Harnessing Diverse Bioinformatics Approaches to Repurpose Drugs for Alzheimer's Disease

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Acknowledgments

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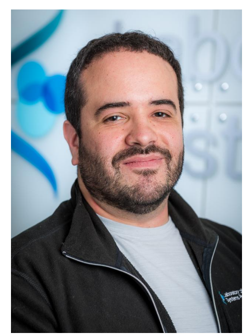


MASSACHUSETTS GENERAL HOSPITAL
MASSGENERAL INSTITUTE FOR NEURODEGENERATIVE DISEASE

Laboratory of Systems Pharmacology

Imperial College London

Massachusetts Institute of Technology

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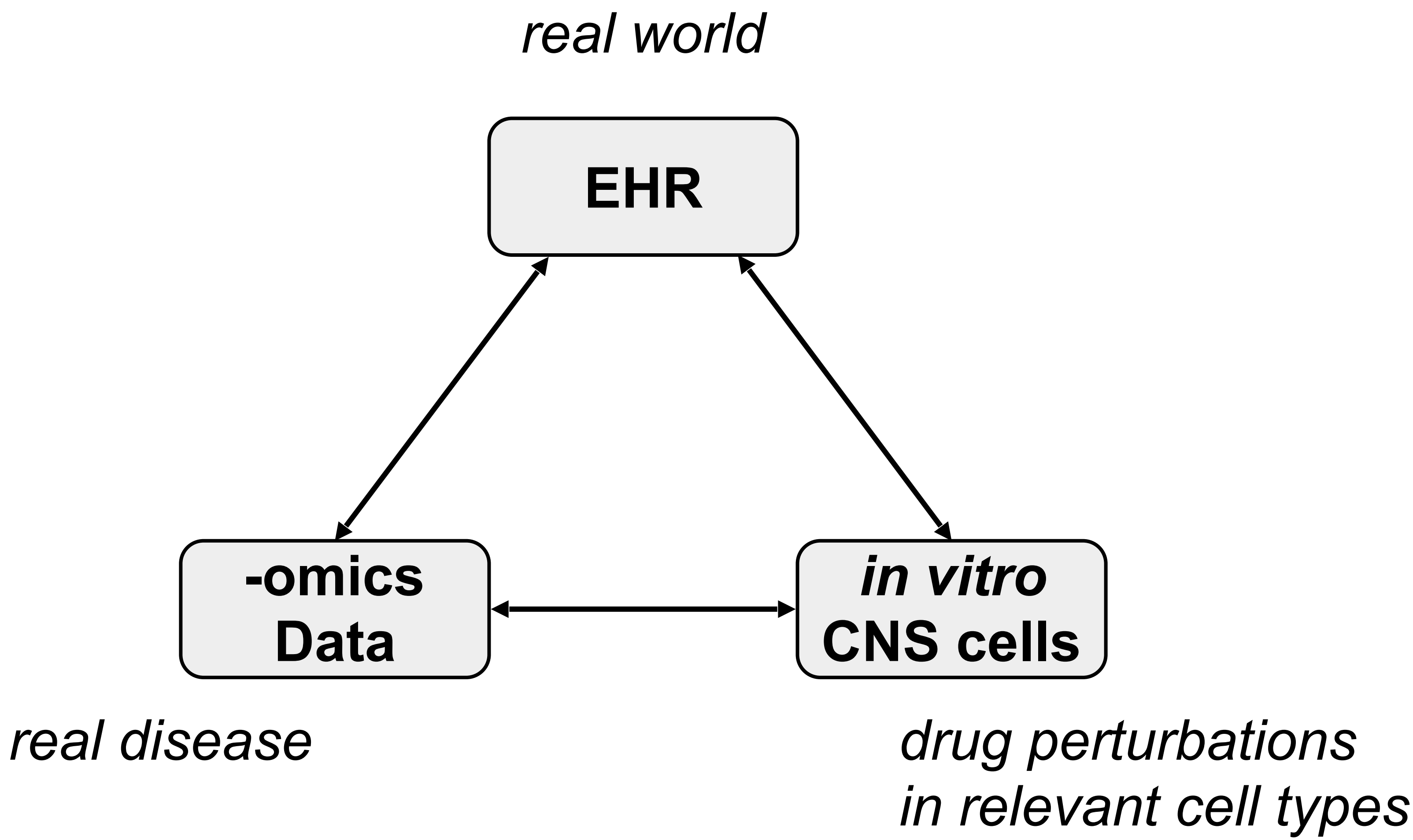
Funding:
R56 AG058063 Partners
P50 AG005134 Springboard

Integrating three data sources with two informatics approaches



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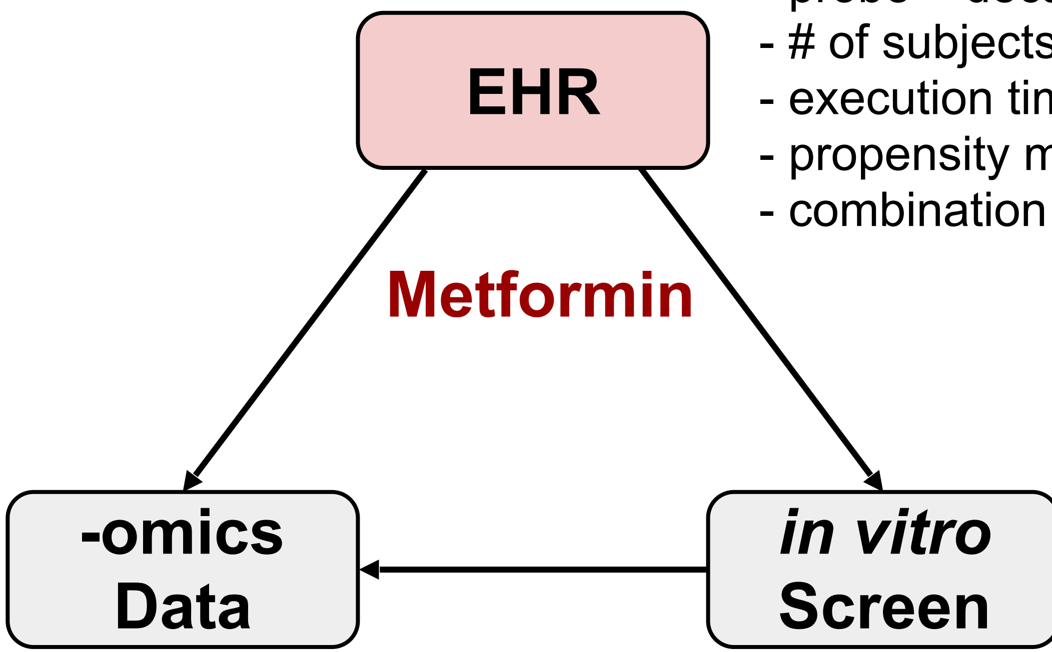
EHR analysis evaluates potential off-label use that may delay symptoms of Alzheimer's disease



- probe ≥ decade preclinically
- # of subjects > clinical trials
- execution time is shorter
- propensity matching
- combination therapies

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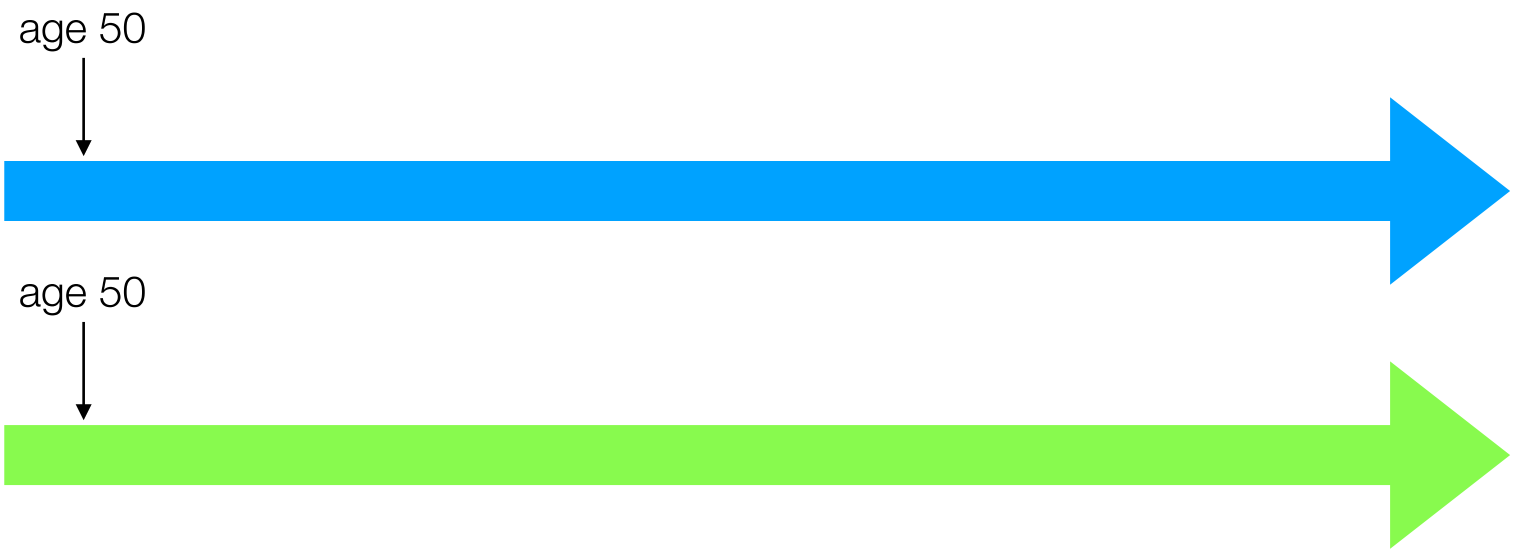
In silico drug trials - longitudinal EHR analyses

