

Next Generation Machine Intelligence For Drug Development & Clinical Trial Failure Reduction



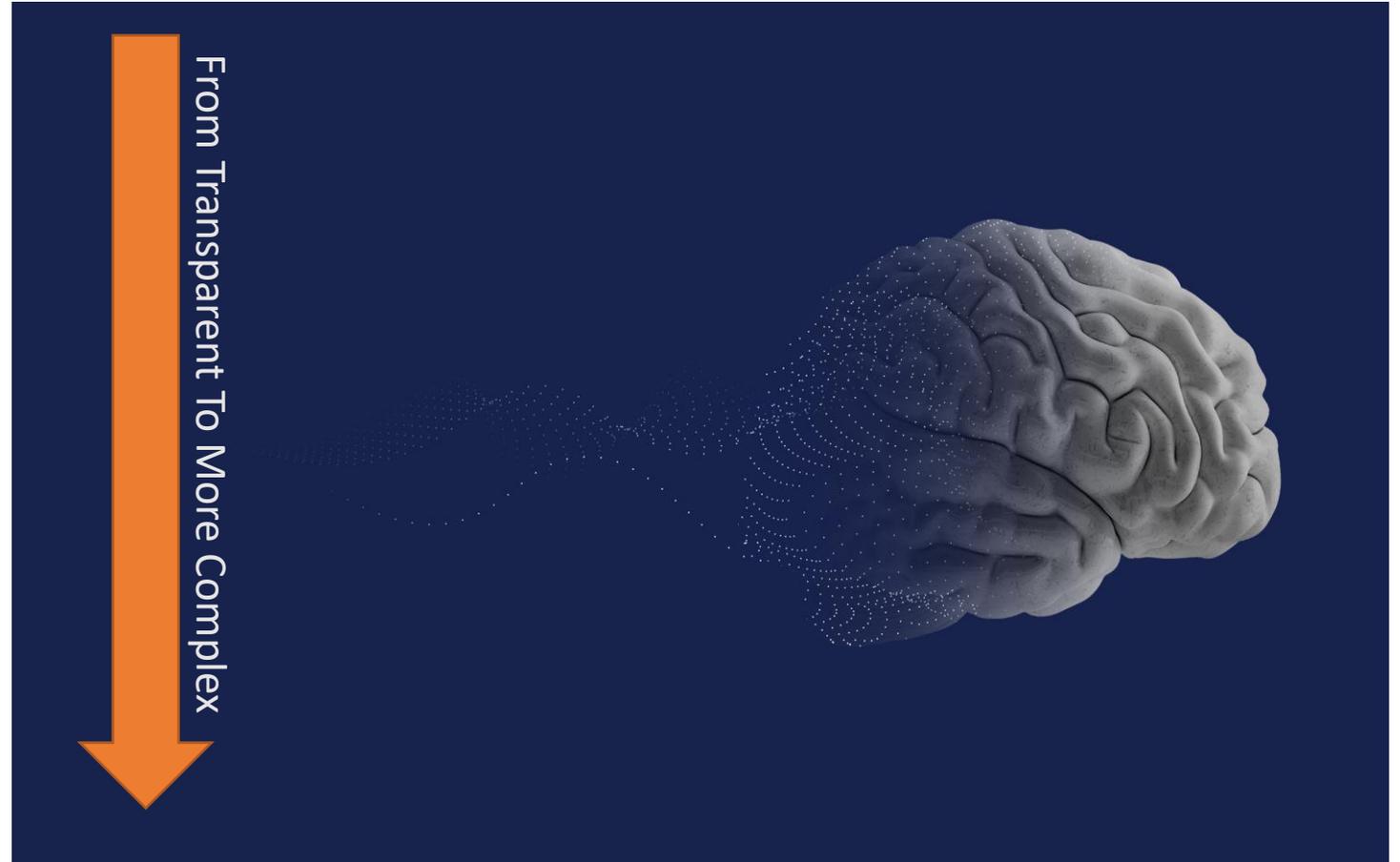
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Disclosures

