ApoE Genotype Directed Drug Repositioning and Combination Therapy for Alzheimer's Disease

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UCSF, the Gladstone Institutes

NIA-AA Symposium

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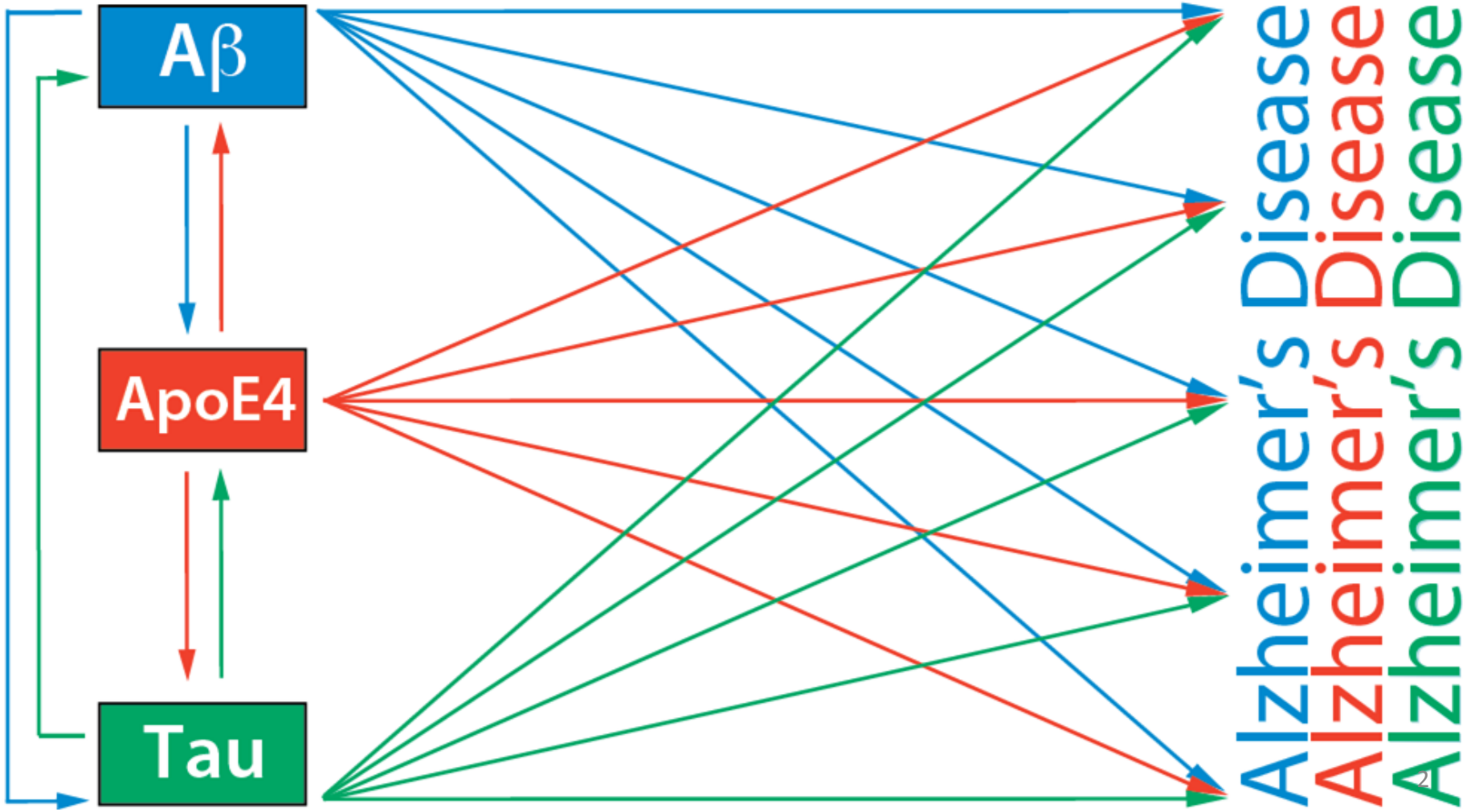
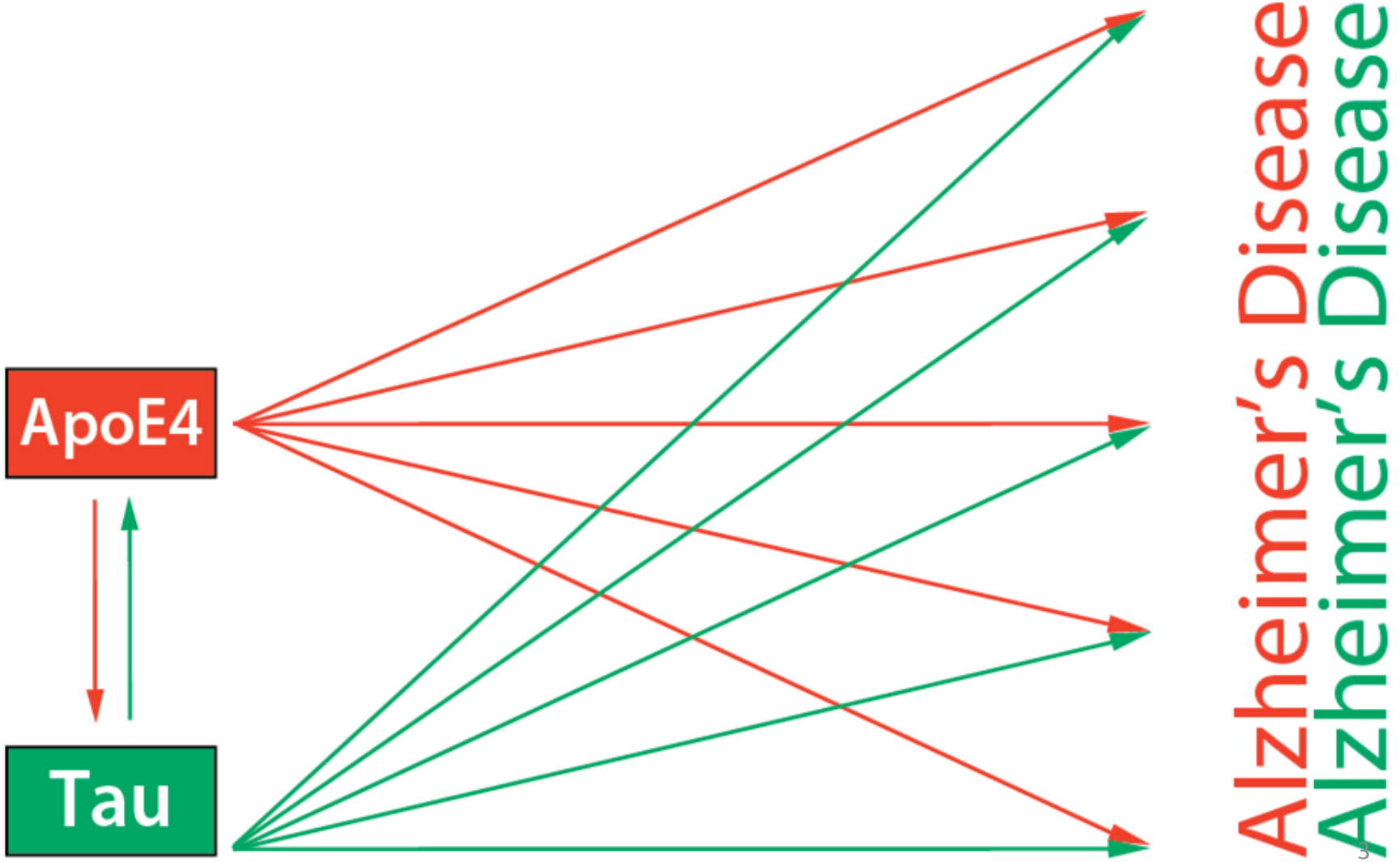
The Multifactorial Nature of Alzheimer's Disease