Initiation trial (asymptomatic to diagnosis):



Ioanna Tzoulaki

Imperial College London

Massachusetts Institute of Technology

CPRD
- NHS of UK
- 20 million patients
- longitudinal data from 1990's

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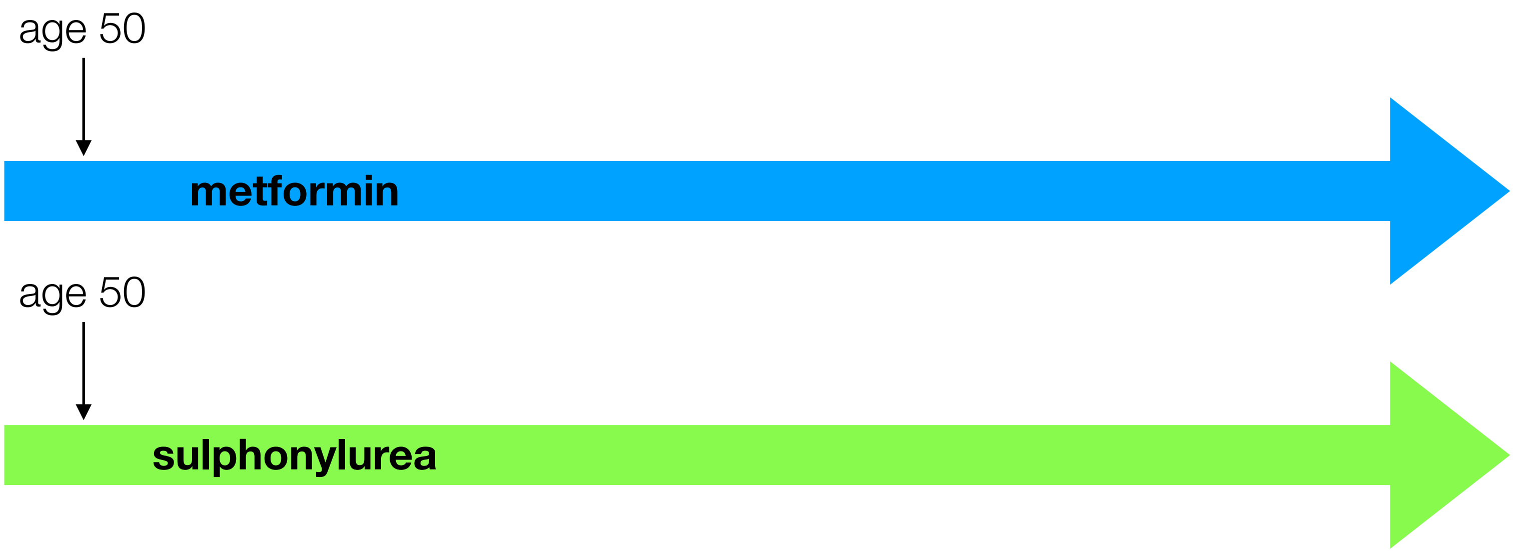

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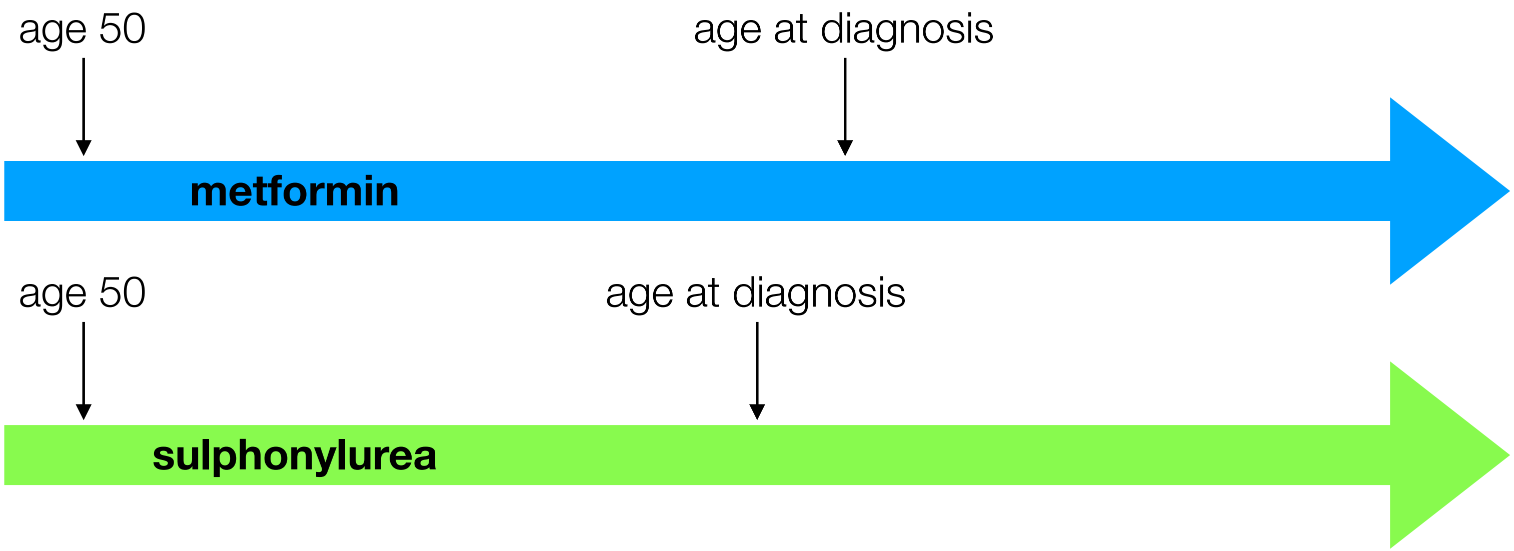

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Metformin reduces progression to dementia relative to sulphonylurea in diabetics

Strata	Number of obs	Hazard Ratio	P-value	[95% Conf. Interval]	
Follow-up for up to 10 y					
Model 1: (age and gender)					
Metformin	128,727	**0.615**	<0.001	0.589	0.643
Model 2: fully adjusted					
Metformin	64,288	**0.502**	<0.001	0.434	0.581

Fully adjusted includes age at prescription, gender, socioeconomic status, vascular comorbidities, smoking, BMI, and HbA1c level

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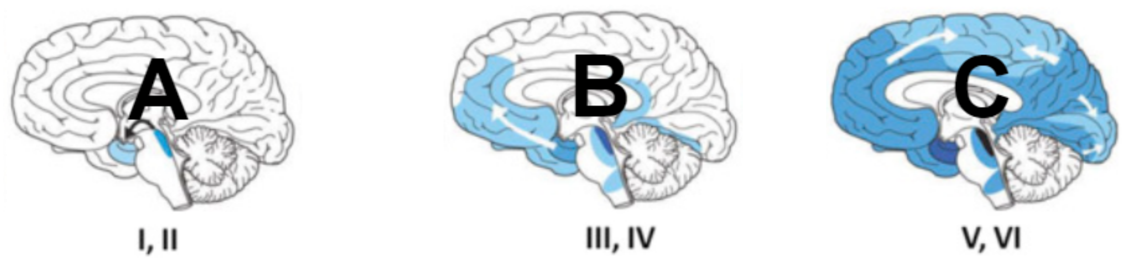
Model 2: fully adjusted					
Metformin	64,288	**0.502**	<0.001	0.434	0.581
Follow-up >=10 years					
Model 1: (age and gender)					
Metformin	76,065	**0.825**	<0.001	0.779	0.874
Model 2: fully adjusted					
Metformin	22,943	**0.696**	<0.001	0.613	0.789

