

THE PRODIGY STUDY FREQUENTLY ASKED QUESTIONS

Medtronic

1. What is the PRODIGY Study?

PRODIGY (**P**rediction of **O**pioid-induced respiratory **D**epression **I**n patients monitored by capno**G**raph**Y**)¹ is a Medtronic-sponsored, prospective, multicenter, international cohort study. The study identifies patients at risk of opioid-induced respiratory depression (OIRD), a potentially life-threatening form of respiratory compromise (RC). Until now, no standardized tool has been available to assess risk of developing respiratory depression (RD), a form of RC. The easy-to-use PRODIGY Risk Prediction Tool is important because it serves as a guide to identify which patients would benefit most from continuous monitoring.¹

2. Why is PRODIGY important?

RC may occur when a combination of risk factors leads to decompensation into respiratory insufficiency, respiratory failure/arrest, and potentially death. "Enhanced monitoring enabling early identification and intervention might prevent or mitigate decompensation."²

3. What risk variables were assessed?

46 potential risk factors were assessed and five were found to be most predictive for development of respiratory compromise. The primary risk variables assessed for prediction of RC include³:

- Age ≥ 60 by decade
- Sex
- Opioid naivety
- Sleep disordered breathing
- Chronic heart failure

4. What are the key findings of the PRODIGY study?

- Respiratory depression episodes (RDEs) were detected in 46 percent of the 1,335 general care floor (GCF) patients continuously monitored for a median 24 hours.³
- Patients with ≥1 RDEs were more likely to experience an adverse event (AE) that required action.³
 - Relative risk (RR) of 1.36 for AE requiring prolonged hospitalization³
 - RR of 2.46 for AE requiring rescue, including rapid response team activation³
- Mean hospital length of stay was three days longer in patients with ≥1 RDE.³
- The average hospital cost for U.S. patients with 1 or more RDEs was significantly higher (\$4,446 on average) and the mean cost for "high-risk" scored patients with 1 or more RDEs was \$6,448 higher than for "high-risk" patients without RDEs.⁴

5. How were patients monitored and what were the endpoints?

Patients were monitored using Microstream™ and Nellcor™ monitoring technology, with displays blinded and alarms silenced throughout the monitoring period. This technology provided data on etCO₂, respiratory rate, and SpO₂, along with the Integrated Pulmonary Index™ (IPI) algorithm, and was used to help identify patients experiencing respiratory depression. Endpoints include monitor confirmed RC (i.e., etCO₂ ≤ 15 or ≥ 60 mmHg for ≥ 3 continuous minutes, SpO₂ ≤ 85 percent for ≥ 3 continuous minutes, RR ≤ 5 breaths per minute for ≥ 3 continuous minutes, or an apnea episode lasting > 30 seconds) or any Respiratory Opioid Related Adverse Drug Event (rORADE).

6. What is the PRODIGY Risk Prediction Tool and how can the scores be used to risk-stratify patients?

The PRODIGY study found a 46 percent incidence of respiratory depression in patients on the GCF receiving parenteral opioids. A novel respiratory depression Risk Prediction Tool was developed. This tool includes five patient variables: age ≥ 60 by decade, sex, opioid naivety, sleep disorders, and chronic heart failure.³ Each of these variables is given a point value as noted in the chart below. The PRODIGY Risk Score distribution is divided into three terciles: low risk (< 8 points), intermediate risk (≥8 to < 15 points), and high risk (≥15 points).³ For example, a 75-year-old male (12 points for age, 8 points for male) with a history of chronic heart failure (7 points) would receive a score of 27. This patient would be in the high-risk category.

