PAC-DEE: An Extension of the Praxis Analysis of Concordance Framework for Establishing the Predictive Validity of Preclinical Seizure Models across Broad Developmental and Epileptic Encephalopathies

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Background

- Developmental and epileptic encephalopathies (DEEs) are devastating neurological disorders presenting in infancy and early childhood, often characterized by severe, frequent seizures, behavioral comorbidities and increased early mortality.
- Treatment options are sub-optimal, often associated with safety and tolerability issues, with many patients refractory to current standard of care.
- Central to the development of novel treatments is testing of antiseizure activity in preclinical seizure models. While various models exist, the predictive validity of each across the spectrum of epilepsy indications, including broad DEEs, is less clear.
- The Praxis Analysis of Concordance (PAC) framework was recently developed to assess the translational concordance of common preclinical seizure models for focal onset seizures (FOS) and generalized epilepsies.

➢ *Here, we sought to establish concordance between traditional preclinical seizure models, genetic epilepsy models and broad DEEs, thus further extending our work to capture pediatric DEEs and neurogenetic syndromes*

Methods

Praxis Analysis of Concordance

- The PAC framework was implemented to assess the translational concordance between *preclinical* and *clinical ASM response* across DEEs and neurogenetic syndromes for 32 FDA-approved ASMs that are available in the United States.
- *Preclinical ASM responses* in seizure models that have been used historically and that have been established by the Epilepsy Therapy Screening Program (ETSP) were collected from searches performed in PubMed and the ETSP PANAChE database. *Preclinical ASM responses* in genetic epilepsy models were similarly collected.
- *Clinical ASM responses* were collected based on searches performed in PubMed, American Epilepsy Society, Epilepsy Foundation and National Institute for Health Care and Excellence websites.

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 ASM responses* for each preclinical seizure/genetic epilepsy model and clinical indication combination.
- Scores were then summed and normalized to generate a *global translational concordance score.*

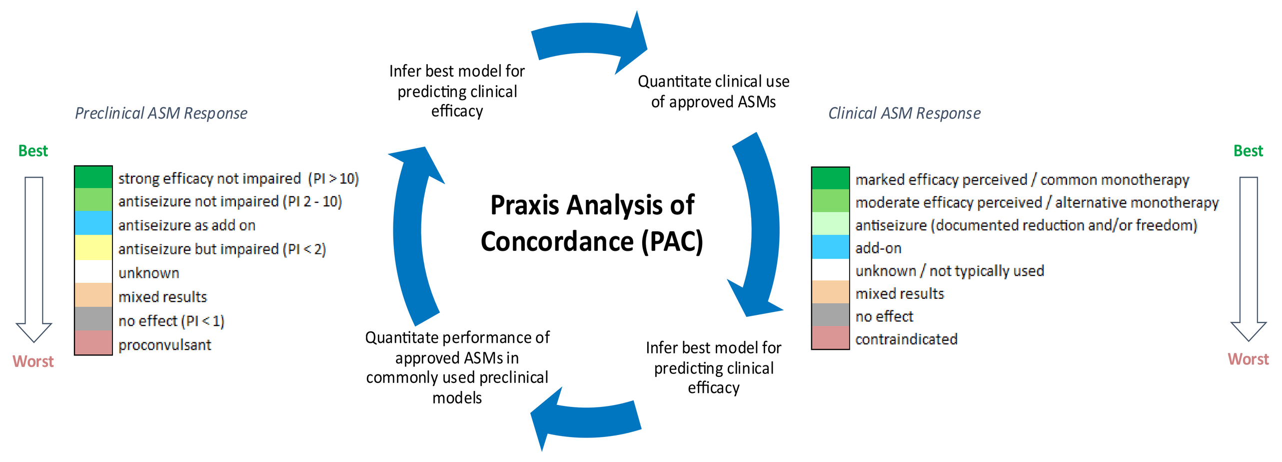

Figure 1. PAC Analysis Framework. An overview of the PAC analysis framework. Performance of approved ASMs in traditional seizure models as well as genetic epilepsy models was evaluated based on reported TD_{50} and ED_{50} values, with *preclinical ASM response* for each model graded according to a weighted scale. Clinical use of approved ASMs was similarly evaluated based on established reports, with *clinical ASM response* for each indication graded according to a weighted scale.