AMP-AD Knowledge Portal

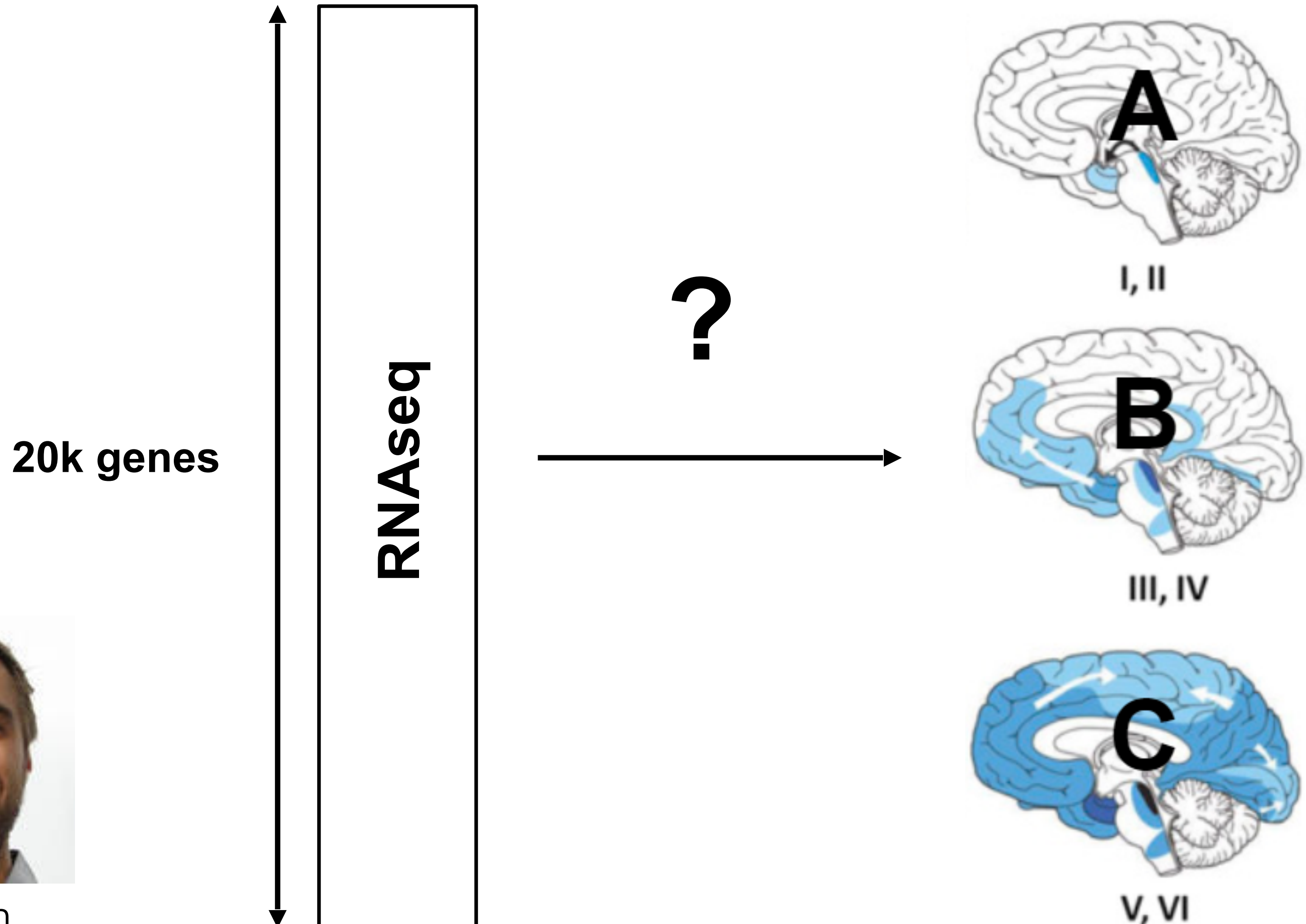
Braak Score

	0	1	2	3	4	5	6
ROSMAP Dorsolateral prefrontal cortex	**7**	**51**	**54**	**176**	**210**	**133**	**7**



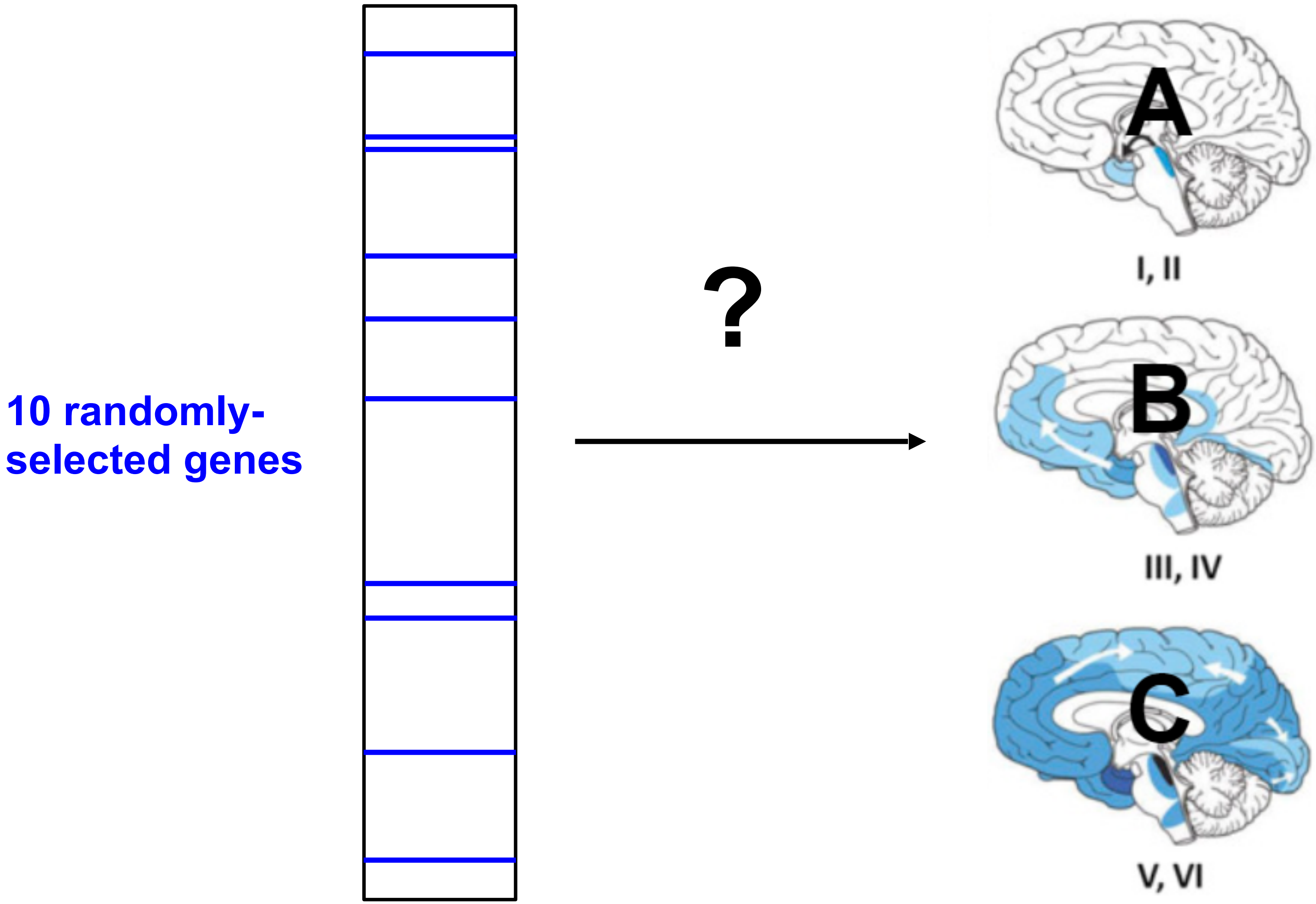
https://www.synapse.org/#!Synapse:syn2580853

Task definition: given an RNAseq profile, predict disease stage (AB, AC, BC, Ordinal)



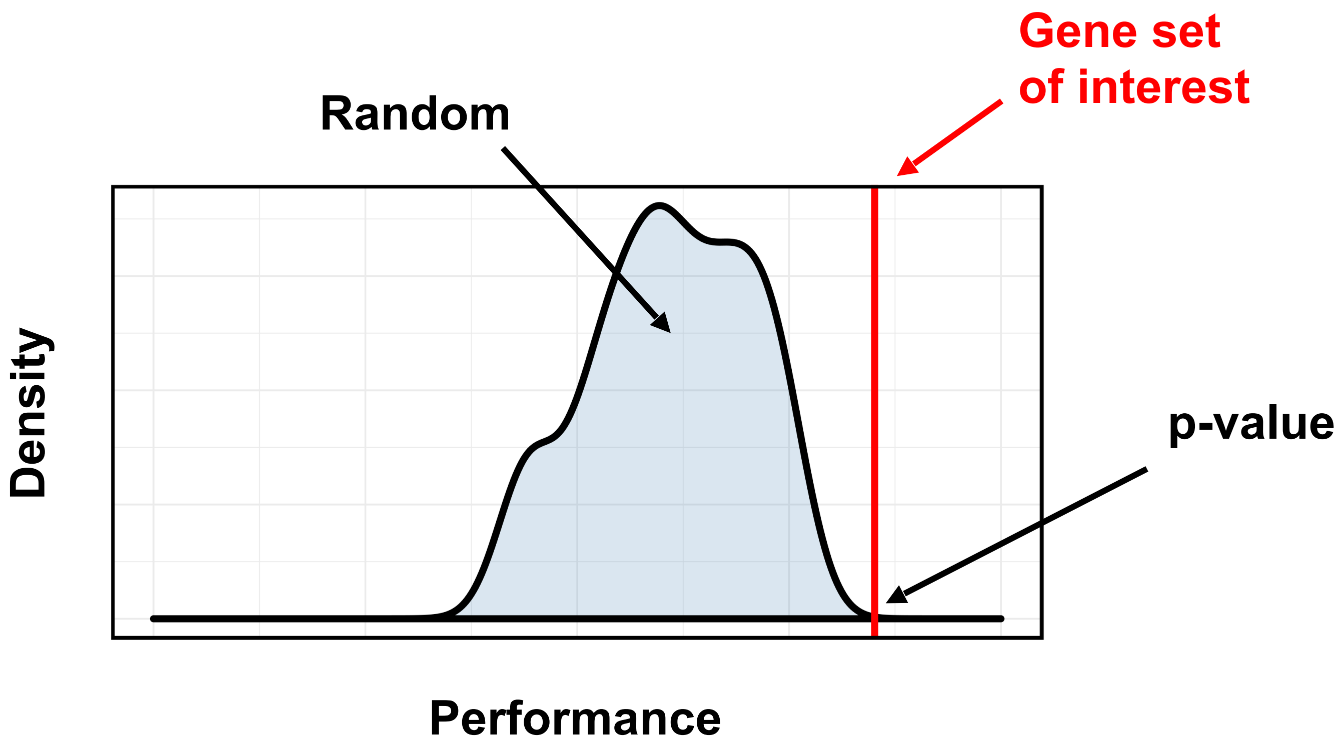
Artem Sokolov

Begin by asking how well does a randomly-selected subset of genes predict disease stage