The Multifactorial Nature of Alzheimer's Disease
(Targeting/Removing One Factor Would not Work Well)



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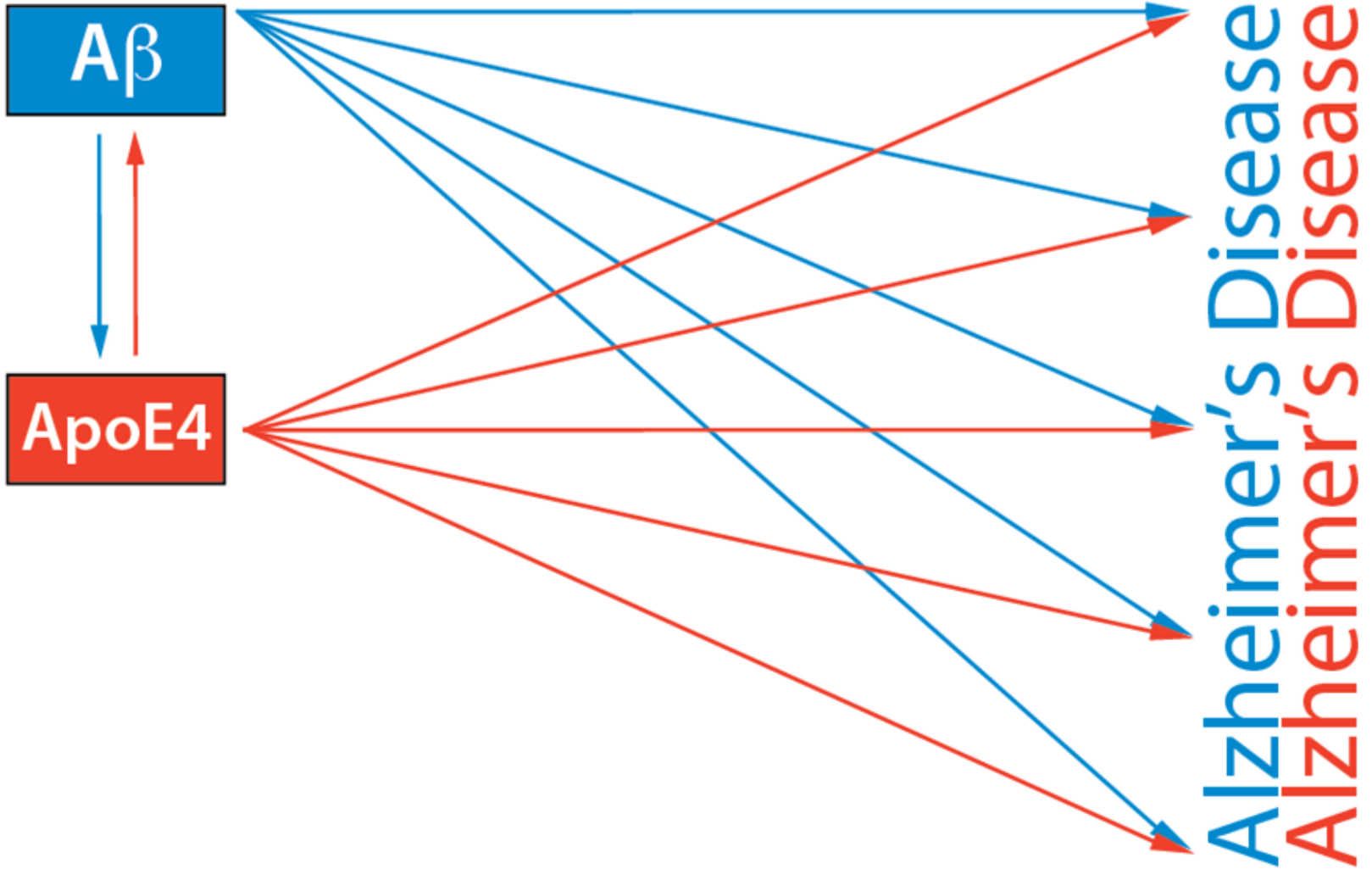

