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Title page

Title: Is the crystal ball broken? Another external validation of the post-withdrawal seizure relapse prediction model.

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Letter

We read with interest the work of Contento et al.[1] They performed the third external validation of the Lamberink Prediction Model (LPM), which assesses seizure relapse risk following withdrawal of antiseizure medications (ASMs).[2]

In a first external validation,[3] Lin et al. reported an area under the curve (AUC) of 0.71. They showed the LPM outperformed predictions based on the single largest RCT to date,[4] though somewhat overpredicted observed probabilities. Chu et al.[5] provided a second Chinese cohort (AUC 0.61, again some overprediction). In contrast, Contento et al. concluded that model accuracy was inadequate because no single cutoff point provided high sensitivity and specificity.

We agree the LPM has limitations. Recruitment occurred mostly pre-2000 thus lacked in newer ASMs, genetics, and MRIs. In contrast, in Contento et al. all patients underwent MRI which could influence variables in the model such as EEG interpretation or focality explaining some divergence.

However, we have several concerns about their conclusions. First, the LPM was created from a large (N=1,769) diverse ($N_{countries}$=7) dataset, using 'leave one out' internal-external cross-validation which essentially performed 10 external validation steps in addition to Lin and Chu's 2 more. We suggest caution before discounting the LPM in light of essentially only 1 out of 13 validation steps suggesting poor performance. It would seem very surprising if the 12 variables contained in LPM (epileptiform EEG, number of seizures, duration seizure-free, etc.)

predicted relapse no better than chance as Contento et al's modified ROC curve (AUC ~0.5) suggests. Moreover, validation is only as strong as the external data source. Selection mechanisms going from 4,154 patients diagnosed with epilepsy down to just 205 (5%) who discontinued their ASM are not described, and another 36/205 were excluded due to missing data or incomplete follow-up. Including only 3% of those diagnosed with epilepsy raises concerns that the strong selection process determining discontinuation could explain divergence from the Chinese results.

Second, sensitivity and specificity are not the only metrics by which to judge a model. Observed versus predicted calibration may be a more intuitive way to assess model fit. Also, Contento et al's Discussion focuses on LPM's inability to provide a single best cutoff. However, we believe that the predicted probability itself is the quantity of interest, rather than seeking an arbitrary dichotomous prediction. Even a perfectly accurate model could not inform what constitutes 'high' versus 'low', which varies from patient to patient.

Third, Contento et al. interpreted Lin et al.'s decision curve analysis as showing usefulness only within limited ranges. However, that range (30%-65%) actually contains the majority of patients. It would be interesting if a future study compared the accuracy of clinician predictions versus the LPM, given it is generally the rule rather than the exception that big data-driven individualized prediction models outperform clinician intuition alone (a recent example[7]).

Ultimately, showing predicted probabilities to patients influences decisions[8], and we acknowledge that ability to predict outcomes is imperfect[9,10] encouraging future work. We appreciate enthusiasm for critically appraising the best available science to move the field forwards.

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Conflicts of interest

The authors report no conflicts of interest. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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