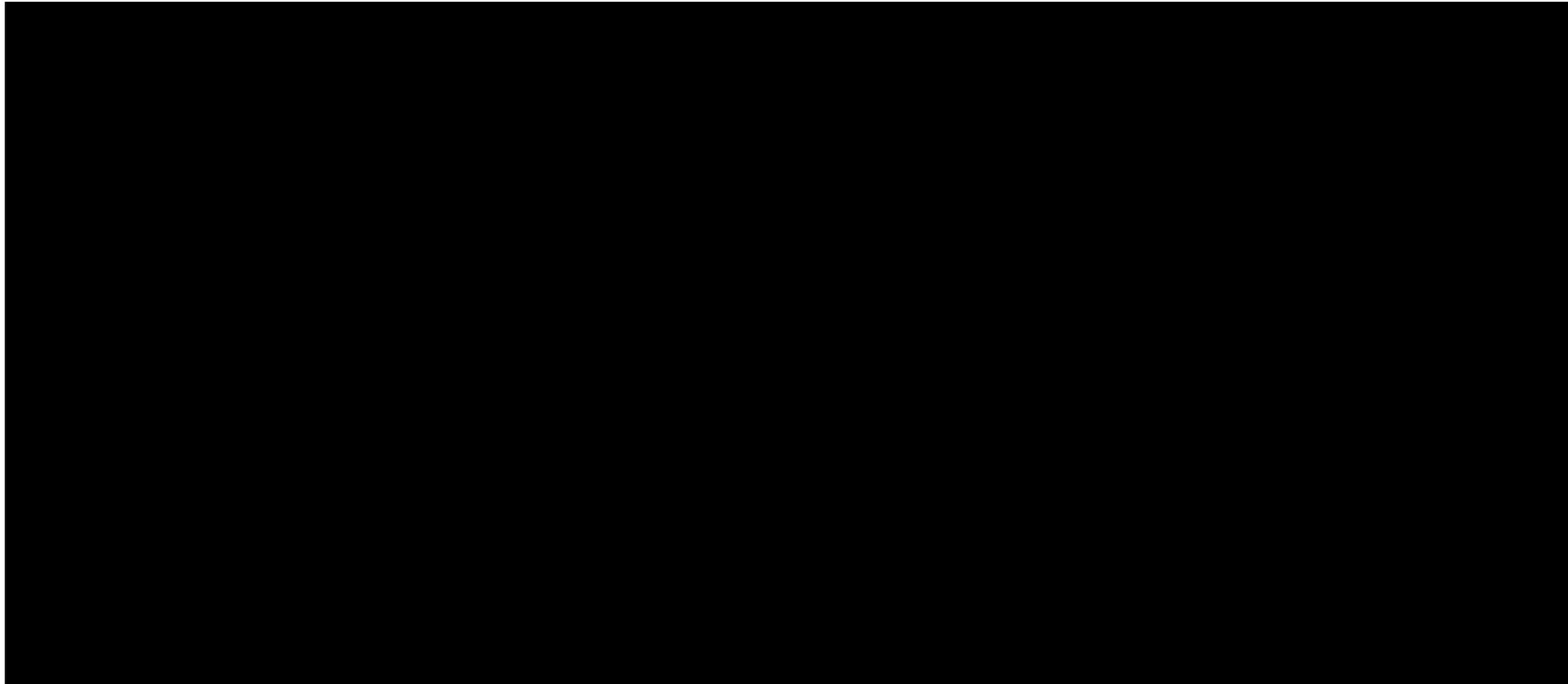
- Major Shareholder and a director of Nurosene Health Inc (MEND)
- Major Shareholder of NetraMark Corp

A Brief Review Of Machine Intelligence/AI

- Statistical methods that rely on correlations
- Software that take **unlabeled** data as input and outputs potential ways they cluster, and for what reason
- Software that takes **labeled** data as input and outputs predictive models
- Some of these methods use sets of decisions trees that work together, some use geometric methods and other mathematical tricks, and some...
- Some methods attempt to mimic what we think neurons are doing – we call these methods Deep Neural Networks, though there are new and less popular methods emerging in this class

