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

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Acknowledgments

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Integrating three data sources with two informatics approaches.

- EHR
- -omics Data
- in vitro CNS cells

real world

real disease

drug perturbations in relevant cell types

Systems Pharmacology
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

Systems Pharmacology
In silico drug trials - longitudinal EHR analyses

**Initiation** trial (asymptomatic to diagnosis):

- age 50
- age 50

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

Ioanna Tzoulaki

Imperial College London

Massachusetts Institute of Technology
In silico drug trials - longitudinal EHR analyses

**Initiation** trial (asymptomatic to diagnosis):

- Age 50
- Metformin
- Sulphonylurea

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In silico drug trials - longitudinal EHR analyses

**Initiation** trial (asymptomatic to diagnosis):

- **metformin**
- **sulphonylurea**

Ioanna Tzoulaki

CPRD
- NHS of UK
- 20 million patients
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Metformin reduces progression to dementia relative to sulphonylurea in diabetics

<table>
<thead>
<tr>
<th>Strata</th>
<th>Number of obs</th>
<th>Hazard Ratio</th>
<th>P-value</th>
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<td>Metformin</td>
<td>128,727</td>
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<tr>
<td>Metformin</td>
<td>64,288</td>
<td>0.502</td>
<td>&lt;0.001</td>
<td>0.434</td>
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Fully adjusted includes age at prescription, gender, socioeconomic status, vascular comorbidities, smoking, BMI, and HbA1c level
Metformin reduces progression to dementia relative to sulphonylurea in diabetics

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<td><strong>Follow-up &gt;=10 years</strong></td>
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<td>Model 1: (age and gender)</td>
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<td>Metformin</td>
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<td>22,943</td>
<td>0.696</td>
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Braak Score

0  1  2  3  4  5  6

ROSmap
Dorsolateral prefrontal cortex

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<tr>
<th></th>
<th>7</th>
<th>51</th>
<th>54</th>
<th>176</th>
<th>210</th>
<th>133</th>
<th>7</th>
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https://www.synapse.org/#!Synapse:syn2580853
Task definition: given an RNAseq profile, predict disease stage (AB, AC, BC, Ordinal)
Begin by asking how well does a randomly-selected subset of genes predict disease stage?

10 randomly-selected genes
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
Converting drug names to gene sets

Example: Metformin

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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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 (N₆) + Unique Molecular Identifier (N₁₀)

**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

Mined
Size: 64
AUC: 0.632
pval: 0.79

Experimental
Size: 65
AUC: 0.637
pval: 0.73

Combined
Size: 472
AUC: 0.736
pval: 0.06

DGE-derived
Size: 901
AUC: 0.780
pval: 0.01
Integrating three data sources

- EHR
- -omics Data
- in vitro CNS cells

real world
Validation

real disease
drug perturbations in relevant cell types

Systems Pharmacology
Integrating three data sources

EHR

-omics Data

in vitro CNS cells

real world

Validation

real disease

Discovery

drug perturbations in relevant cell types

Systems Pharmacology
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

<table>
<thead>
<tr>
<th>Pathway</th>
<th>Gene ranks</th>
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<th>p-value</th>
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Initiation trial (asymptomatic to diagnosis):

age 50

age 50

Ioanna Tzoulaki
Initiation trial (asymptomatic to diagnosis):

Age 50

Age at diagnosis

Age 50

Age at diagnosis

Ioanna Tzoulaki
**Initiation** trial (asymptomatic to diagnosis):

- **Age 50**
  - **Metformin**
  - **Age at diagnosis**
- **Age 50**
  - **Sulphonylurea**
  - **Age at diagnosis**

Ioanna Tzoulaki
**Initiation** trial (asymptomatic to diagnosis):

- age 50
- age at diagnosis
- **metformin**

**Progression** trial (diagnosis to moderate stage):

- age at diagnosis
- age at moderate stage milestone
- **sulphonylurea**