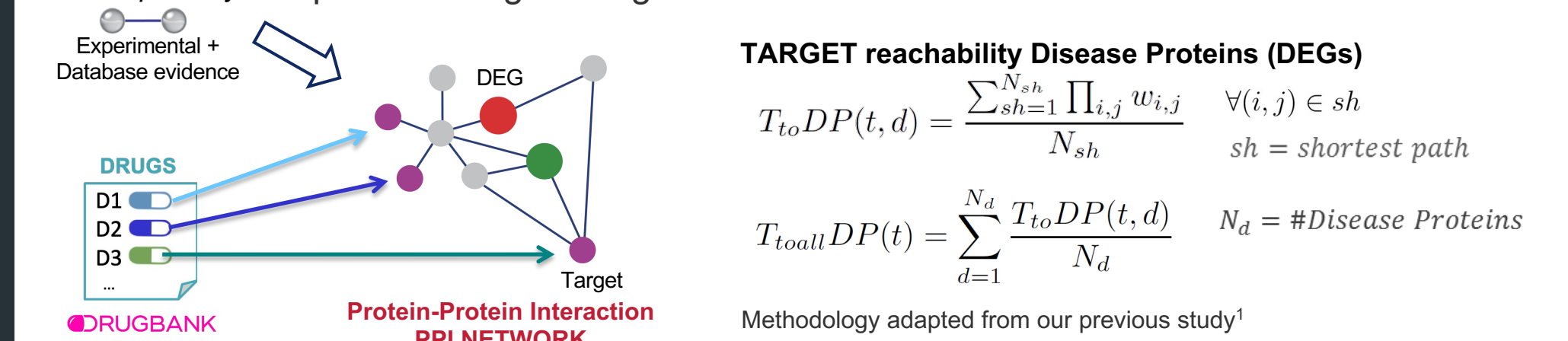


INTRODUCTION

- Alzheimer's disease (AD) is a multifactorial disorder driven by dysregulation of several molecular pathways.
- Disease risk and progression are strongly modulated by biological sex, endocrine aging, and apolipoprotein E (APOE) genotype, yet current therapeutic discovery strategies rarely account for these factors or computationally evaluate drug combinations.
- We developed an integrative computational framework to prioritize precision drug combinations for AD by jointly modeling network topology, pathway-level disease perturbation, and null-controlled drug simulation effects.

METHODS

- Brain RNAseq to select Differentially Expressed Genes (DEGs)
- For 15-month acyclic APOE ϵ 4/ ϵ 4 (E4) vs 9-month regular APOE ϵ 3/ ϵ 3 (E3)
- DEGs mapped onto an APOE4-endocrine-age-specific AD protein-protein interaction (PPI) network using high-confidence interactors.
- Network topology metrics to prioritize non-hub bridge nodes as pharmacological targets.



NETWORK COMBO RANKING

Drug-level reachability score

$$R_d = 1 - \prod_{t \in T(D)} (1 - T_{total}DP(t))$$

Bayesian Drug-target confidence score

Penalize drugs with many out-of-network targets

$$\theta_d \sim \text{Beta}(n_d^{in} + 1, n_d^{out} + 1)$$

$$C_d = \mathbb{E}[\theta_d] = \frac{n_d^{in} + 1}{n_d^{in} + n_d^{out} + 2}$$

Drug Pair Score

$$CombinedScore_d = R_d \cdot C_d$$

$$ComboScore(D_1, D_2) = CombinedScore_{D_1} \cdot CombinedScore_{D_2}$$

Exclude pairs with MODERATE / MAJOR drug-drug interactions

Null Distribution → Significant Combinations

vs 1,000,000-pair targets p<0.001, FDR adjusted

Network combination score on KEGG pathways

$ComboScore$
 $w_1 = 2.0$

$Pathway coverage$
 $w_2 = 1.5$

$Target in pathway$
 $w_3 = 1.0$

weighted geometric mean · scaled to [0,1]
⇒ $CompositeScore(D_1, D_2)$

DRUG ACTION SIMULATION

KEGG PATHWAY

Value	Value
Strong positive/negative regulation	±1.0
Moderate negative regulation	~0.5
Weak positive/negative	±0.3
Neutral	0.0

DEGS

Value	Value
Up	+1.0
Down	-1.0

DRUG ACTION

Value	Value
Strong activating/inhibitory	±1.0
Weak activating/inhibitory	±0.5

Simulation of drug pair-actions in pathway p

$$x_p = (I - \alpha A_p)^{-1} B_p$$

A_p = signed pathway matrix,
 $0 < \alpha < 1$ = diffusion parameter,
 B_p = drug perturbation matrix