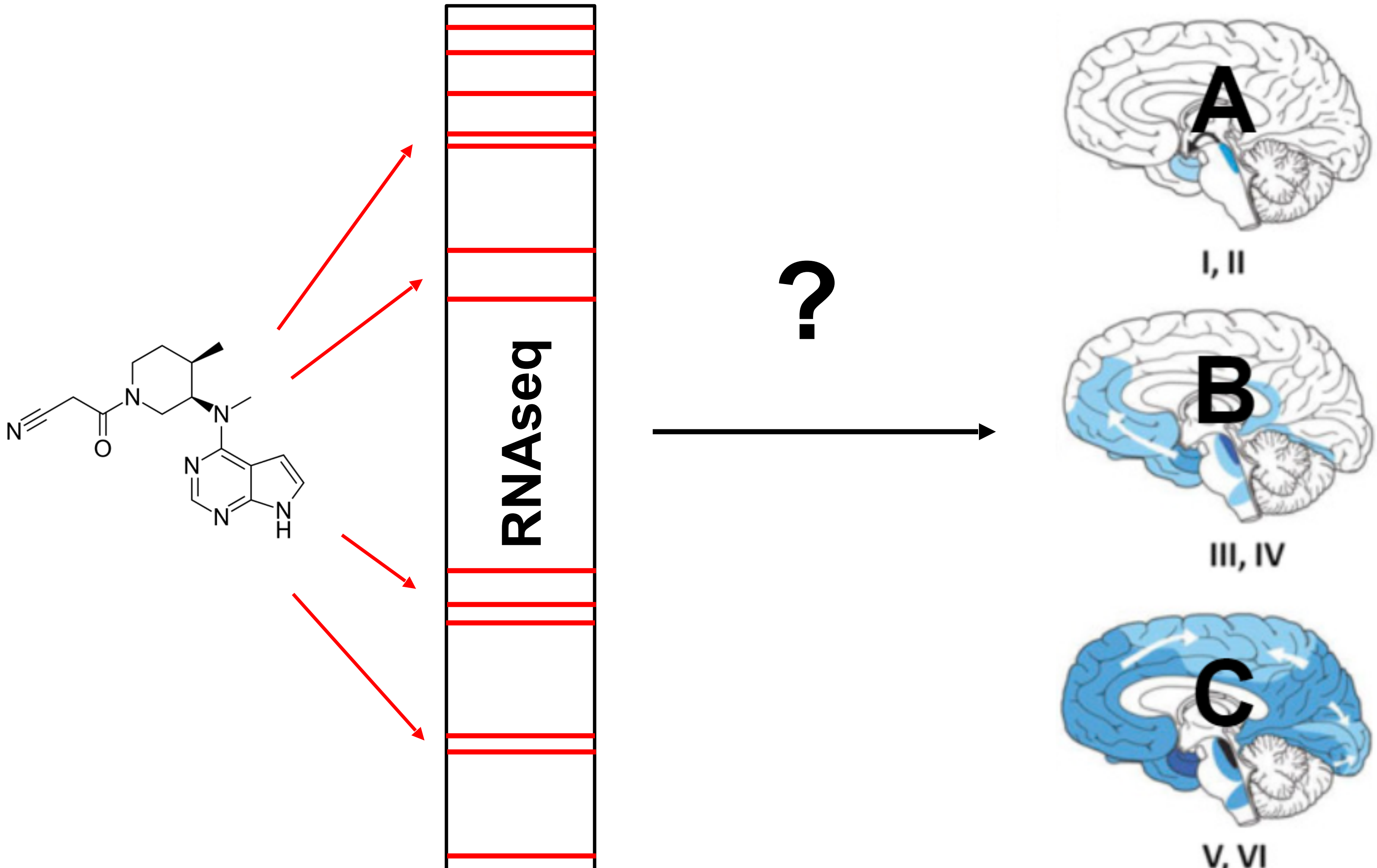
Gene set as a unit of prior knowledge

Intuition: if a gene set of interest is important for predicting phenotypic state, we expect to see higher prediction performance than with a randomly selected gene set of the same cardinality.



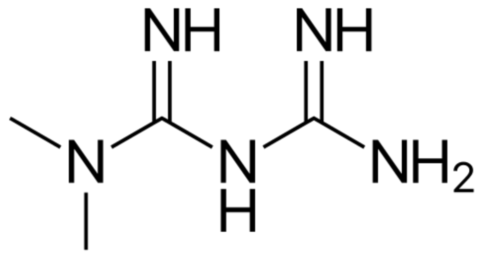
https://github.com/ArtemSokolov/ampad

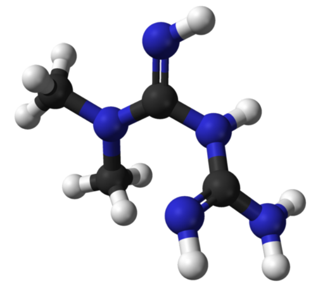
Repurposed drug perturbations to gene expression levels as the gene set of interest



Converting drug names to gene sets

Example:
Metformin





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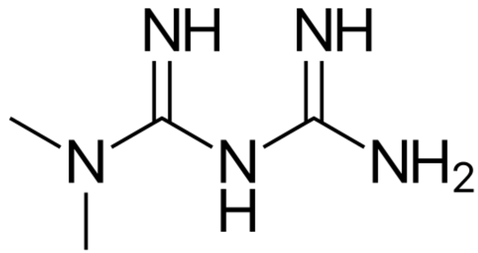

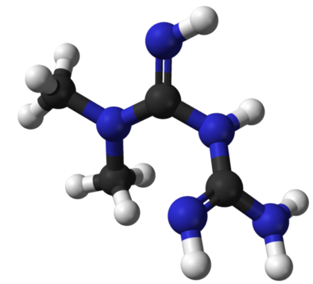

Deciphering Signaling Pathway Networks to Understand the Molecular Mechanisms of Metformin Action

Jingchun Sun, Min Zhao, Peilin Jia, Lily Wang, Yonghui Wu, Carissa Iverson, Yubo Zhou, Erica Bowton, Dan M. Roden, Joshua C. Denny, Melinda C. Aldrich, Hua Xu, Zhongming Zhao

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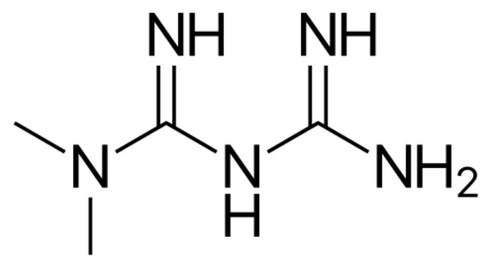

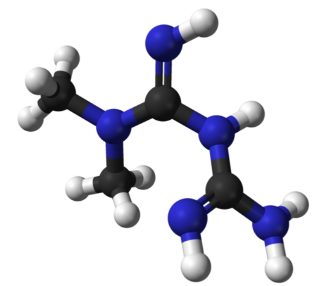

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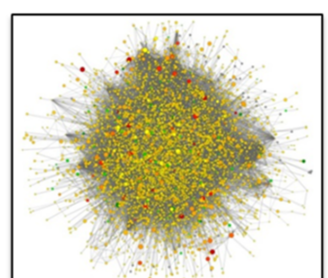
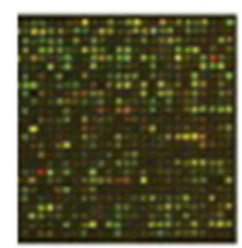
Metformin upstream genes

- Drug targets (DrugBank)
- Pharmacogenomic genes
- Drug PD/PK pathways
- Literature mining