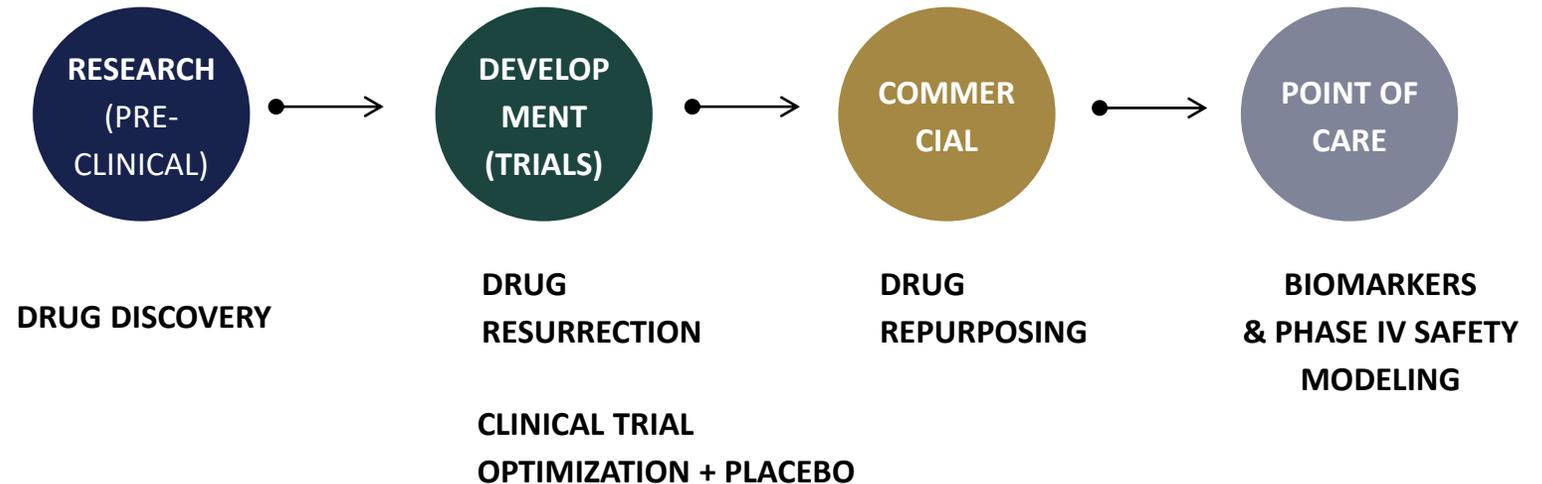


Augmented Intelligence & Closing The Gap Between MDs and AI – A demo