Aggregate drug-pair effect across pathways:

$$DrugEFF(D_1, D_2) = \left(\sum_p \sqrt{n_p} \cdot Effect_p \right) / \sum_p \sqrt{n_p}$$

where per-pathway effect score (F-measure) is

$$Effect_p(D_1, D_2) = 2 \frac{Recall \cdot Precision}{Recall + Precision}$$

Confusion matrix on regularized DEGs,
 n_p = #DEGs in pathway p, standardize Z vs null

FINAL DRUG-PAIR RANKING

$$FinalScore(D_1, D_2) = \frac{w_c CompositeScore + w_e DrugEFF}{w_c + w_e}$$

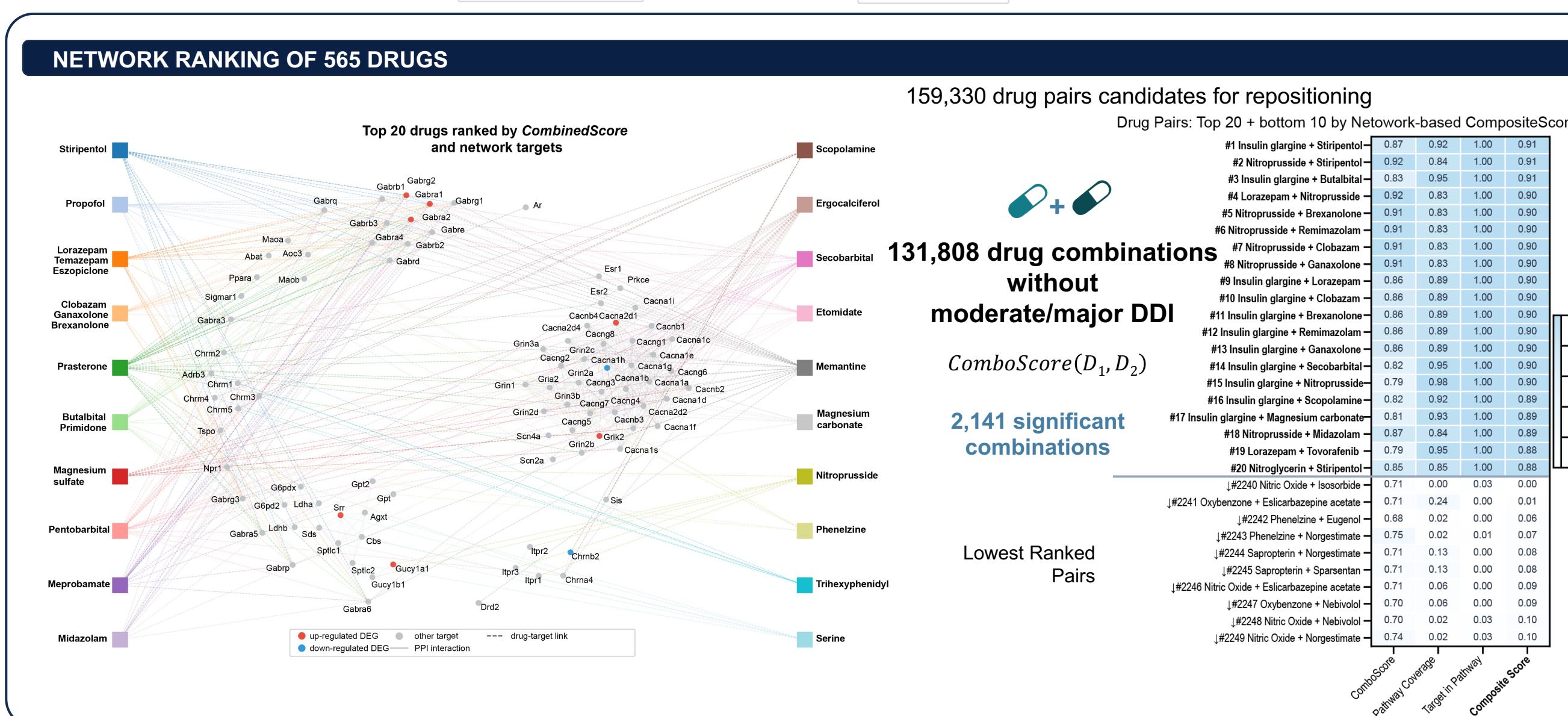
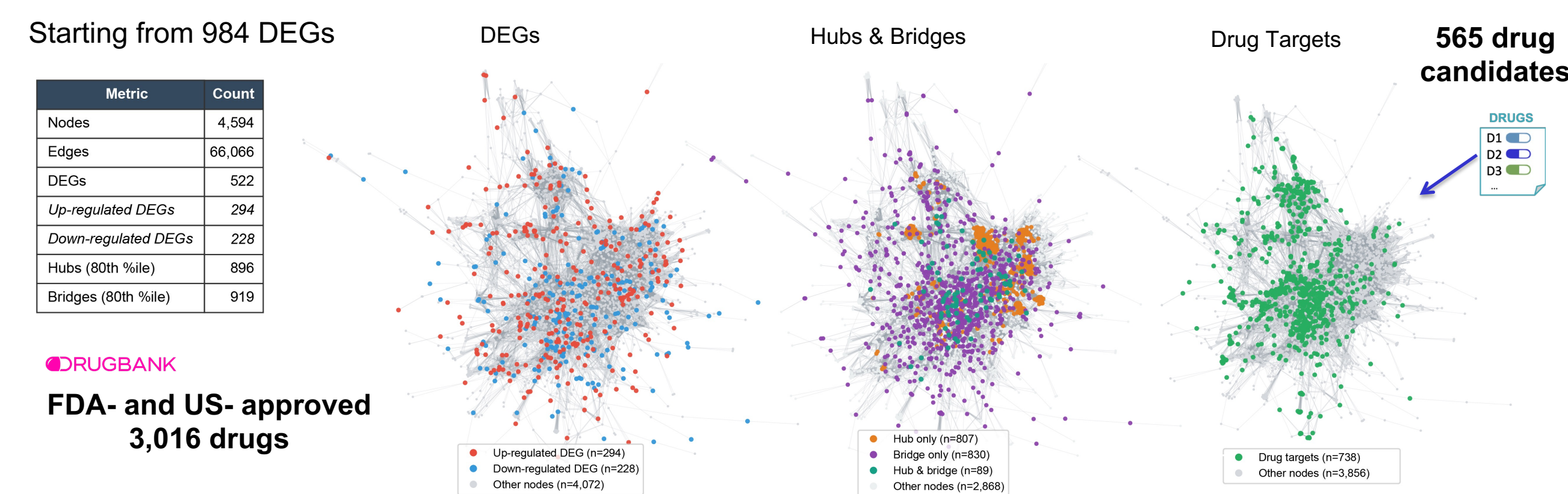
Ranked by FDR p-value and effect size