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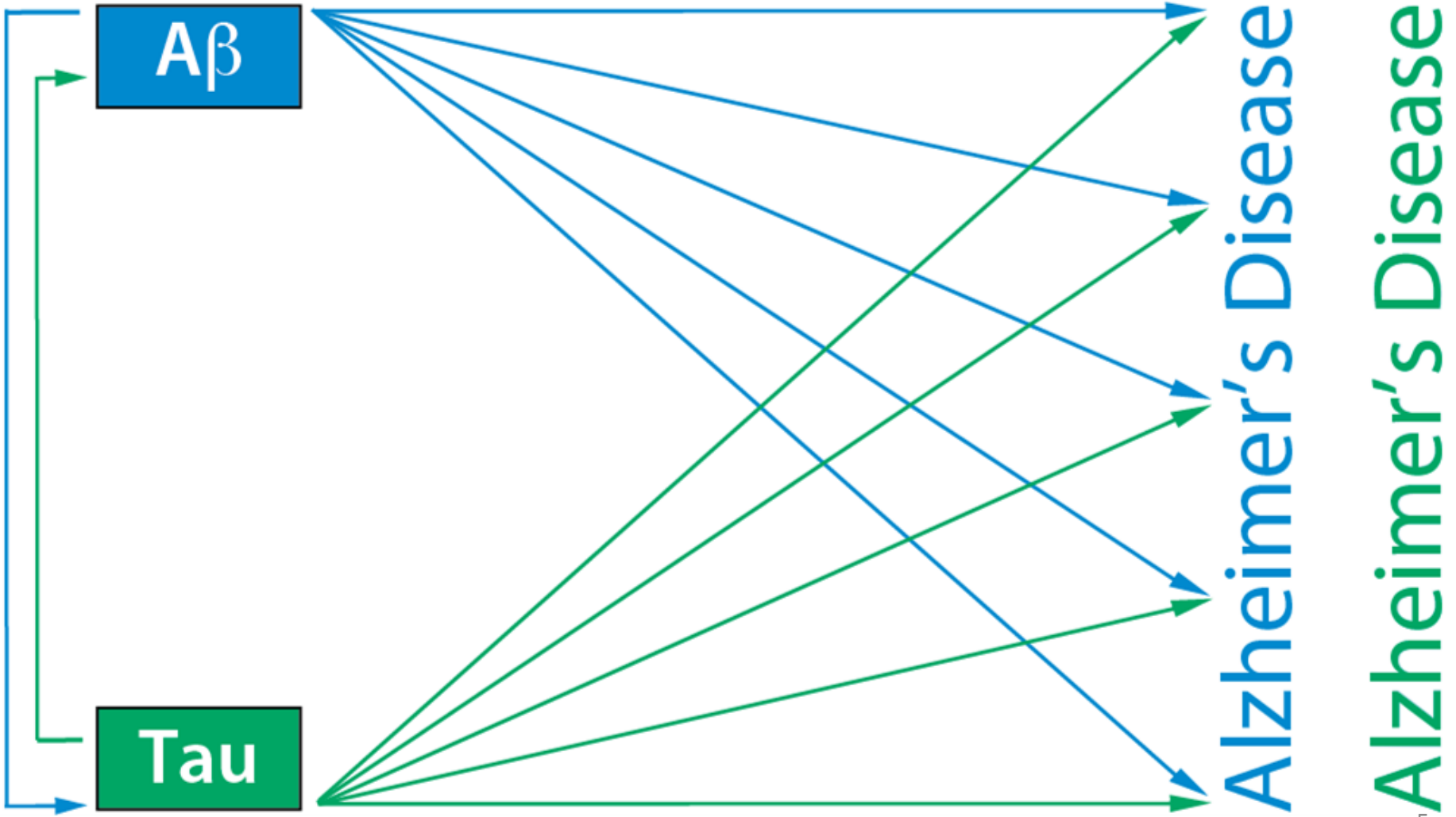
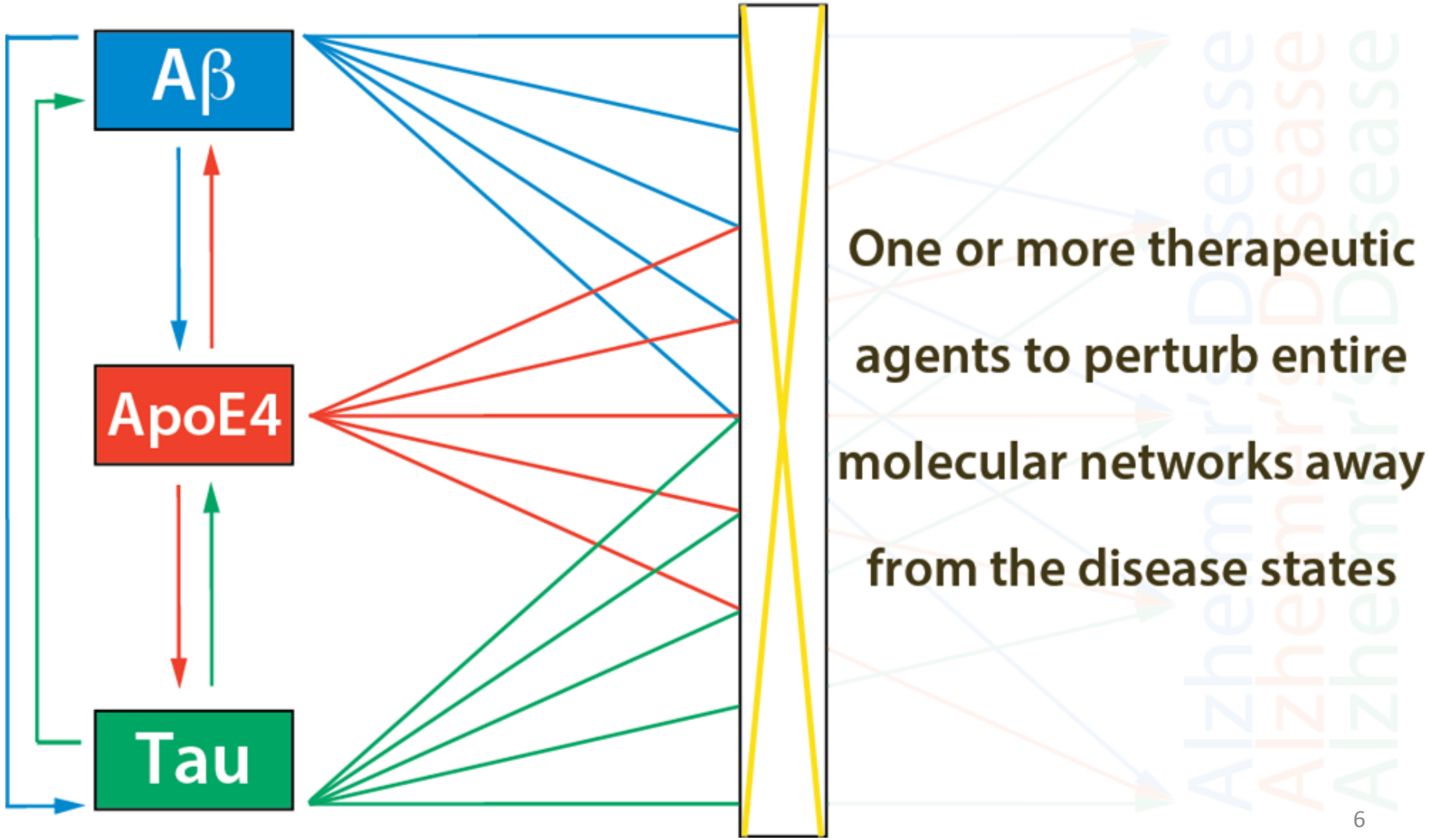