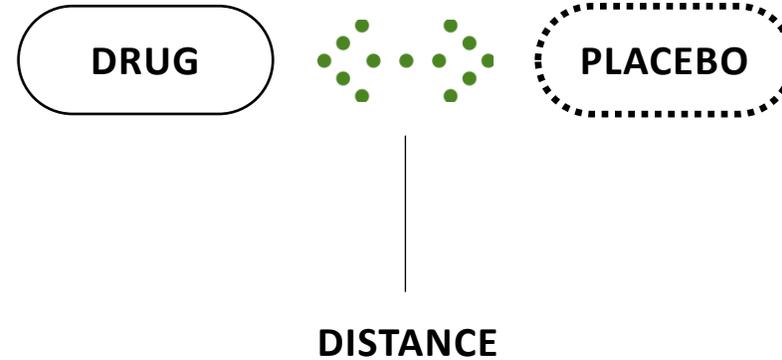
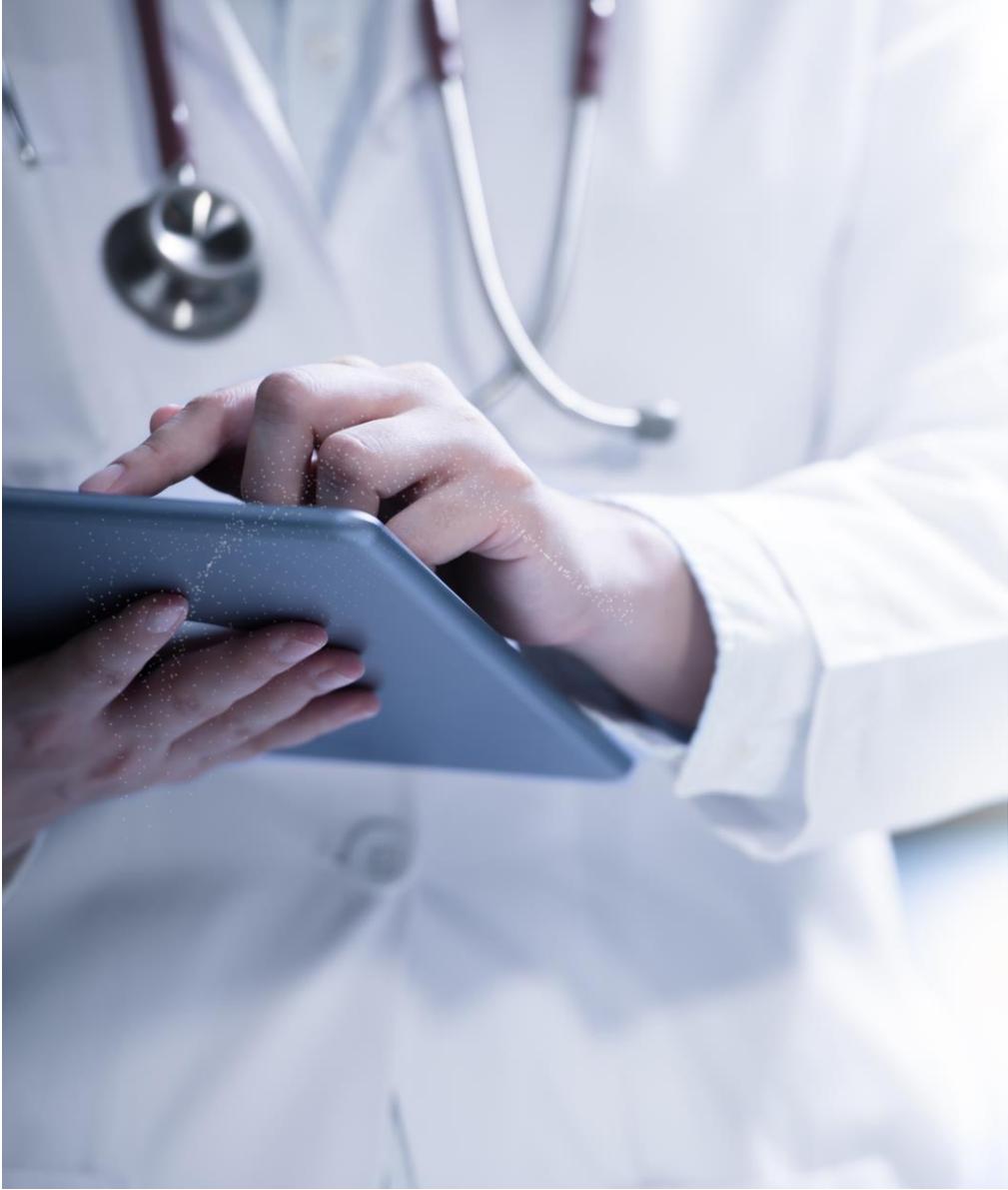