PAC-DEE Identifies Superior Translational Concordance Between Genetic Epilepsy Models and Broad DEEs

- Findings from our PAC-DEE framework revealed variable levels of concordance between commonly used preclinical seizure models and the broad spectrum of DEEs.
- While certain traditional preclinical seizure models exhibit predictive validity for specific DEEs, in general, genetic models demonstrate greater concordance than preclinical seizure models with DEEs and neurogenetic syndromes, albeit with limited data depth (**Fig. 5**).

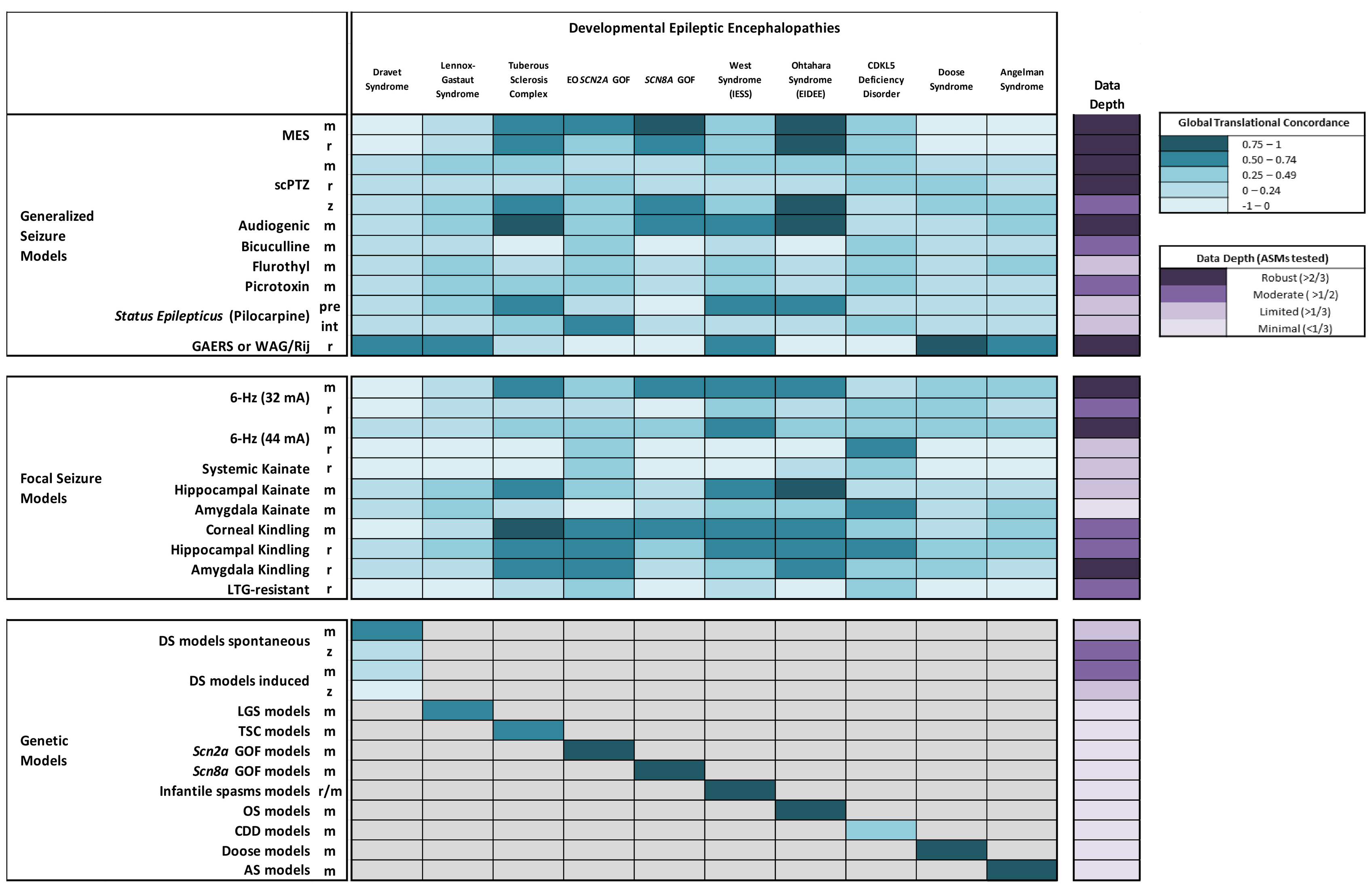

Figure 5. Translational Concordance for Genetic Epilepsies. Global translational concordance of each preclinical model (traditional seizure models and genetic epilepsy models) across DEEs and neurogenetic syndromes. Teal shading corresponds to weighted scale from highest (0.75 to 1) to lowest (-1 to 0) concordance scores. Data depth (purple shading) was similarly scored on a weighted scale from robust to minimal, based on the number of ASMs that have been tested in each model. AS=Angelman Syndrome; CDD=CDKL5 Deficiency Disorder; DS=Dravet Syndrome; EIDEE=Early Infantile Developmental and Epileptic Encephalopathy; EO=early onset; GOF=gain of function; IESS=Infantile Epileptic Spasms Syndrome; LGS=Lennox-Gastaux Syndrome; OS=Ohtahara Syndrome