The Network Concept of Drug Targets for Alzheimer's Disease



Four Major Publically Available Transcriptional Studies in the Temporal Cortex of Control and AD Patients with ApoE Genotype Information (Total N = 956)

Study ID	Online Source	Data Source	n	ApoE Genotype	Brain Region	Analytic Method	Quality Control
GSE15222[a]	GEO expression Omnibus	U. Miami Myers Lab	240	Yes	Temporal cortex	Illumina, microarray	Yes[a]
Syn3157255[b]	Sage synapse Amp-AD	UFL-MAYO-ISB (MayoEGWAS)	399	Yes	Temporal cortex	Illumina, whole genome DASL	Yes[b]
Syn5550404[c]	Sage synapse Amp-AD	UFL-MAYO-ISB (MayoRNA-seq)	192	Yes	Temporal cortex	RNA-Seq, HiSeq 200	Yes
Syn3157743[d]	Sage synapse Amp-AD	Mt. Sinai Brain Bank	125	Yes	Temporal cortex	RNA-Seq HiSeq 2500	Yes[e]

a. Webster JA, Gibbs JR, Clarke J, et al. Genetic control of human brain transcript expression in Alzheimer disease. *Am J Hum Genet.* 2009;84:445–458.

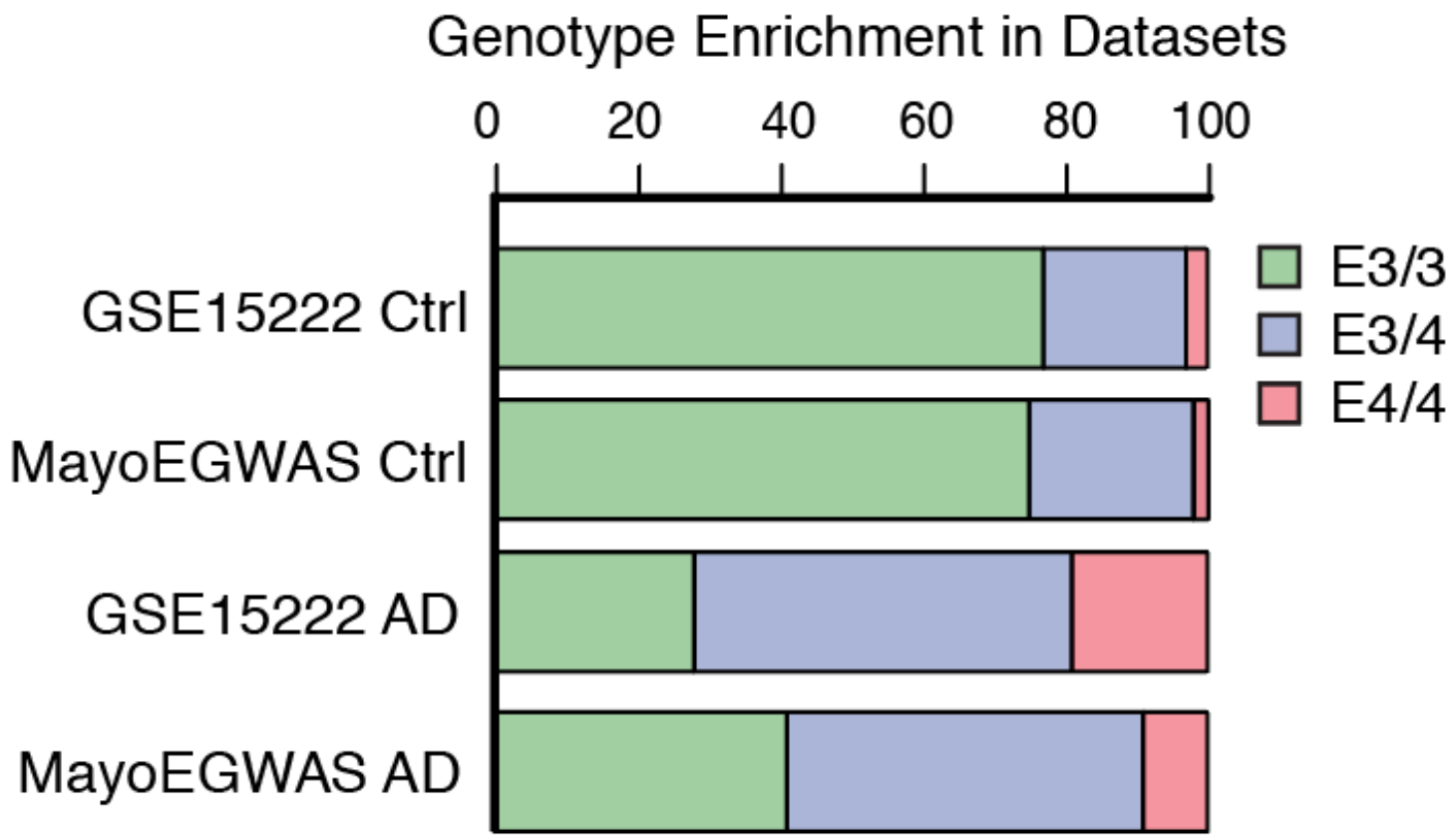
b. Zou F, Chai HS, Younkin CS, et al. Brain expression genome-wide association study (eGWAS) identifies human disease-associated variants. *PLoS Genet.* 2012;8:e1002707.

c. For Syn5550404 (MayoRNA-seq), temporal lobar brain samples were taken from the Mayo Clinic Brain Bank and Banner Sun Health Research Institute.

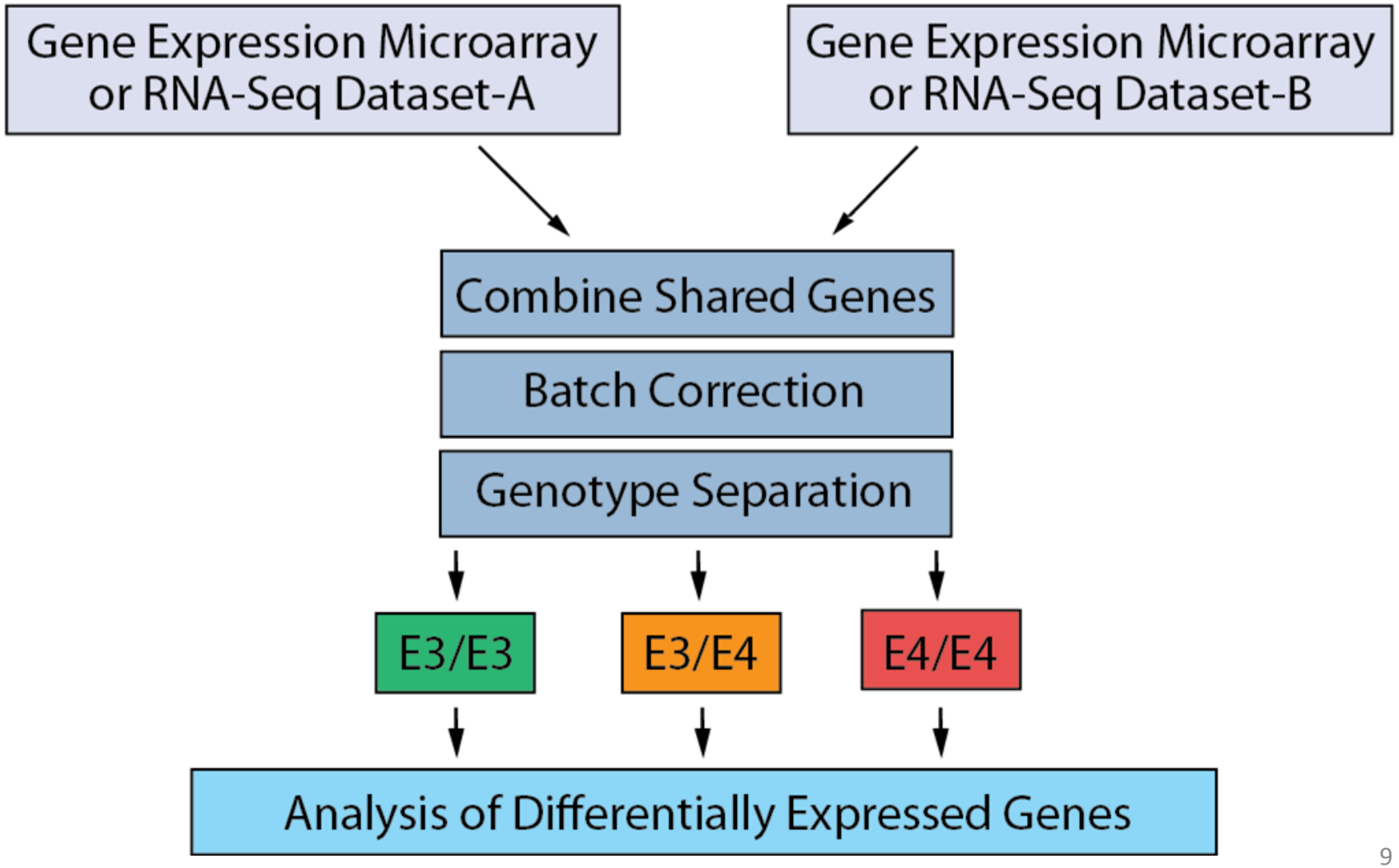
d. For Syn3157743 (MSBB), temporal cortex samples were taken from the Mt. Sinai Brain Bank.

