AI–Derived Subgroups from Phase 2 Data Applied Post hoc to Phase 3 MDD: Could Prior Design Adjustments Have Prevented Failure?

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Methodological Issue Being Addressed Late phase MDD trials often fail as treatment response variability and placebo response increase
from Phase 2 to Phase 3. To address this, we examined whether a ML-enabled predictive enrichment paradigm could identify model derived subgroups (MDS) from Phase 2 data that drove clinical response. These clinically interpretable baseline variable combinations were applied post hoc to an independent negative Phase 3 study using the same compound. The goal was to assess whether applying these MDS prospectively could have improved effect size and treatment–placebo separation.

Introduction Heterogeneity in MDD can obscure treatment effects in unselected samples. Failure to reduce
this heterogeneity can lead to clinical trial failure. Use of traditional subgrouping approaches or single feature filters rarely improve clinical trial response. We utilized an explainable ML method to identify Phase 2 MDS. These MDS were applied retrospectively as hypothetical selection criteria for a negative Phase 3 trial. Their performance was evaluated both precisely and with relaxed parameters to test robustness and operational feasibility. As a negative-control comparison, pre-specified single-variable filters were also applied to illustrate superiority of synergistic multi-variable criteria over isolated predictors.

Methods Discovery (Phase 2, N=61): A sub-insight learning model was trained on baseline variables from a successful Phase 2 trial. Subgroups were restricted to combinations of 2–4 variables that maximized MADRS drug-placebo separation between. The approach optimized bias–variance trade-off, a central principle of ML generalization. Translation (Phase 3, N=214): The top Phase 2 MDS were applied to an independent negative Phase 3 study (N=214), with two a priori operating definitions:

- o Strict Phase 2-derived MDS: HAMD Somatic Symptoms GI = 2 and Systolic BP 108–131 mmHg.
- o Loosened Phase 2-derived MDS: HAMD Somatic Symptoms GI >0 and Systolic BP 108–136 mmHg.
- o Single-variable Phase 2-derived MDS: HAMD Somatic Symptoms GI>0 or >1

Comparators: Single variable filters to compare with multivariable MDS

Results Strict Phase 2–derived MDS applied to Phase 3: Significant drug–placebo difference (MADRS Δ Day 28: placebo −12.58, drug −18.51; Cohen's d = 0.57; p = 0.016; N = 79/208).
Loosened Phase 2–derived MDS applied to Phase 3: Separation at Days 7,14, trending toward separation at Day 28 (MADRS Δ Day 28: placebo −13.46, drug −17.23; Cohen's d = 0.346; p = 0.053; N = 126/208).
These findings contrast with minimal separation in the unfiltered Phase 3 ITT population.
Phase 2-derived single-variable MDS applied to Phase 3 data: No single-variable MDS showed drug-placebo separation although SS GI=2 approached significance at Day 28 (Cohen's d: 0.356; p=.0622; N=117/208).
The single-variable MDS in Phase 2 reflects a strong but high-variance signal typical of smaller, high-effect studies. The multivariate MDS reduces variance by capturing 2 synergistic variables, offering greater stability in more heterogeneous Phase 3 settings. Combining both balances bias and variance, ensuring Phase 2 signal isn't over-interpreted without structural support for generalization in larger trials. This cautionary step was validated as single variable persona failed to replicate in the holdout Phase 3 for the endpoint across all timepoints.

Conclusion If the Phase 2-discovered enrichment rules had been prespecified and applied ahead of Phase
3, the trial would likely have demonstrated a detectable treatment effect within a sizable, clinically interpretable subgroup. Iterative loosening of the Phase 2 rule preserved directionality while improving operational inclusivity, highlighting a pragmatic path for prospective enrichment or stratification in future protocols. Single variable filters are inadequate substitutes for the synergistic multivariable MDS that capture the relevant phenotype. This framework offers a regulator-aligned, reproducible way to carry Phase 2 signal into Phase 3 success.

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Guidelines I have read and understand the Poster Guidelines

Disclosures Dr. Joseph Geraci is the founder of NetraMark and is a significant shareholder of NetraMark Holdings, which is a publicly traded company. Drs Jan Sedway, Luca Pani, Bessi Qorri, Larry Alphs and Paul Leonchyk as well as Mike Tsay, Christian Cumbaa and Adam Gogacz are employed by NetraMark. Dr. Luca Pani's Disclosures (past 3 years): AbbVie, USA; Acadia, USA; Alexion, Italy; BCG, Switzerland; Boehringer Ingelheim International GmbH, Germany; Compass Pathways, UK; EDRA-LSWR Publishing Company, Italy; Ferrer, Spain; Gedeon-Richter, Hungary; GLG-Institute, USA; Immunogen, USA; Inpeco SA, Switzerland; Ipsen-Abireo, France; Johnson & Johnson USA; NeuroCog Trials, USA; Novartis-Gene Therapies, Switzerland; Sanofi-Aventis-Genzyme, France and USA; NetraMark, Canada*; Otsuka, USA; Pfizer Global, USA; PharmaMar, Spain; Relmada Therapeutics, USA*; Takeda, USA; Vifor, Switzerland; WCG-VeraSci/Clinical Endpoint Solutions, USA (* options / shares)