VALIDATION IN REAL-WORLD CLAIM INSURANCE DATA

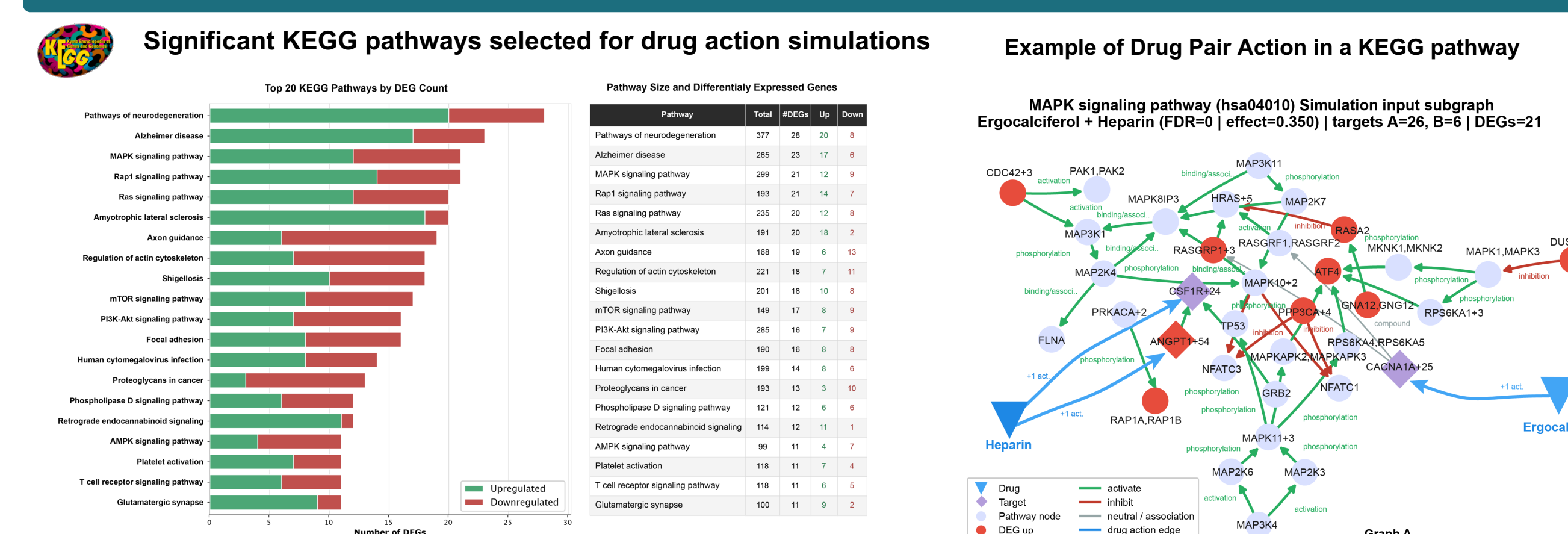
- US-based PearlDiver-Mariner insurance claims database (~170M patients) was used to evaluate whether top ranked candidate drug pairs were associated with reduced AD risk.
- Women with a menopausal disorder diagnosis (ICD10-N95.x) were included.
- Treated vs Untreated cohort was matched by age, cci, and comorbidities (diabetes, hypertension, cerebral vascular disease, renal disease, other cerebrovascular disease and COPD).
- Relative risk ratios with 95% confidence intervals were calculated to evaluate associations between drug pair exposures and overall AD incidence.