e. Levin JZ, Yassour M, Adiconis X, et al. Comprehensive comparative analysis of strand-specific RNA sequencing methods. *Nat Methods.* 2010;7:709–715.

Precision Medicine is Paramount to Accuracy in Mapping Disease Networks



First Step: Identifying ApoE Genotype-Specific Gene Expression Signatures of Alzheimer's Disease

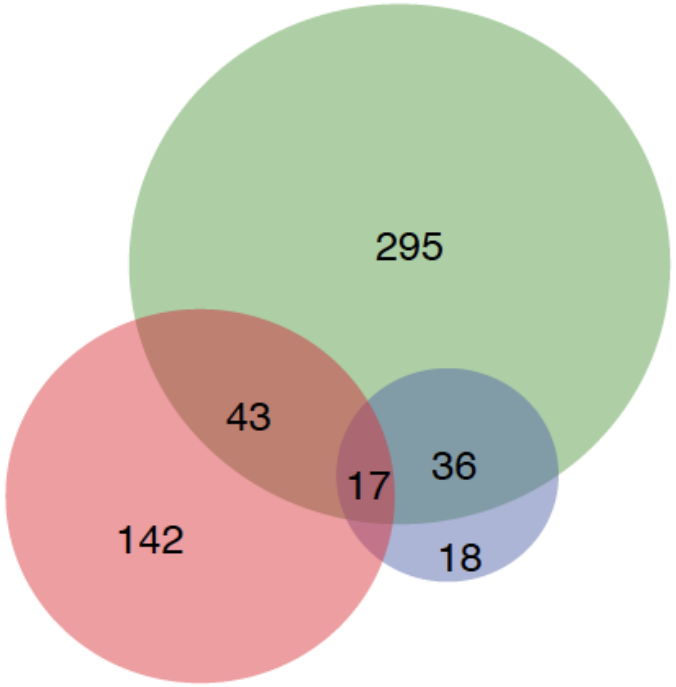


ApoE Genotype-Specific Gene Expression Signatures of Alzheimer's Disease (N=639)