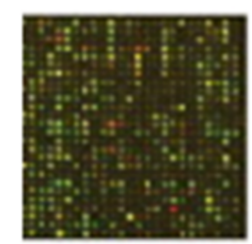
Human SPNetwork



Metformin downstream genes

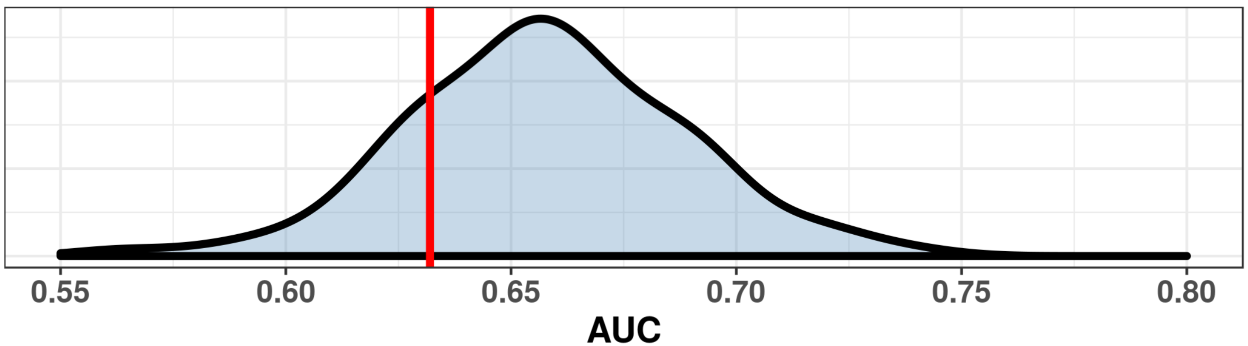


Control

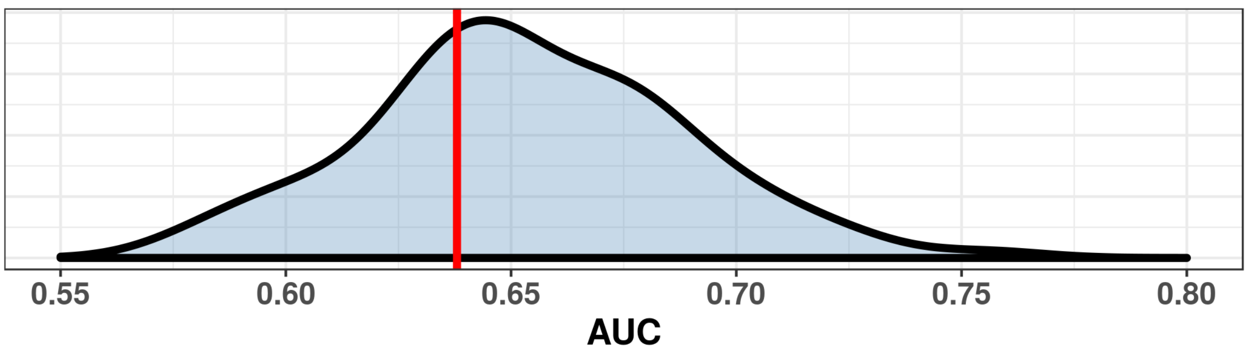


Treatment

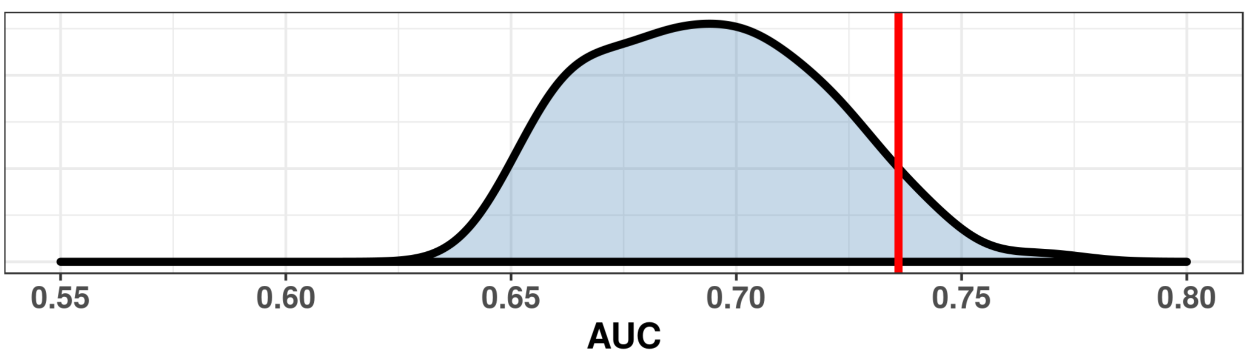
Compare drug-related gene set against random sets for Metformin in the Break predictor



Mined
Size: 64
Area UC: 0.632
pval: 0.79

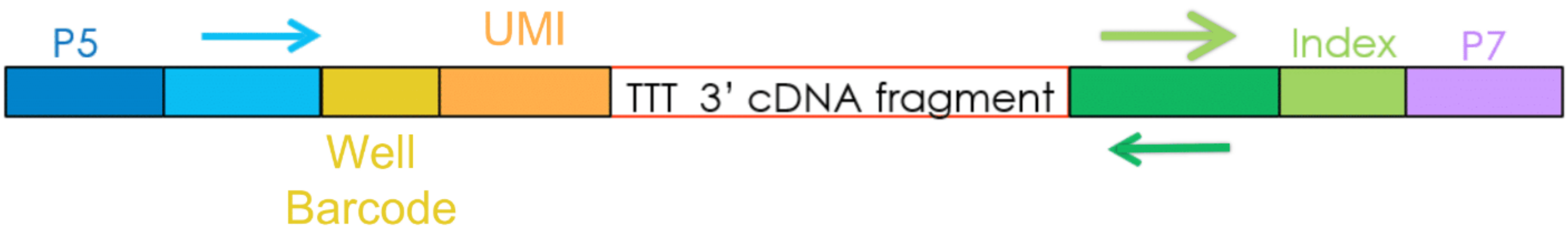


Experimental
Size: 65
Area UC: 0.637
pval: 0.73



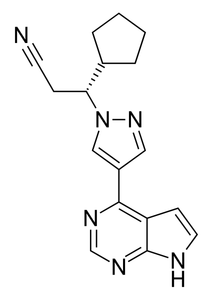
Combined
Size: 472
Area UC: 0.736
pval: 0.06

3' Digital Gene Expression (DGE) allows for high-throughput profiling of multiple 384-well plates



Barcode: **Well/Cell index (N_6) + Unique Molecular Identifier (N_{10})**

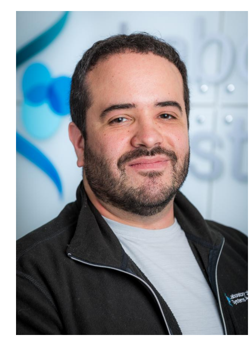
Index: **Plate indexing**



DMSO

ReNcell VM
Human

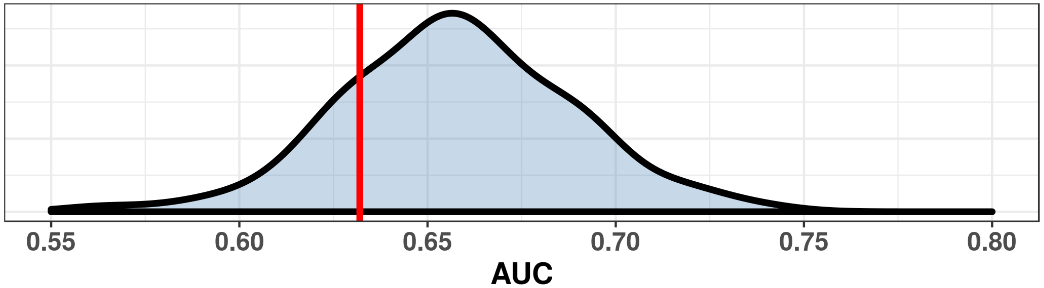
Song…. Albers, Mitchison, Sorger, under review



Steve Rodriguez

Sarah Boswell

Human neuron profiles yield improved performance for Metformin



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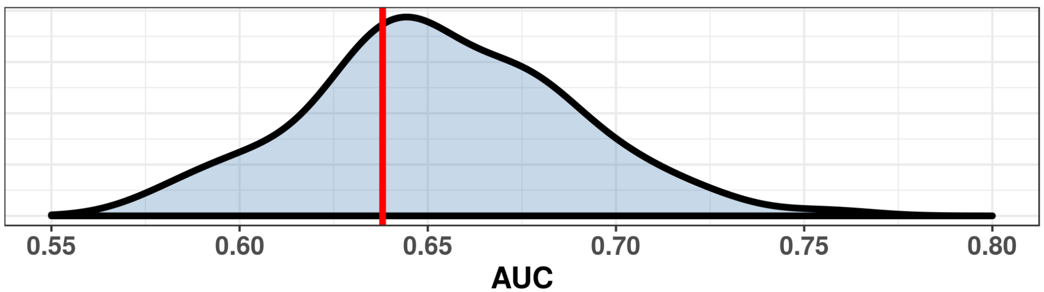

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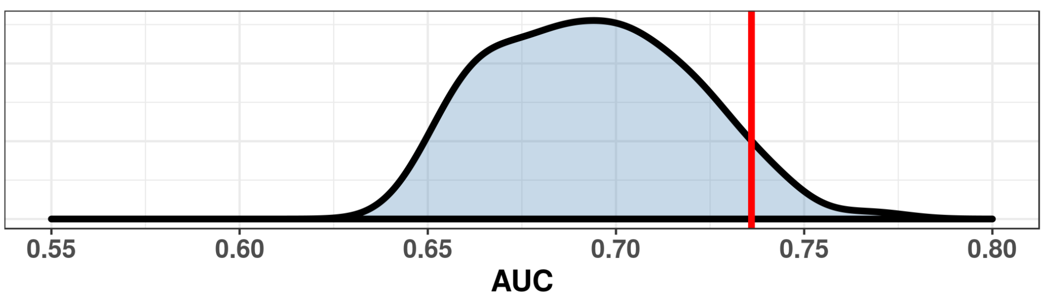

