



# PAC-PAIN: Application of the Praxis Analysis of Concordance Framework for Establishing the Predictive Validity of Preclinical Pain Models

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## BACKGROUND

- Pain is a prevalent and often debilitating condition that remains inadequately controlled for many patients, underscoring the urgent need for improved treatments.
- Novel options should provide effective relief with improved safety and tolerability.
- Central to the discovery of new treatments is the assessment of analgesic activity in preclinical pain models. However, the predictive validity of current models across the spectrum of pain indications is less clear.
- The Praxis Analysis of Concordance (PAC) framework was originally developed to assess the translational concordance of common preclinical seizure models for focal and generalized onset seizures, and more recently for broad developmental and epileptic encephalopathies (Poster 11-002).
- Here, we build on the PAC framework to establish the translational concordance between preclinical pain models and clinical efficacy, presenting preliminary findings for acute post-operative pain (PAC-APOP).

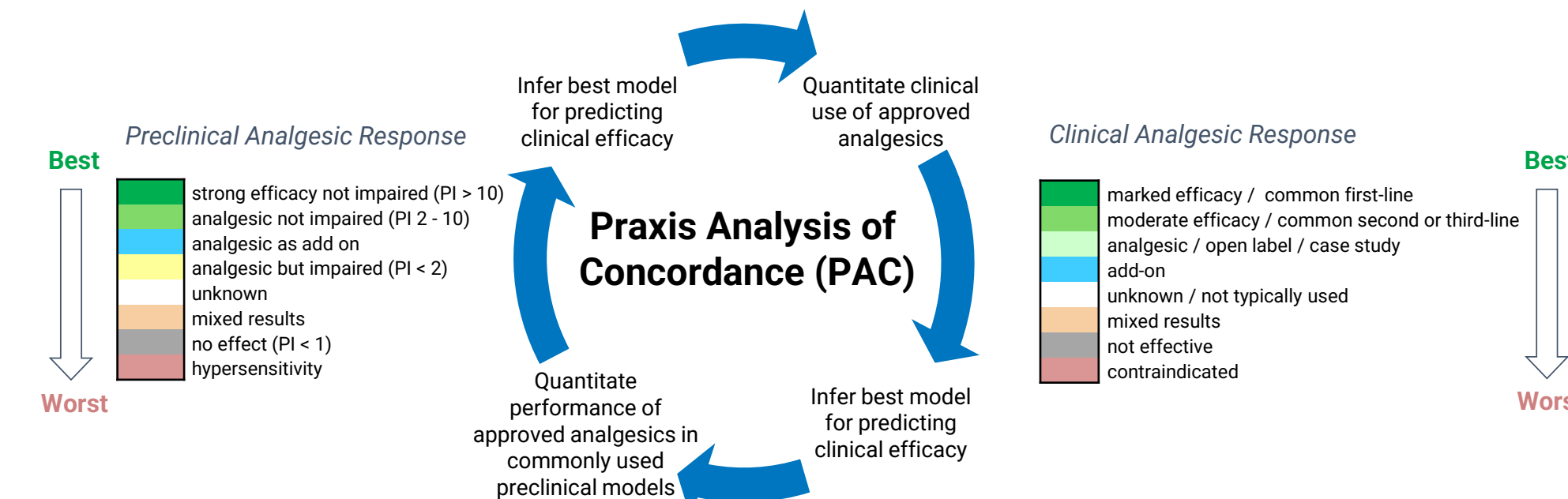
## METHODS

### Praxis Analysis of Concordance

- The PAC framework was implemented to assess the translational concordance between preclinical and clinical analgesic response for 58 FDA-approved drugs, including anesthetics, antiepileptic medications (ASMs), opioids, NSAIDs, opioids and antidepressants.
- Preclinical analgesic responses in pain models that have been used historically and have been established by the National Institutes of Health (NIH) HEAL Initiative were collected from searches performed in PubMed, NIH Preclinical Screening Platform for Pain and ETSP PANACHE databases.
- Clinical analgesic responses were collected based on searches performed in PubMed and FDA-Approved Drugs database.