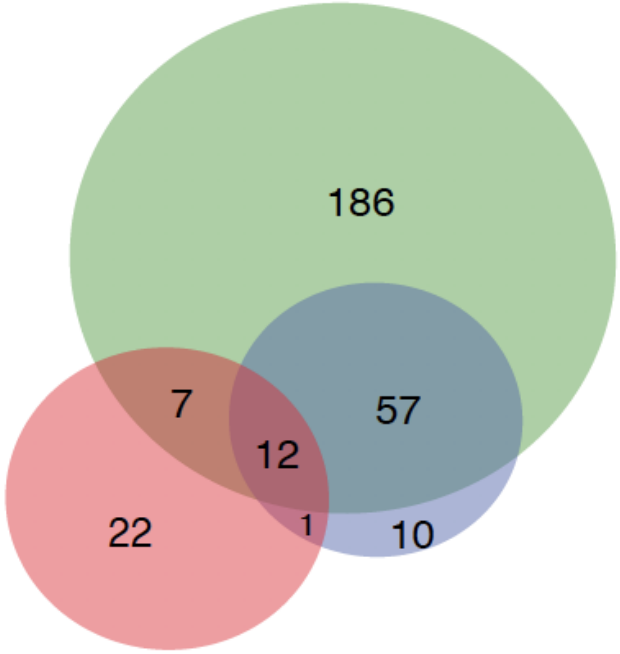
Sample Numbers

E3/E3		E3/E4		E4/E4	
AD	CTRL	AD	CTRL	AD	CTRL
106	236	147	69	46	7

Upregulated Genes



Downregulated Genes



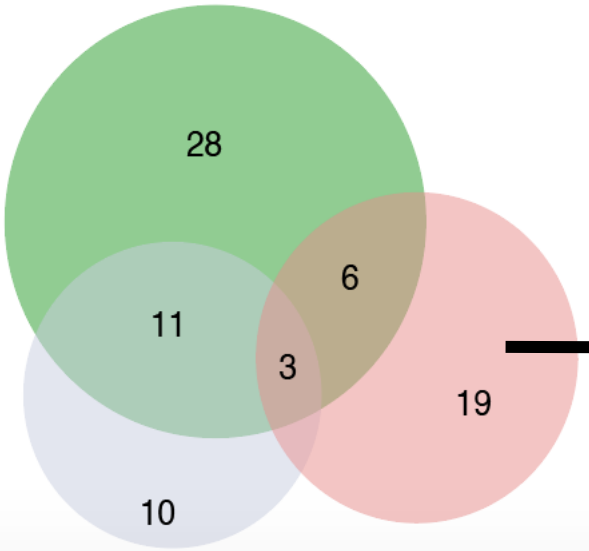
ApoE Genotype-Specific Gene Expression Signatures of Alzheimer's Disease (N=639)

Dysregulated Pathways in ApoE4/4 AD

E4/E4	
AD	CTRL
46	7

E3/E4	
AD	CTRL
147	69

E3/E3	
AD	CTRL
106	236



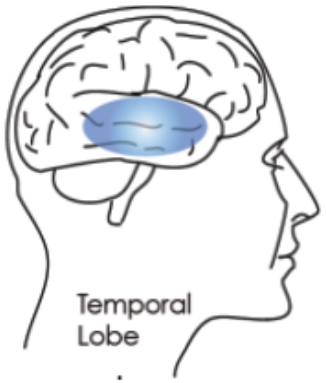
Ingenuity.Canonical.Pathways	p.value
Glutamate Dependent Acid Resistance	0.000200
GABA Receptor Signaling	0.000437
Coagulation System	0.001480
cAMP–mediated signaling	0.001550
Neuroinflammation Signaling Pathway	0.001740
Glutamate Degradation III (via 4–aminobutyrate)	0.001950
G–Protein Coupled Receptor Signaling	0.002040
G-alpha-s Signaling	0.004900
IL–12 Signaling and Production in Macrophages	0.004900
VDR/RXR Activation	0.005010
Synaptic Long Term Depression	0.005250
Pathogenesis of Multiple Sclerosis	0.006760
Glutamate Receptor Signaling	0.008710
Phagosome Formation	0.010700
Cholesterol Biosynthesis I	0.014100
Cholesterol Biosynthesis II (via 24,25–dihydrolanosterol)	0.014100
Cholesterol Biosynthesis III (via Desmosterol)	0.014100
Agranulocyte Adhesion and Diapedesis	0.019500
Mechanisms of Viral Exit from Host Cells	0.020400
NRF2–mediated Oxidative Stress Response	0.020400
Role of Hypercytokinemia/hyperchemokinemia in the Pathogenesis of Influenza	0.022900
Tight Junction Signaling	0.032400
Cell Cycle: G2/M DNA Damage Checkpoint Regulation	0.032400
CCR3 Signaling in Eosinophils	0.038000
L–serine Degradation	0.041700
N–acetylglucosamine Degradation I	0.041700
Factors Promoting Cardiogenesis in Vertebrates	0.041700
Actin Cytoskeleton Signaling	0.043700

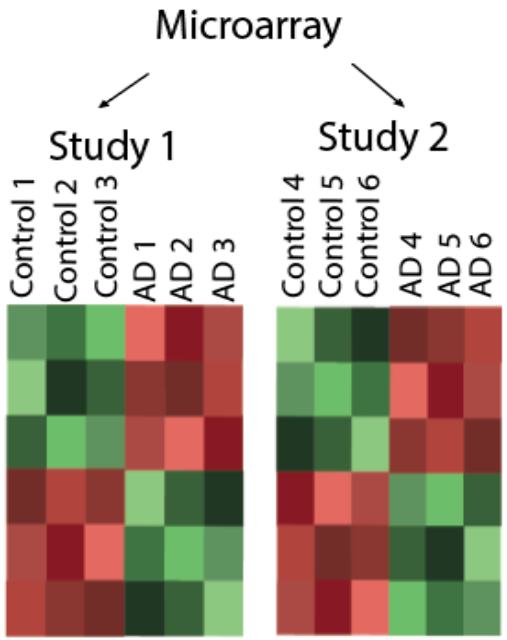
E4/4 Unique

Drug Repositioning Pipeline

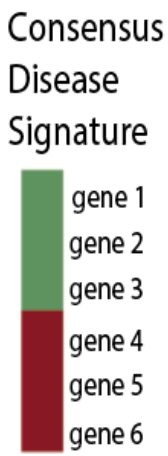
Gene Expression Signatures of AD

a





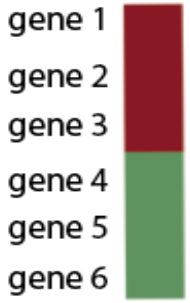
b

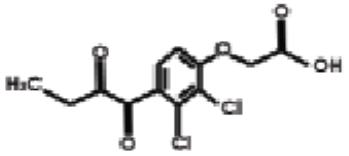


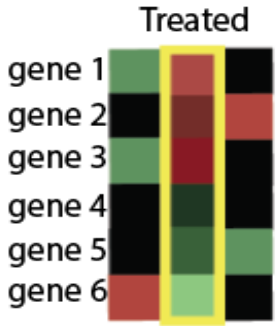
Drug Repositioning with Full Gene Singature