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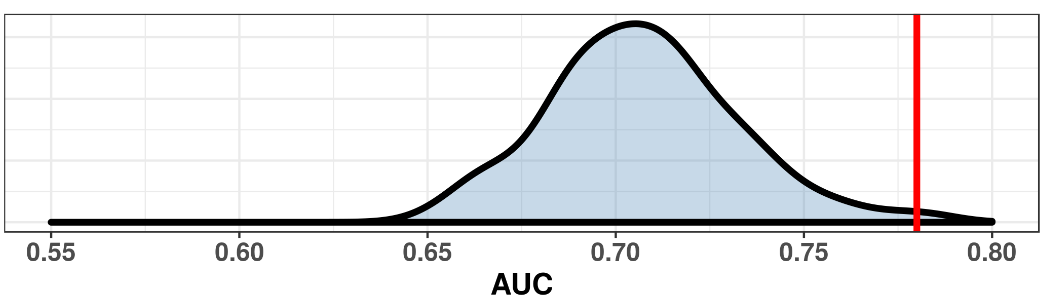
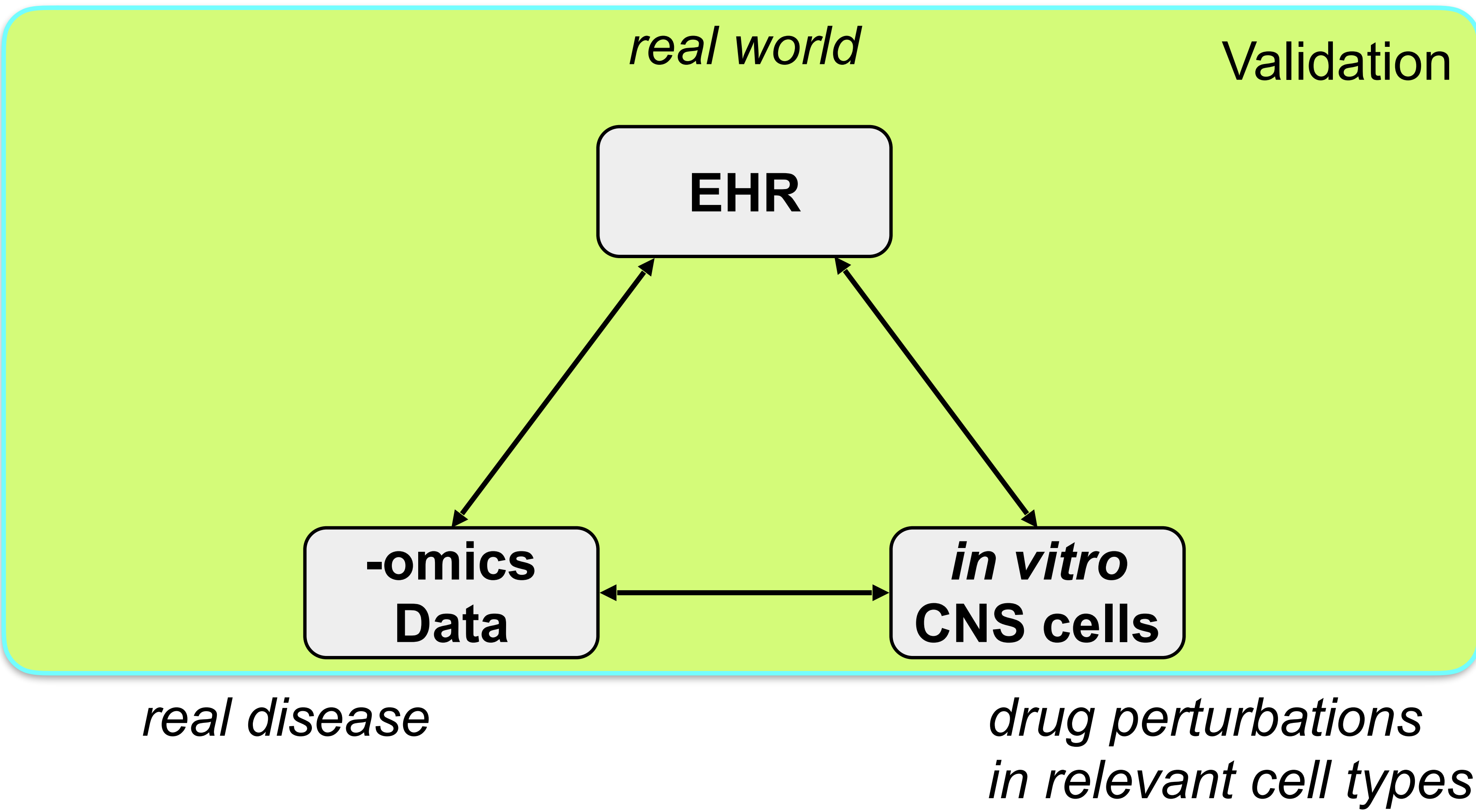


DGE-derived
Size: 901
AUC: 0.780
pval: 0.01

Integrating three data sources



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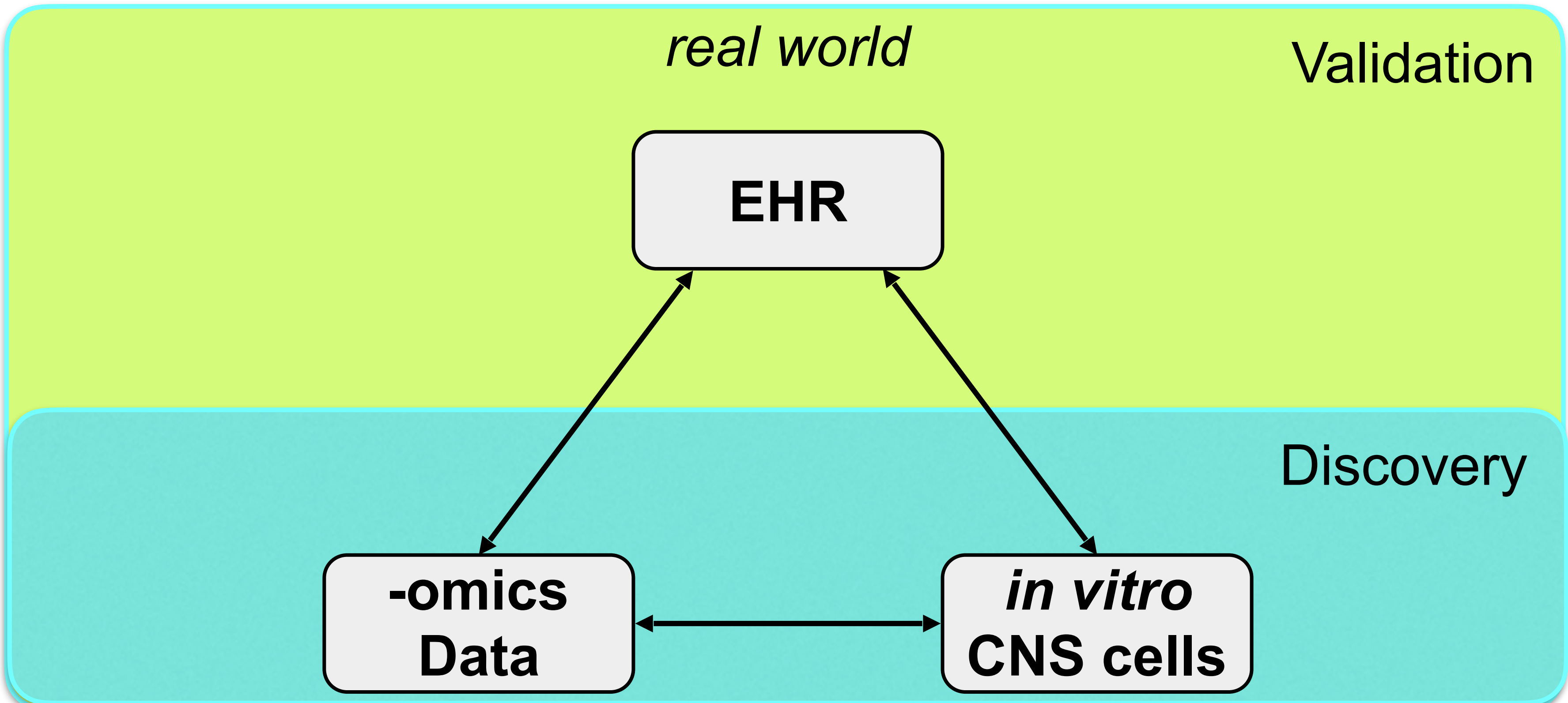
Integrating three data sources