RESULTS

E4 15M Acyclic vs E3 9M Regular PPI Network

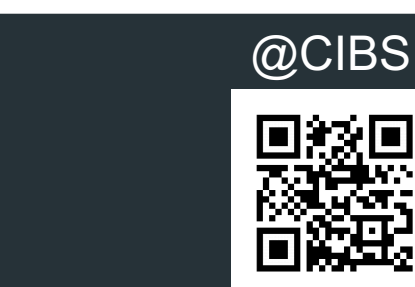


SIMULATION OF DRUG COMBINATION ACTION



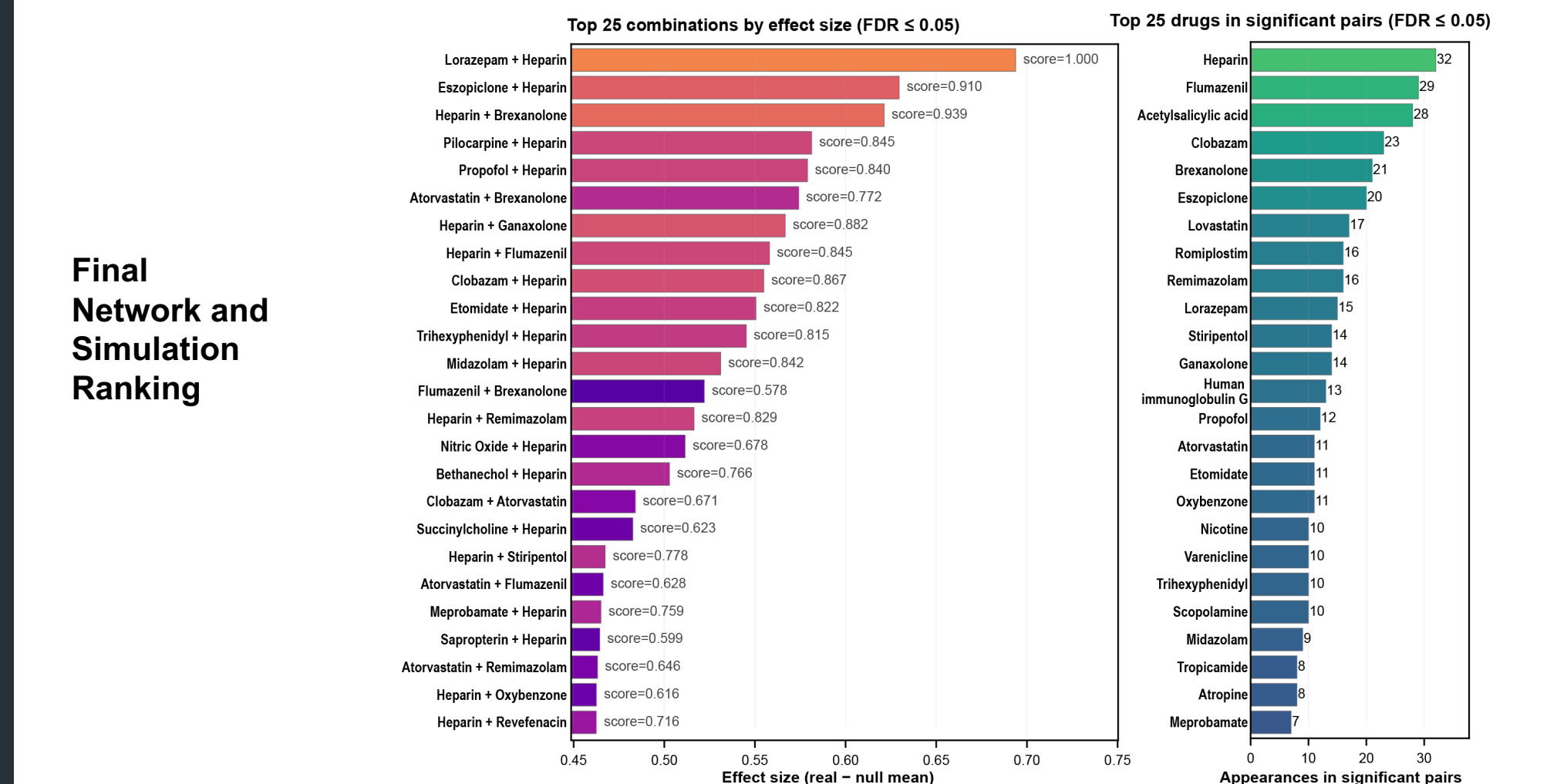
Simulation of drug pair actions in pathways

