) (**Figure 2**).

Figure 2. Percent risk of CINV vs risk score



- Patients with a total score ≥ 16 would be considered at high risk of CINV (**Table 4**).

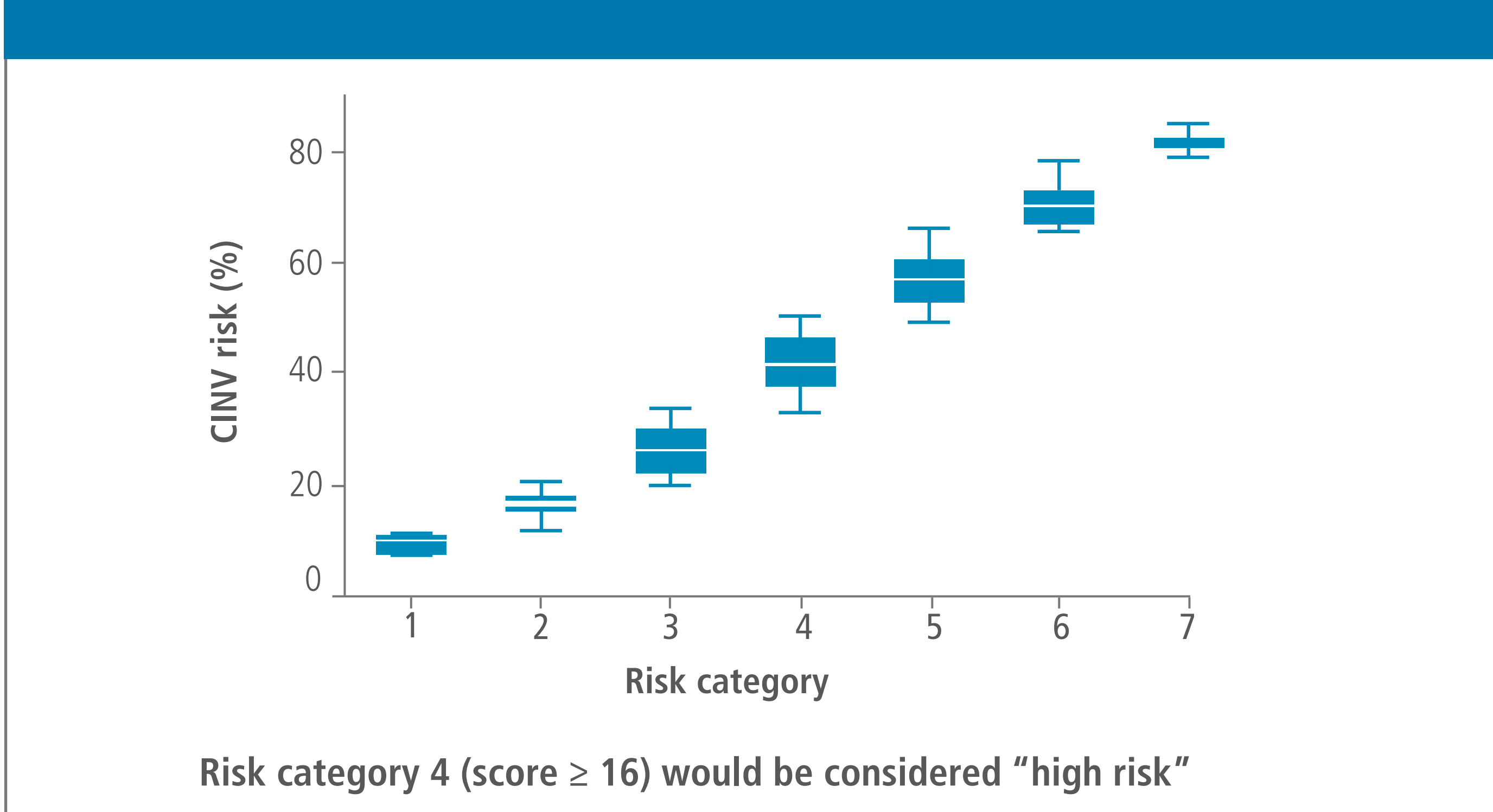
Table 4. Accuracy of the Prediction Model

Score cut point	CINV incidence*	Sensitivity	Specificity	Likelihood ratio
< 8	12.5%	100%	0%	1.0
≥ 8 to < 12	13.6%	99.8%	1.2%	1.01
≥ 12 to < 16	23.1%	97.9%	10.7%	1.10
≥ 16 to < 20	43.7%	87.4%	38.4%	1.42
≥ 20 to < 24	57.6%	51.2%	75.7%	2.11
≥ 24 to < 28	72.8%	18.8%	94.8%	3.60
≥ 28	87.9%	2.1%	99.8%	9.08

\*As observed in the patient sample.

- Moving from one scoring category to another increases CINV risk by 80% (OR = 1.80; p < 0.001) (**Figure 3**).

Figure 3. Percent Risk of CINV vs Risk Category Score



- To maximize model sensitivity, patients with CINV probability ≥ 43.7% would be considered "high risk".
  - Therefore, a patient receiving a low emetogenic (LEC) regimen would be reclassified as moderately emetogenic (MEC) if their calculated CINV probability were ≥ 43.7%.
  - Similarly, a patient receiving a MEC regimen would be reclassified as highly emetogenic (HEC) if their calculated CINV probability were ≥ 43.7%.
- Limitations of the prediction tool include:
  - The ROC analysis suggested that there is additional room to improve the accuracy of the prediction tool.
  - Only readily measurable variables were considered by the model; hence, not all the variability was accounted for (eg pharmaco-economic factors).
  - The models do not replace clinical judgement but provide additional information to support medical decision-making.

## CONCLUSIONS

- This robust pooled database evaluated risk factors associated with the development of CINV in approximately 1200 patients receiving almost 4200 cycles of chemotherapy.
- Aside from chemotherapy emetogenicity, a number of patient-related risk factors were shown to be strongly predictive of CINV following chemotherapy.
- There exists a need for greater awareness of the role that patient-related factors may play in increasing emetic risk, apart from type of chemotherapy. This may be particularly relevant in the moderately emetogenic (MEC) setting which encompasses a broad range of chemotherapies known to elicit emesis in 30%-90% of patients.
- A CINV risk assessment tool has been developed based on this study to assist physicians in comprehensively assessing patients' risk of developing CINV (this will be available soon at [www.cinvrisk.org](http://www.cinvrisk.org)).
- The clinical application of this risk assessment prediction tool should enhance patient care by optimizing the use of the antiemetics in a proactive manner.

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If questions, please contact George Dranitsaris at [george.dranitsaris@gmail.com](mailto:george.dranitsaris@gmail.com)