real disease

drug perturbations
in relevant cell types

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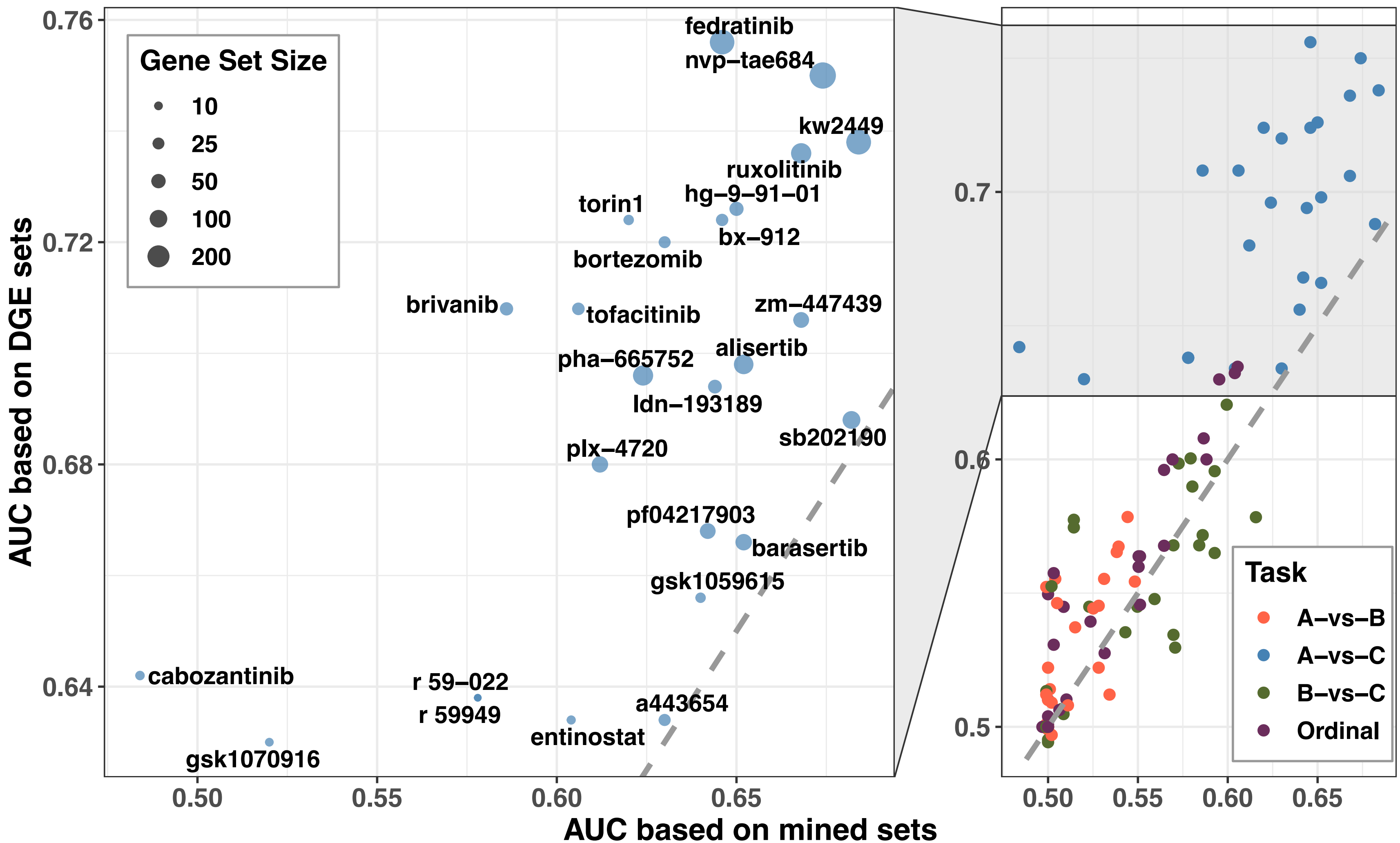
Discovery efforts have identified 20 more drug perturbations that associate with disease progression



Summary

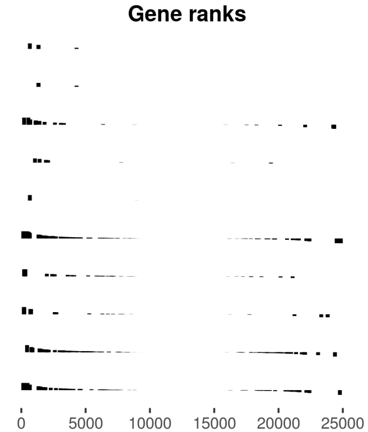
1. In silico drug trials in EHR can evaluate a repurposed drug candidates. The hazard ratio of diabetics on metformin to develop dementia is significantly reduced relative to diabetics on sulfonylurea.

2. Genes differentially expressed by metformin in human CNS cell types predict stage of AD in human brains.

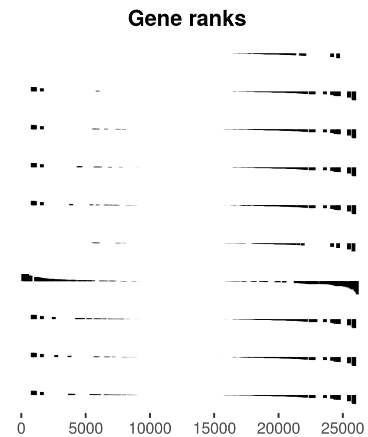
3. Cellular context matters. Drug induced patterns of differentially expressed genes in human CNS cell types predict stage of AD better than drug induced patterns derived from non-CNS cell types.

Induction of defensins and reduced translation by Metformin in human CNS cells

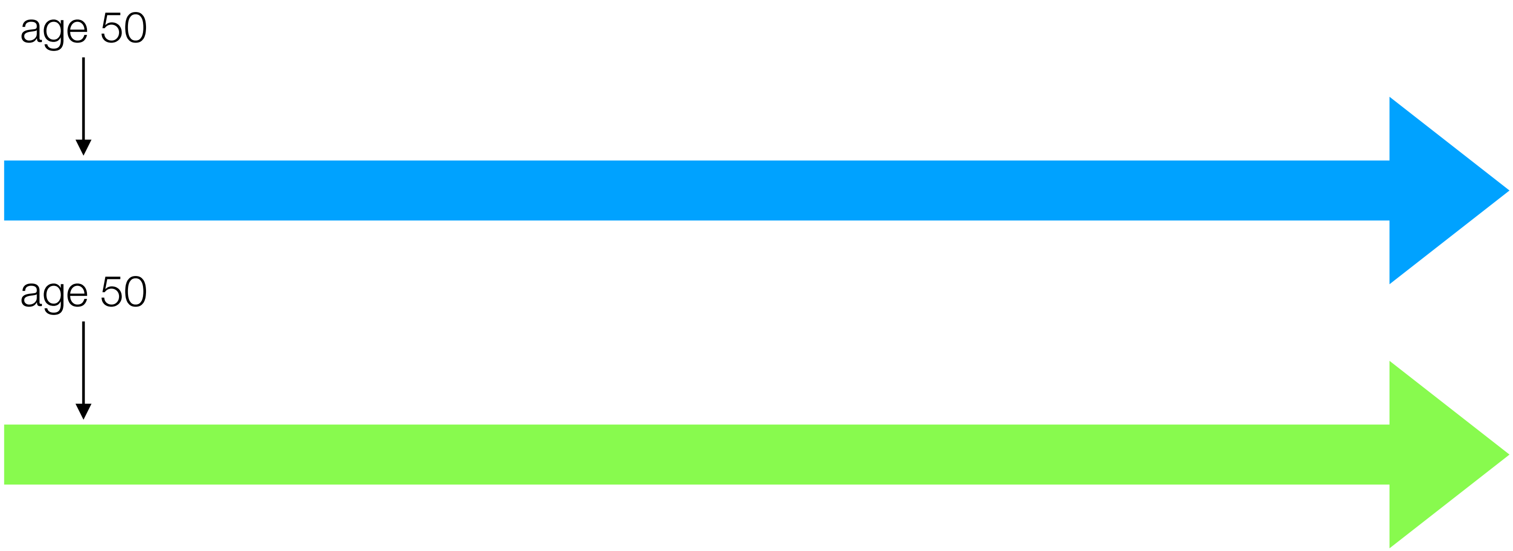
Pathway	Size	NES	p-value
REACTOME_DEFENSINS	14	1.87	< 0.001
REACTOME_BETA_DEFENSINS	11	1.68	0.006
KEGG_TASTE_TRANSDUCTION	31	1.63	0.008
REACTOME_ACETYLCHOLINE_NEUROTRANSMITTER_RELEASE_CYCLE	10	1.63	0.012
REACTOME_BINDING_AND_ENTRY_OF_HIV_VIRION	4	1.47	0.013
REACTOME_GLYCEROPHOSPHOLIPID_BIOSYNTHESIS	77	1.42	0.014
ST_G_ALPHA_I_PATHWAY	34	1.52	0.018
REACTOME_STEROID_HORMONES	27	1.55	0.019
REACTOME_GLYCOSAMINOGLYCAN_METABOLISM	104	1.34	0.021
KEGG_GLYCEROPHOSPHOLIPID_METABOLISM	69	1.39	0.023



Pathway	Size	NES	p-value
KEGG_RIBOSOME	88	-1.82	< 0.001
REACTOME_PEPTIDE_CHAIN_ELONGATION	111	-1.59	< 0.001
REACTOME_3_UTR_MEDIATED_TRANSLATIONAL_REGULATION	132	-1.57	< 0.001
REACTOME_INFLUENZA_VIRAL_RNA_TRANSCRIPTION_AND_REPLICATION	127	-1.56	0.001
REACTOME_SRP_DEPENDENT_COTRANSLATIONAL_PROTEIN_TARGETING_TO_MEMBRANE	134	-1.52	0.001
REACTOME_FORMATION_OF_THE_TERNARY_COMPLEX_AND_SUBSEQUENTLY_THE_43S_COMPLEX	58	-1.63	0.001
KEGG_NEUROACTIVE_LIGAND_RECEPTOR_INTERACTION	238	-1.42	0.001
REACTOME_INFLUENZA_LIFE_CYCLE	160	-1.48	0.001
REACTOME_NONSENSE_MEDIATED_DECAY_ENHANCED_BY_THE_EXON_JUNCTION_COMPLEX	132	-1.51	0.002
REACTOME_TRANSLATION	173	-1.44	0.003