Assessing Translational Concordance Between Preclinical and Clinical Responses to Define the Predictive Validity of Traditional Preclinical Models and Genetic Epilepsy Models

Preclinical ASM Response – Traditional Seizure Models

- We previously reported the predictive performance of 32 FDA-approved ASMs across traditional seizure models
  - Sodium channel blockers tend to perform best in maximal electroshock seizure (MES), have mixed effects in subcutaneous pentylenetetrazole (scPTZ) and are less efficacious (or efficacious at impairing doses) in 6-Hz.
  - GABAergics and modulators of SV2A (synaptic vesicle protein 2A) tend to perform best in 6-Hz, with less efficacy in MES.
  - Most ASMs show efficacy in the audiogenic seizure model, with a wide range of PI values.

Preclinical ASM Response – Genetic Epilepsy Models

- We further sought to evaluate the predictive performance of these ASMs across models of genetic epilepsies relevant to broad DEEs and neurogenetic syndromes to examine whether these models improve translational concordance with clinical responses (**Fig. 2**).

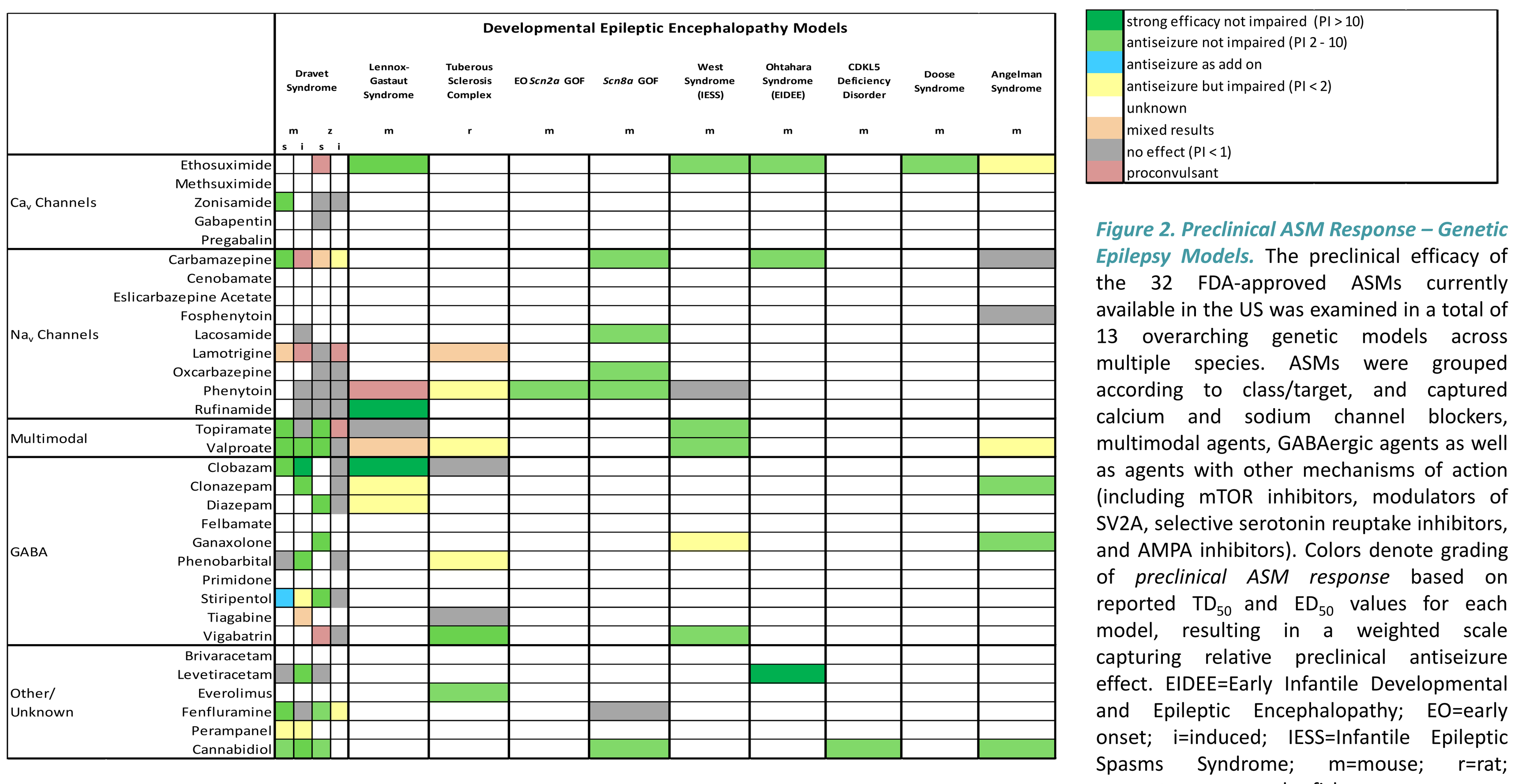

Figure 2. Preclinical ASM Response – Genetic Epilepsy Models. The preclinical efficacy of the 32 FDA-approved ASMs currently available in the US was examined in a total of 13 overarching genetic models across multiple species. ASMs were grouped according to class/target, and captured calcium and sodium channel blockers, multimodal agents, GABAergic agents as well as agents with other mechanisms of action (including mTOR inhibitors, modulators of SV2A, selective serotonin reuptake inhibitors, and AMPA inhibitors). Colors denote grading of *preclinical ASM response* based on reported TD_{50} and ED_{50} values for each model, resulting in a weighted scale capturing relative preclinical antiseizure effect. EIDEE=Early Infantile Developmental and Epileptic Encephalopathy; EO=early onset; i=induced; IESS=Infantile Epileptic Spasms Syndrome; m=mouse; r=rat; s=spontaneous; z=zebrafish

Clinical ASM Response

- Use patterns tend to vary across DEEs (**Fig. 3**).