### Translational Concordance Scoring

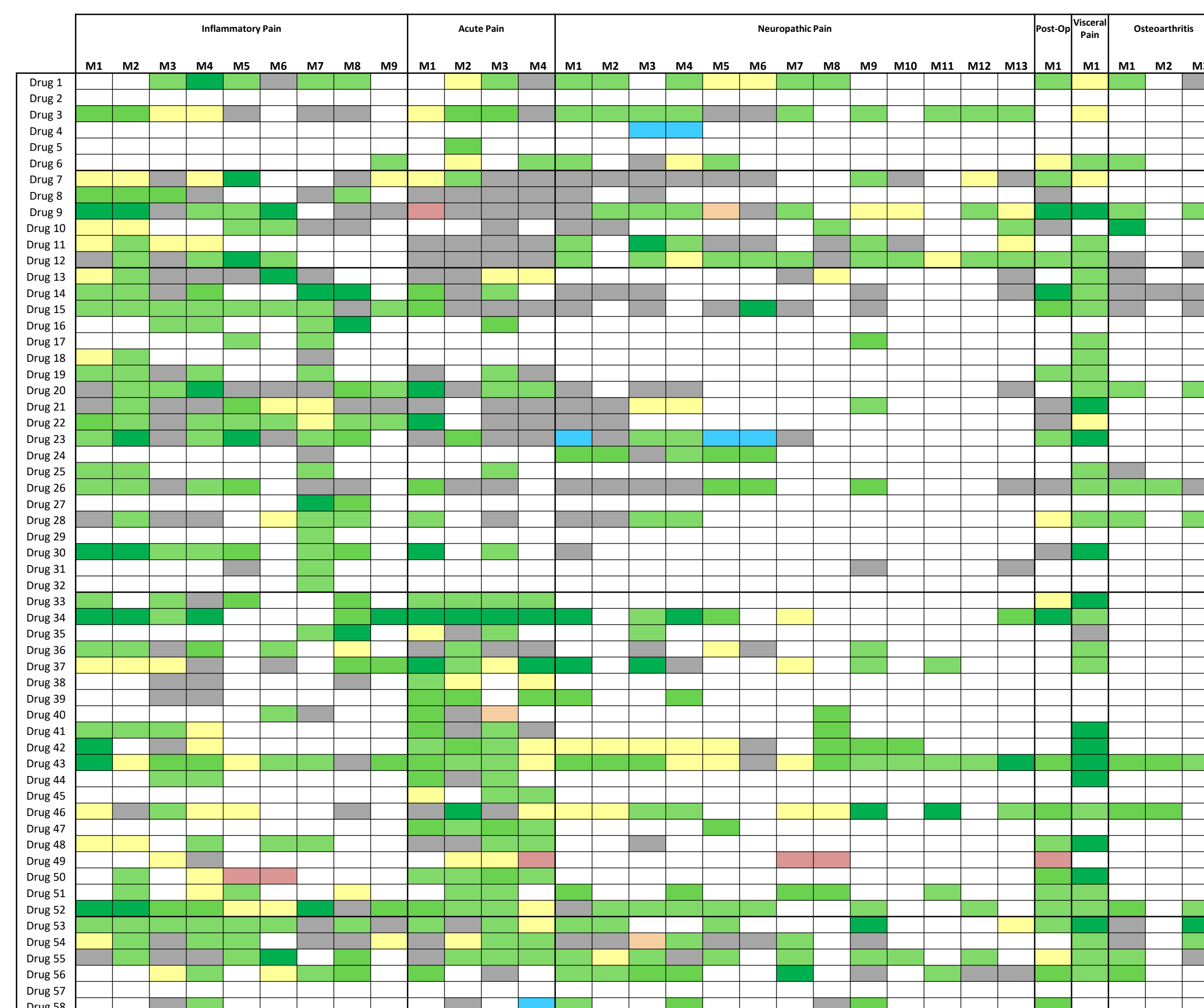
- In order to assess and compare the predictive validity of preclinical models, a unified scoring matrix was developed to assign a translational score that captured the spectrum of complete discordance (-1) to complete concordance (1) between preclinical and clinical analgesic responses for each preclinical pain model and clinical indication combination.
- Scores were then summed and normalized to generate a global translational concordance score.