Initiation trial (asymptomatic to diagnosis):



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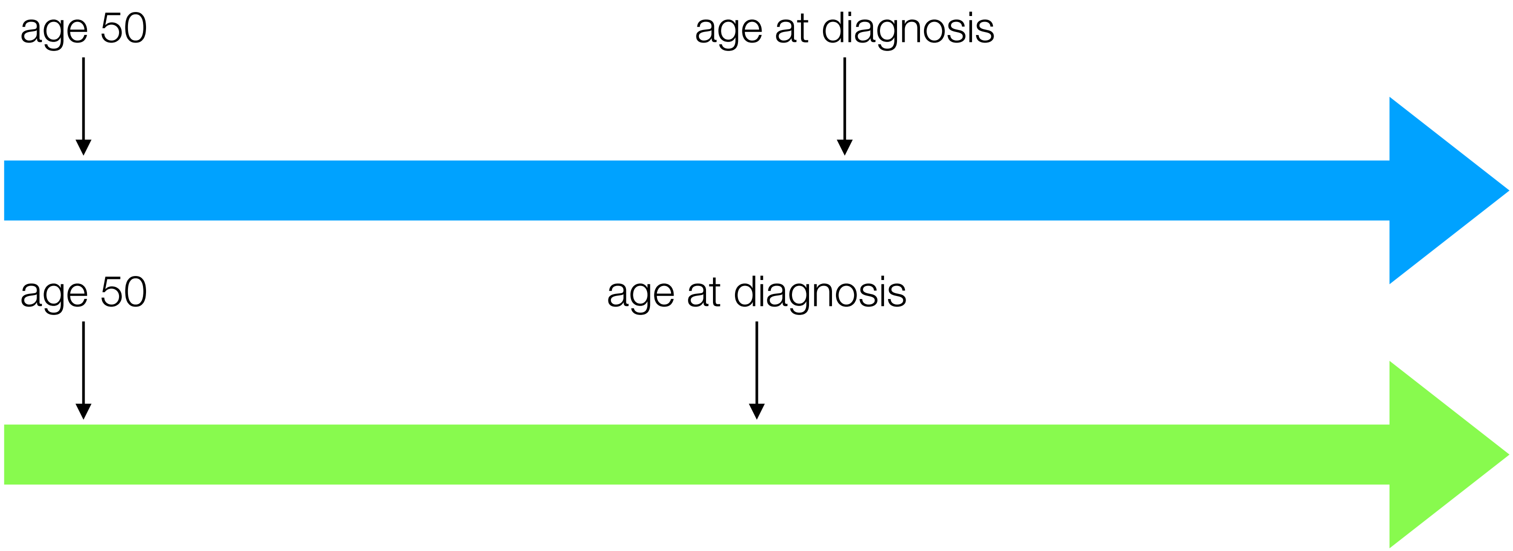

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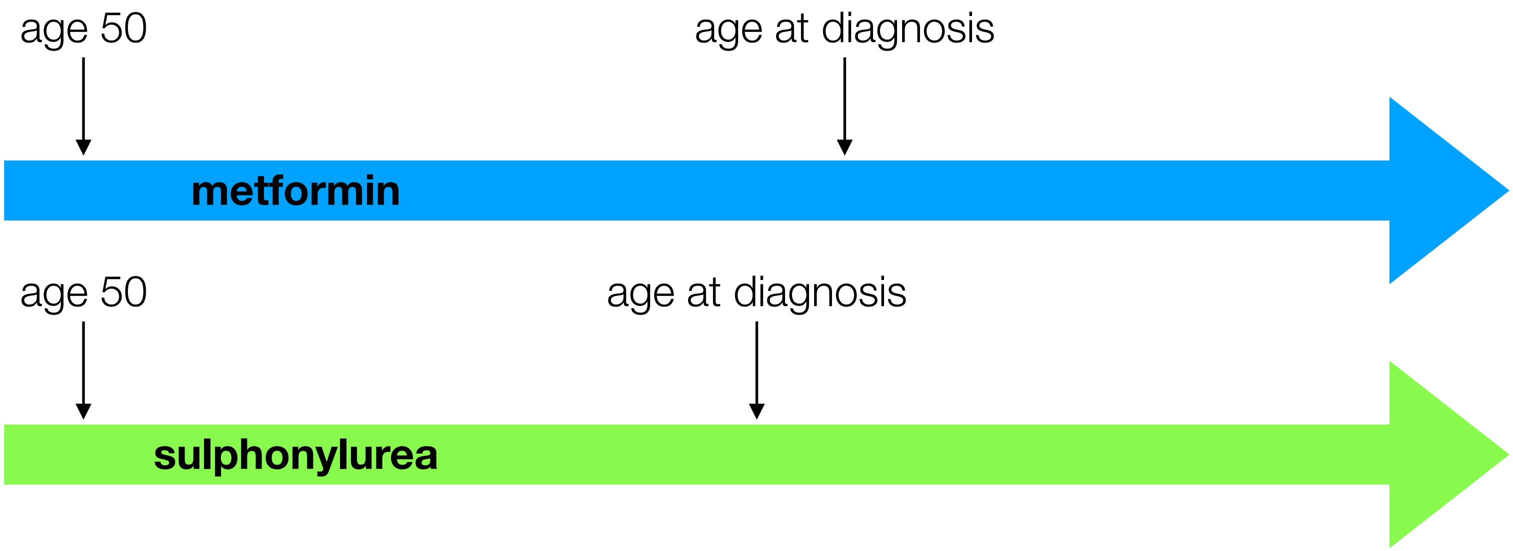

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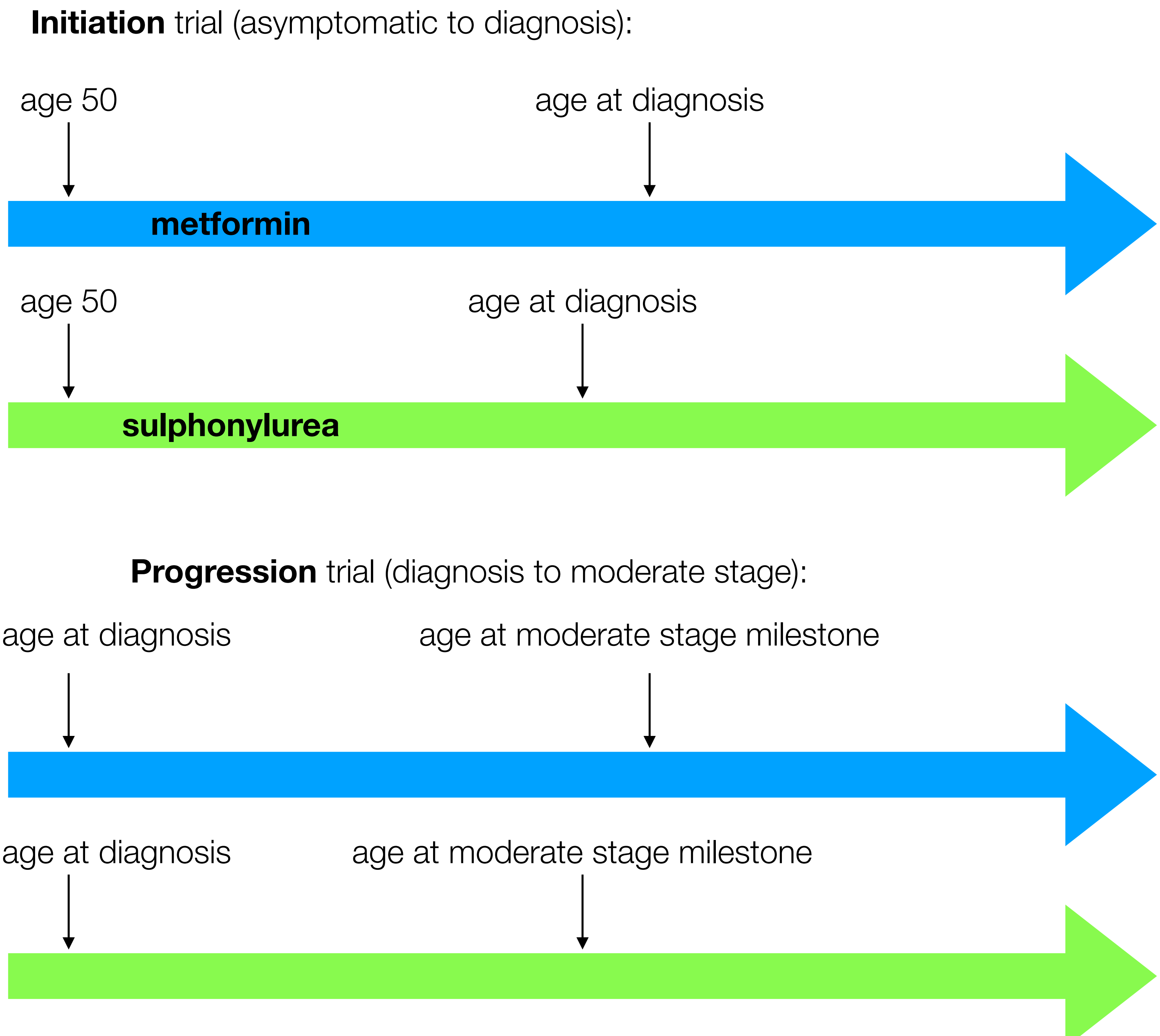

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