Clinical Trial Optimization and De-Risking

- The previous augmented intelligence provides insights generated by the AI and physicians together to optimize clinical trials



Example: Drug To Placebo 'Distance'



- There are several groups offering placebo response mitigation tools and ML based tools are on the rise
- Several groups are utilizing a scale designed to capture psychological and attitudinal information and by using statistical and shallow ML methods, feedback is given to the pharma company so that they can improve recruitment in phase III trials
- By assigning a score to each patient in terms of their placebo response tendency, one can prepare for their next trial(s)
- A major problem is that one may not want to remove too many placebo responders as they are likely responders to the active therapy
- Thus some groups are studying how to evaluate the drug and how 'far' it is from placebo through statistics that arise from powerful patient stratification methods

Biomarkers are hard Part 1: The *Monster* We Are Trying To Tame

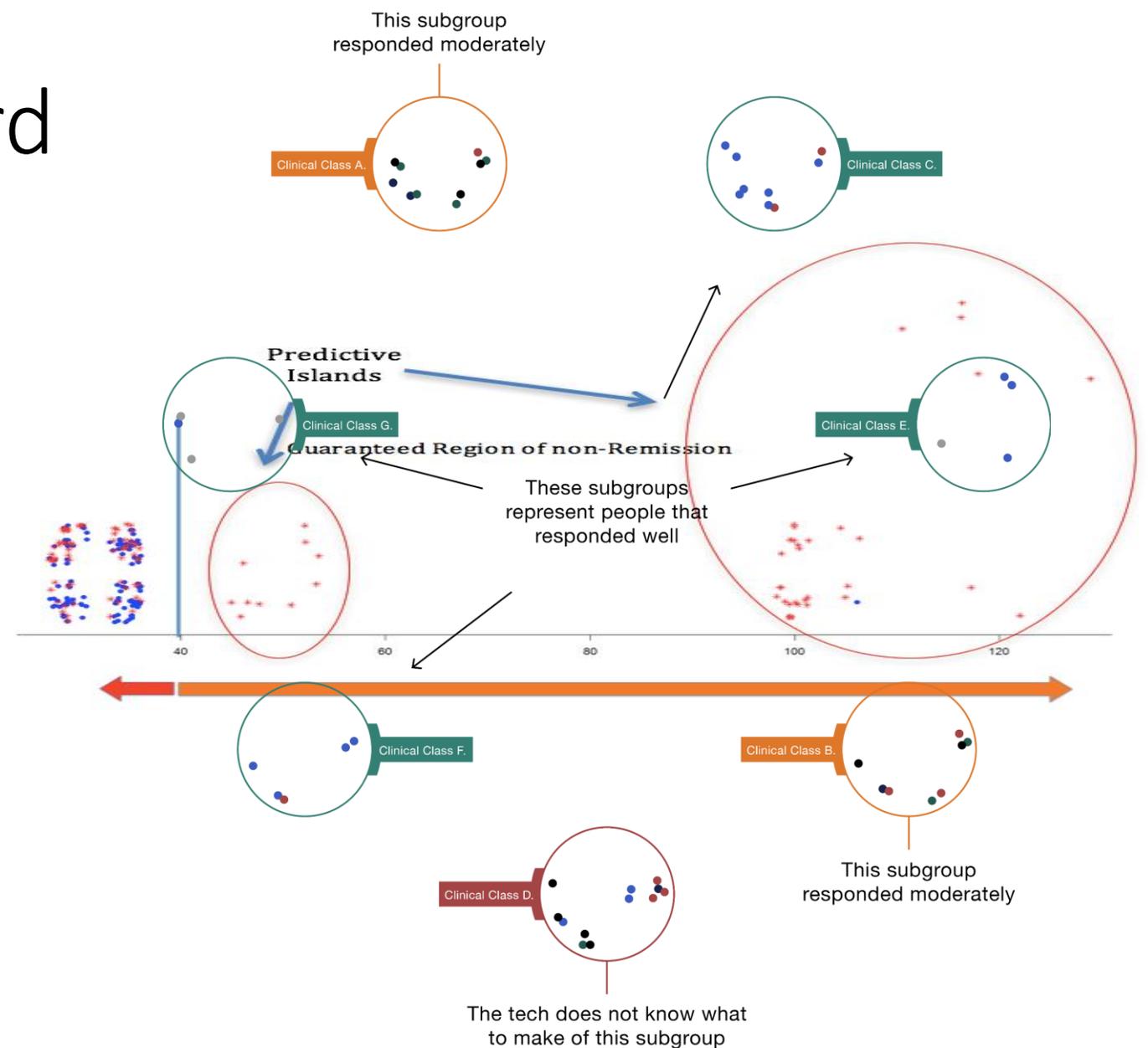
- Do you know that every time you thoroughly shuffle a deck of cards, you are holding a unique signature of your existence?
- If you were capable of shuffling a deck of cards every minute for the entire history of the universe, it is highly unlikely that the same sequence would occur
- Imagine how difficult it is to find an optimal combination of genes for a biomarker!
- Methods are now being devised to deal with this problem in ways that go beyond our usual variable importance methods that should improve the creation of biomarkers.



Biomarkers are Hard

Part 2

- You will hear about a large biomarker effort by Dr. Ray Lam who is a colleague of mine from my days at the CANBIND effort on MDD
- This image is from an MDD data set that utilized miRNA and you can see the problem – methods that are not capable of disentangling the different ways that patients relate to each other will create models that will not replicate – this one perspective captures a powerful response signal, but only for about 40 patients out of 150
- Many of these perspectives exist within psychiatric disorders and this is why I believe the RDoC perspective is critical and why causal and explainable AI methods should be used to create mosaics of perspectives for biomarker efforts
- We need to integrate SNPs, expression, methylation, and microbiome to get a more complete picture = \$\$\$ + complexity
- Real world data through apps have the potential to add an incredible amount of resolution through live sampling
- Work on placebo response is confirming that attitude is a powerful factor especially in psychiatry and pain



Inherited Vulnerabilities VS Acquired

- We all know that our environment can affect our health and methylation can provide a sharp glimpse into this
- Through recent work in psychiatry and neurodegeneration it has been noted that an integration of many factors can help improve biomarkers
- In the case on the right these people were able to use a simple ML method to achieve a PPV of 80% on an independent data set derived from 353 patient samples by using just methylation

[nature](#) > [translational psychiatry](#) > [articles](#) > article

Article | [Open Access](#) | [Published: 03 August 2021](#)

A machine learning case–control classifier for schizophrenia based on DNA methylation in blood

[Chathura J. Gunasekara](#), [Eilis Hannon](#), [Harry MacKay](#), [Cristian Coarfa](#), [Andrew McQuillin](#), [David St. Clair](#), [Jonathan Mill](#) & [Robert A. Waterland](#) 