Risk Factors	Scoring Criteria	Points	Score
Patient Age (years)	Age < 60	= 0 pts	
	Age 60–69	= 8 pts	
	Age 70–79	= 12 pts	
	Age ≥ 80	= 16 pts	
Sex	Male	= 8 pts	
	Female	= 0 pts	
Previous Opioid Use	Opioid naïve	= 3 pts	
	Previous opioid use	= 0 pts	
Sleep Disordered Breathing (SDB)	Known SDB or high STOP-BANG score	= 5 pts	
	No SDB or normal STOP-BANG score	= 0 pts	
Chronic Heart Failure (CHF)	Coexisting CHF	= 7 pts	
	No known CHF	= 0 pts	
Total PRODIGY Risk Score			0

PRODIGY Risk Level

- ☐ Low risk of respiratory depression episodes for less than 8 pts
- ☐ Intermediate risk of respiratory depression episodes for 8–14 pts
- ☐ High risk of respiratory depression episodes for 15 pts or higher

7. What patient populations were studied?

Consenting adult patients receiving parenteral opioid therapy (postop or medical) for pain on the hospital surgical and medical GCF were studied. The analysis set included 1,335 patients who received parenteral opioid therapy on the GCF and in whom blinded continuous monitoring was initiated. Monitoring and medical record data was collected from these patients in 16 centers internationally, including 9 centers in the United States, 4 in Europe, and 3 in Asia. This makes PRODIGY one of the

largest studies using continuous capnography and oximetry for monitoring patients receiving opioids on the hospital GCF.

8. What is the potential economic impact for a hospital using the PRODIGY Risk Prediction Tool?

PRODIGY results show that patients with one or more RDE had a mean hospital length of stay that was three days longer compared to patients without RDEs.³ The average hospital cost for U.S. patients with one or more RDE was significantly higher (\$4,446 on average) and the mean cost for “high-risk” patients with one or more RDE was \$6,448 higher than for “high-risk” patients without any RDE.⁴

9. How is the PRODIGY study different from previous studies of this kind?

Based on our own literature review, the PRODIGY study is innovative and groundbreaking in several ways:

- PRODIGY was the largest known study of its kind that analyzed the use of continuous monitoring of capnography and oximetry on 1,335 patients.
- It was a prospective, multicenter (16), international (7 countries) study across academic and private hospitals using top investigators from around the world. This allowed comparison of data from different patient demographics and practice standards.
- PRODIGY was the first study to look at opioid-induced respiratory depression across surgical and medical patients.
- PRODIGY was the first study to derive a validated Risk Prediction Tool specific to opioid-induced respiratory depression based on such extensive monitoring data.
- PRODIGY used a very stringent and novel multi-level adjudication process to ensure monitoring-indicated RC was accurate and not artifactual:
 - Very strict thresholds were set for defining RC, broader than many previous studies.
 - Abnormalities in etCO₂, RR, and SpO₂ must be present for three continuous minutes to be considered a respiratory depression episode (RDE). Artifactual readings generally are short deviations due to patient movement or sensor misplacement.
 - RDEs for each patient were reviewed by a four-physician clinical events committee to confirm accuracy and authenticity.

10. What is the benefit to clinicians of a validated Risk Prediction Tool? Can it be easily integrated into existing practice?

PRODIGY has many potential benefits for clinicians, including the Risk Prediction Tool. With an easy calculation, nurses can identify which patients are at increased risk of developing opioid-induced RDEs and thus most likely to benefit from continuous monitoring when continuous monitoring is not available to all patients.

REFERENCES

1. Medtronic. Prediction of opioid-induced respiratory depression in patients monitored by capnography (PRODIGY). Available from: <https://clinicaltrials.gov/ct2/show/NCT02811302>. ClinicalTrials.gov Identifier: NCT02811302.
2. Morris TA, Gay PC, MacIntyre NR, et al. Respiratory Compromise as a New Paradigm for the Care of Vulnerable Hospitalized Patients. *Respir Care*. 2017;62(4):497–512.
3. Khanna AK, Bergese S, Jungquist CR, et al. Prediction of opioid-induced respiratory depression on inpatient wards using continuous capnography and oximetry: an international prospective, observational trial. *Anesth Analg*. In press 2020.
4. Saager L, Jiang W, Khanna A, et al. Respiratory depression on general care floors increases cost of care: results from the PRODIGY trial. American Society of Anesthesiologists Abstract Publication 2019.