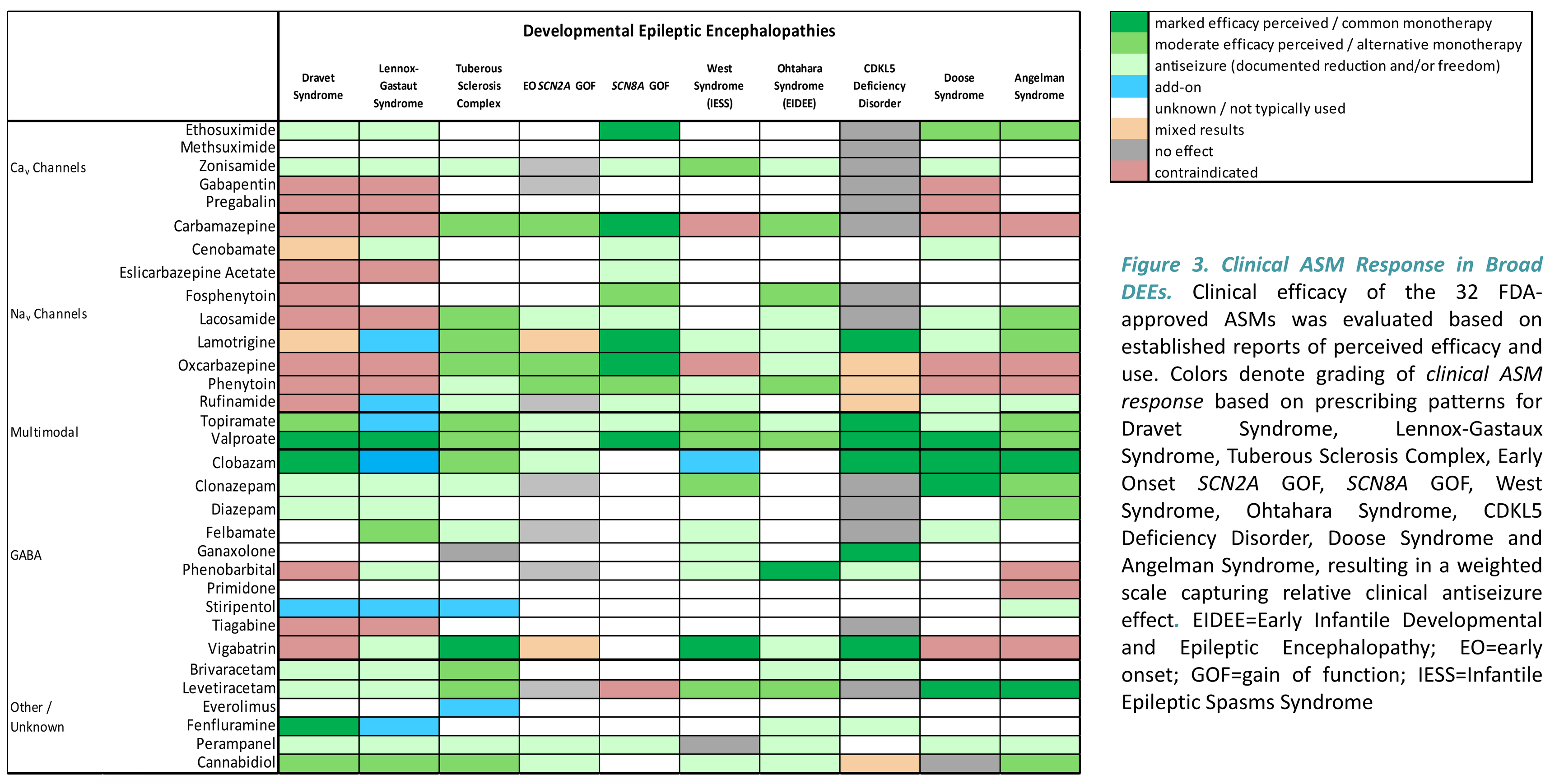

Figure 3. Clinical ASM Response in Broad DEEs. Clinical efficacy of the 32 FDA-approved ASMs was evaluated based on established reports of perceived efficacy and use. Colors denote grading of *clinical ASM response* based on prescribing patterns for Dravet Syndrome, Lennox-Gastaux Syndrome, Tuberous Sclerosis Complex, Early Onset *SCN2A* GOF, *SCN8A* GOF, West Syndrome, Ohtahara Syndrome, CDKL5 Deficiency Disorder, Doose Syndrome and Angelman Syndrome, resulting in a weighted scale capturing relative clinical antiseizure effect. EIDEE=Early Infantile Developmental and Epileptic Encephalopathy; EO=early onset; GOF=gain of function; IESS=Infantile Epileptic Spasms Syndrome

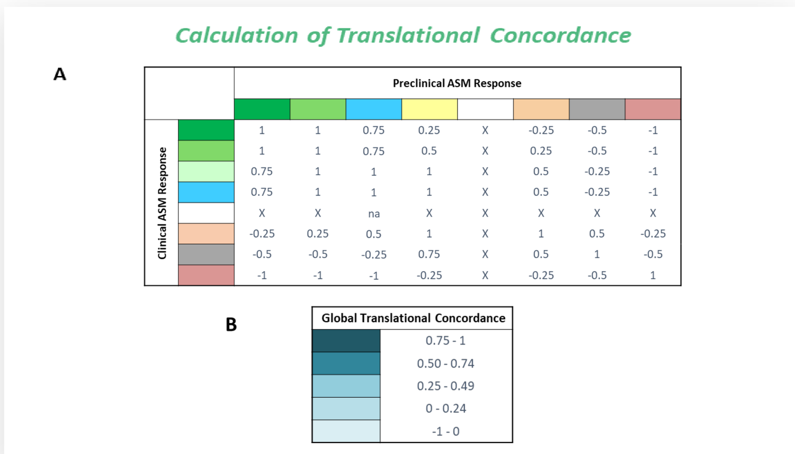

Figure 4. Translational Concordance Scoring. **A)** A unified scoring matrix was developed to assign translational concordance between *preclinical* and *clinical ASM response.* Values ranged from 1 for complete concordance to -1 for complete discordance. **B)** For each preclinical seizure/genetic epilepsy model and clinical indication combination, individual ASM concordance scores were first calculated, then summed and normalized (total translational concordance score/ total number of ASMs with data available) to generate a global translational concordance score, weighted from highest (0.75 to 1) to lowest (-1 to 0) concordance.

Conclusions

- **Using the newly developed PAC framework, findings from this study extend our insights into the predictive validity of traditional seizure models vs genetic epilepsy models across broad DEEs and neurogenetic syndromes, underscoring the importance of appropriate model selection in ASM drug discovery efforts.**
- **Together with previous findings in FOS and generalized epilepsy, we anticipate findings from the PAC-DEE extension to have important implications for accelerating research efforts and promoting efficient resourcing for novel ASM drug development across the full spectrum of human epilepsies.**

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