CMAP Compound Library

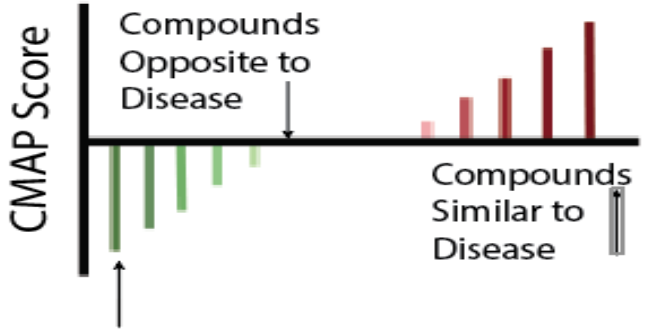
c





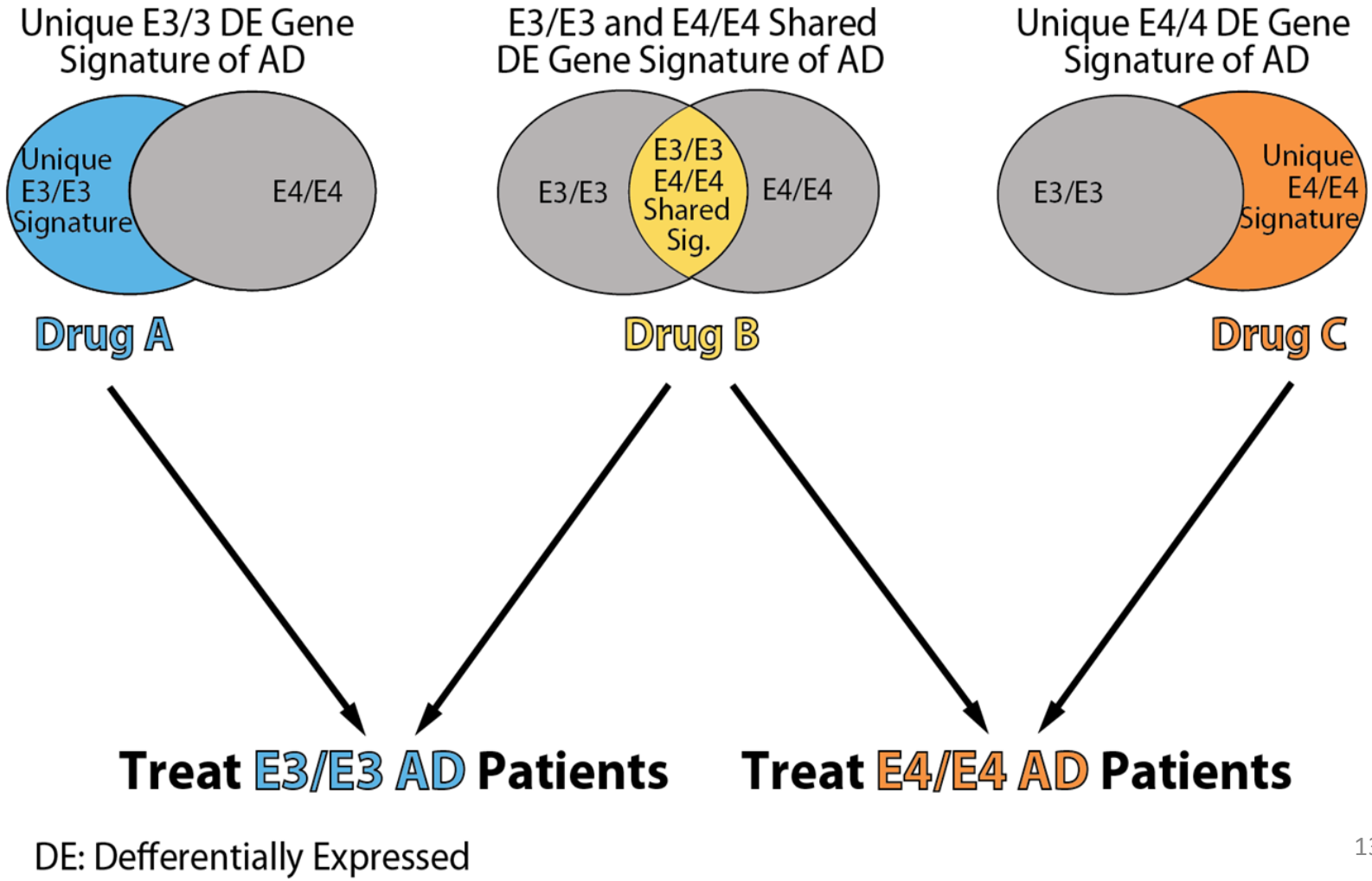


d Opposite Drug Signature



Predicted as a therapeutic agent

Precision Medicine and Combination Therapy of Repurposed Drugs based on ApoE Genotype-Specific Gene Expression Signatures of AD



Conclusions and Further Directions

- Network approach to drug targeting to treat complex disease
- Precision medicine is paramount to efficacious targeting of disease networks
- Developing unique and combinatorial precision medicine-led methods for drug repositioning
- Currently testing lead compounds

Acknowledgements

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