**PAC-PAIN Analysis Framework.** An overview of the PAC-PAIN analysis framework. Performance of approved analgesics, including opioids, NSAIDs, antiepileptic medications and antidepressants in established pain models was evaluated based on reported TD<sub>50</sub> and ED<sub>50</sub> values, with preclinical analgesic response for each model graded according to a weighted scale. Clinical use and perceived efficacy of approved analgesics were similarly evaluated based on established reports, with clinical analgesic response for each procedure graded according to a weighted scale.

## ASSESSING TRANSLATIONAL CONCORDANCE BETWEEN PRECLINICAL AND CLINICAL RESPONSES TO DEFINE THE PREDICTIVE VALIDITY OF PAIN MODELS

### Preclinical Analgesic Response



**Preclinical Analgesic Response.** Preclinical efficacy of 58 FDA-approved drugs was examined in established pain models across multiple species. Where model/species data were unavailable, the next best representative data were used. Colors denote grading of preclinical analgesic response based on reported TD<sub>50</sub> and ED<sub>50</sub> values for each model, resulting in a weighted scale capturing relative preclinical analgesic effect. M=model number evaluated

**A**

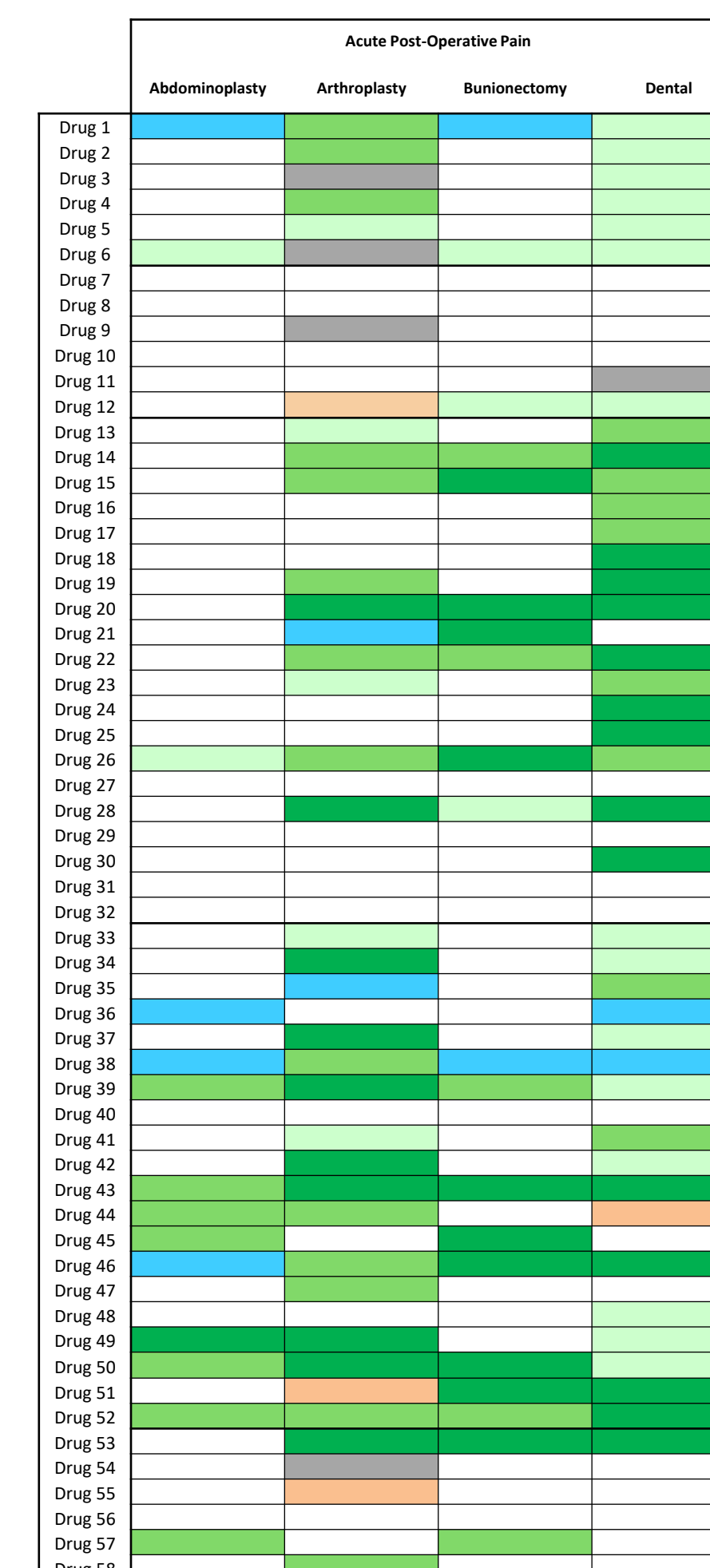
Clinical Analgesic Response	Preclinical Analgesic Response							
	1	1	0.75	0.25	na	-0.25	-0.5	-1
1	1	1	0.5	na	0.25	-0.5	-1	-1
0.75	1	1	1	na	0.5	-0.25	-1	-1
0.25	0.25	0.5	1	na	na	na	na	na
-0.25	-0.25	0.5	1	na	1	0.5	-0.25	-0.25
-0.5	-0.5	-0.25	0.75	na	0.5	1	-0.5	-0.5
-1	-1	-1	-0.25	na	-0.25	-0.5	1	1