Accounting for direction of drug action and mitigation of DEG signature

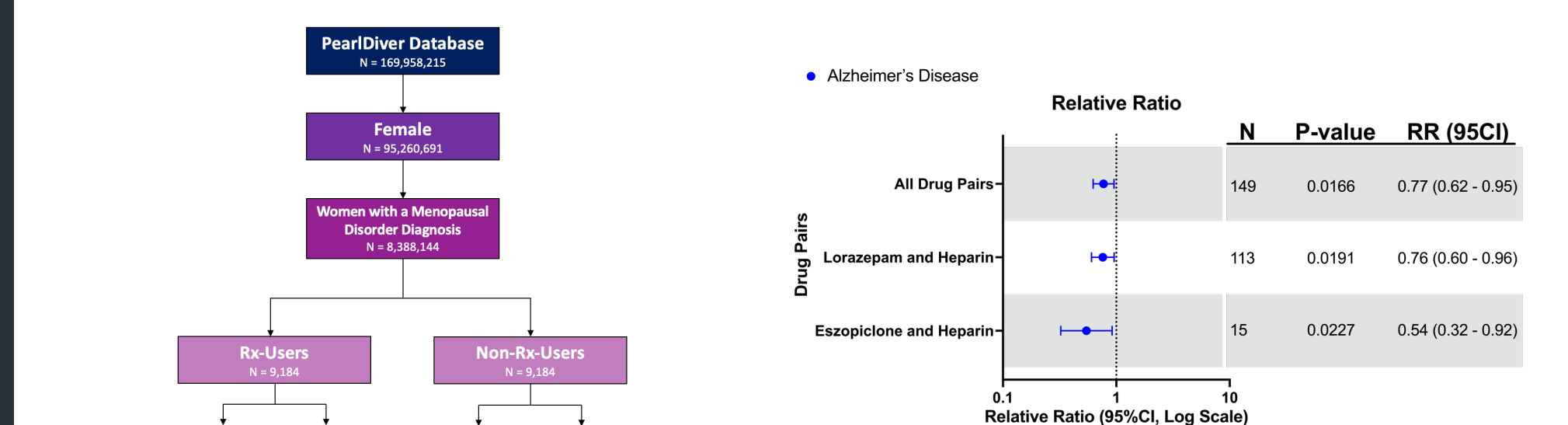


Center for Innovation
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TOP RANKED SYNERGISTIC DRUG COMBINATIONS



MARINER CLAIM INSURANCE DATA VALIDATION



DISCUSSION

- We present an integrative framework that prioritizes precision drug combinations for a female APOE4-, endocrine-, and age-specific disease state.
- APOE4 females show accelerated endocrine aging and the highest Alzheimer's risk when menopause is early, supporting midlife as a critical intervention window²
- Top combinations converge on a neurosteroid/GABAergic × heparin axis that is mechanistically coherent. Allopregnanolone, a GABA-A-acting neurosteroid, promotes neurogenesis and is in clinical development as a regenerative therapeutic for AD³, paralleling the brexanolone/ganaxolone high ranked therapeutics.
- Heparin resulted as the most frequent drug in highly ranked pairs. To support this finding, heparin therapy was associated with a ~1-year delay in AD diagnosis in two large US health systems⁴, mirroring our claims-based protective association.
- Recurrent statin and insulin partners align with sex- and genotype-modified statin-AD associations⁵ and metabolic-endocrine contributions to risk, reinforcing a multi-system, precision-medicine view.

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