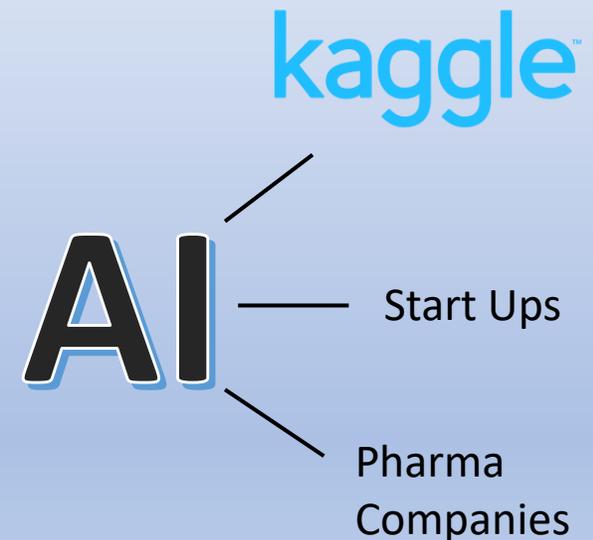
[Translational Psychiatry](#) **11**, Article number: 412 (2021) | [Cite this article](#)

MESSAGE: Future ML based biomarker discovery studies in psychiatry should incorporate methylation in addition to gene expression, SNPs, miRNA, microbiome, and clinical scales that include attitudinal measures.

How Are We Enabling These Programs In Rare Diseases?

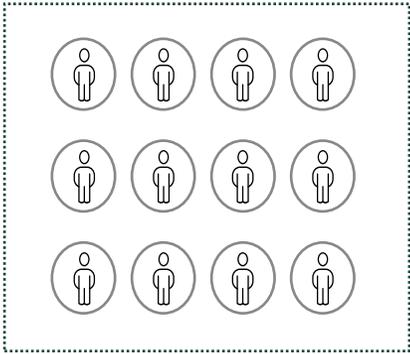
Patient Advocacy

- Patient advocacy improves treatment discovery through enriched data + open science
- This allows AI to integrate many different types of data and to gain access to larger samples, especially for rare diseases

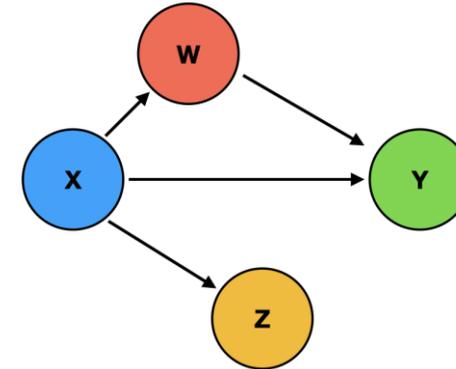
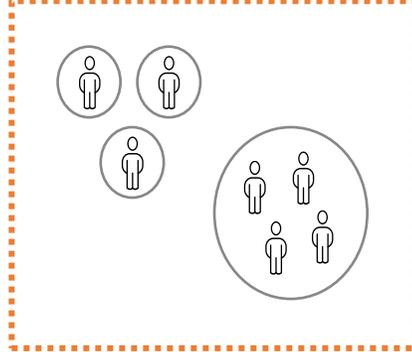


What's Coming: Hypothesis Generating AI As A 'Robot Scientist' – The Emergence Of Causal AI

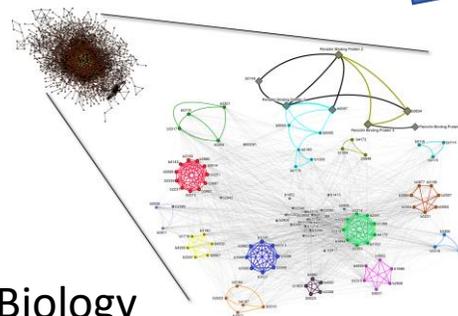
LABELLED PATIENT POPULATION



DISCOVERS DENOISED PURE SUBPOPULATIONS



Causal Genetic Variables



Systems Biology
Computations



FINAL HYPOTHESES

- Mitochondrial deficiencies
- Senescence issues
- Telomere alterations

Example: Aging genetic cohort from a 2 year old to 96 year old. **Only one label:** Over 50 vs Under 50. The goal of the experiment was to see if the machine could learn without much supervision and bias.



THANK YOU

CONTACT

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