**B**

Translational Concordance	
0.75 - 1	0.75 - 1
0.50 - 0.74	0.25 - 0.49
0 - 0.24	0 - 0.24
-1 - 0	-1 - 0

**Translational Concordance Scoring.** A) A unified scoring matrix was developed to assign translational concordance between preclinical and clinical analgesic response. Values ranged from 1 for complete concordance to -1 for complete discordance. B) For each preclinical pain model and clinical indication combination, individual analgesic concordance scores were first calculated, then summed and normalized (total translational concordance score/ total number of analgesics with data available) to generate a global translational concordance score, weighted from highest (0.75 to 1) to lowest (-1 to 0) concordance.

### Clinical Analgesic Response

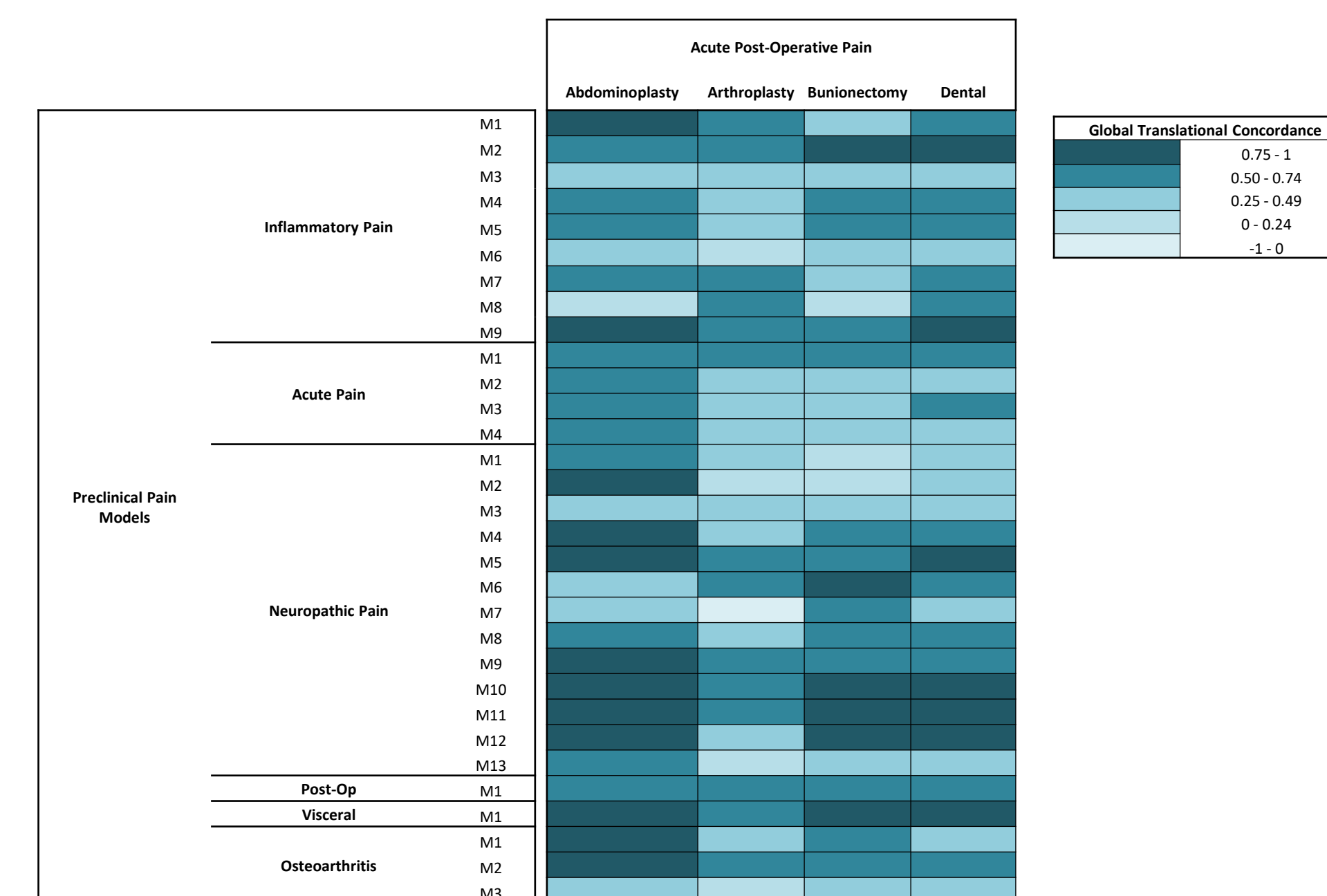


**Clinical Analgesic Response.** Clinical efficacy of the approved analgesics in acute post-operative pain was evaluated based on established reports of perceived efficacy and use. Colors denote grading of clinical analgesic response based on prescribing patterns resulting in a weighted scale capturing relative clinical analgesic effect.

## PAC-PAIN FRAMEWORK IDENTIFIES DIFFERENTIAL TRANSLATIONAL CONCORDANCE BETWEEN PRECLINICAL MODELS AND PAIN INDICATIONS

### PAC-PAIN Translational Concordance

- PAC-APOP findings utilizing the PAC-PAIN framework revealed variable concordance of preclinical models to clinical acute post-operative pain.
- High translational concordance for acute post-operative pain spanned across commonly used preclinical models, with the highest translational predictiveness observed across inflammatory, neuropathic and visceral pain models.



**PAC-APOP Translational Concordance.** Global translational concordance of each evaluated preclinical pain model across acute post-operative pain indications. Teal shading corresponds to weighted scale from highest (0.75 to 1) to lowest (-1 to 0) concordance scores. M=model number evaluated

## CONCLUSIONS

- The PAC-PAIN framework provides a systematic evaluation of the predictive validity of commonly used preclinical pain models.
- Preliminary PAC-APOP findings highlight heterogeneity in translational predictiveness across preclinical models for acute post-operative pain.
- Expansion of the PAC framework to additional pain indications is anticipated to accelerate research efforts and promote efficient utilization of resources for novel analgesic drug discovery.

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