

Keynote 1: Explainable AI in Precision Medicine

- Su-In Lee is an Associate Professor in the Paul G. Allen School of Computer Science & Engineering, and an Adjunct Associate Professor in the Genome Sciences Department, the Department of Electrical Engineering and the Department of Biomedical Informatics and Medical Education at the University of Washington. She has received the National Science Foundation CAREER Award and been named an American Cancer Society Research Scholar.



Explainable Artificial Intelligence in Precision Medicine

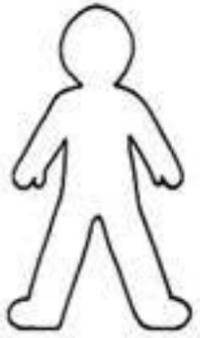
Su-In Lee

Paul G. Allen School of Computer Science & Engineering

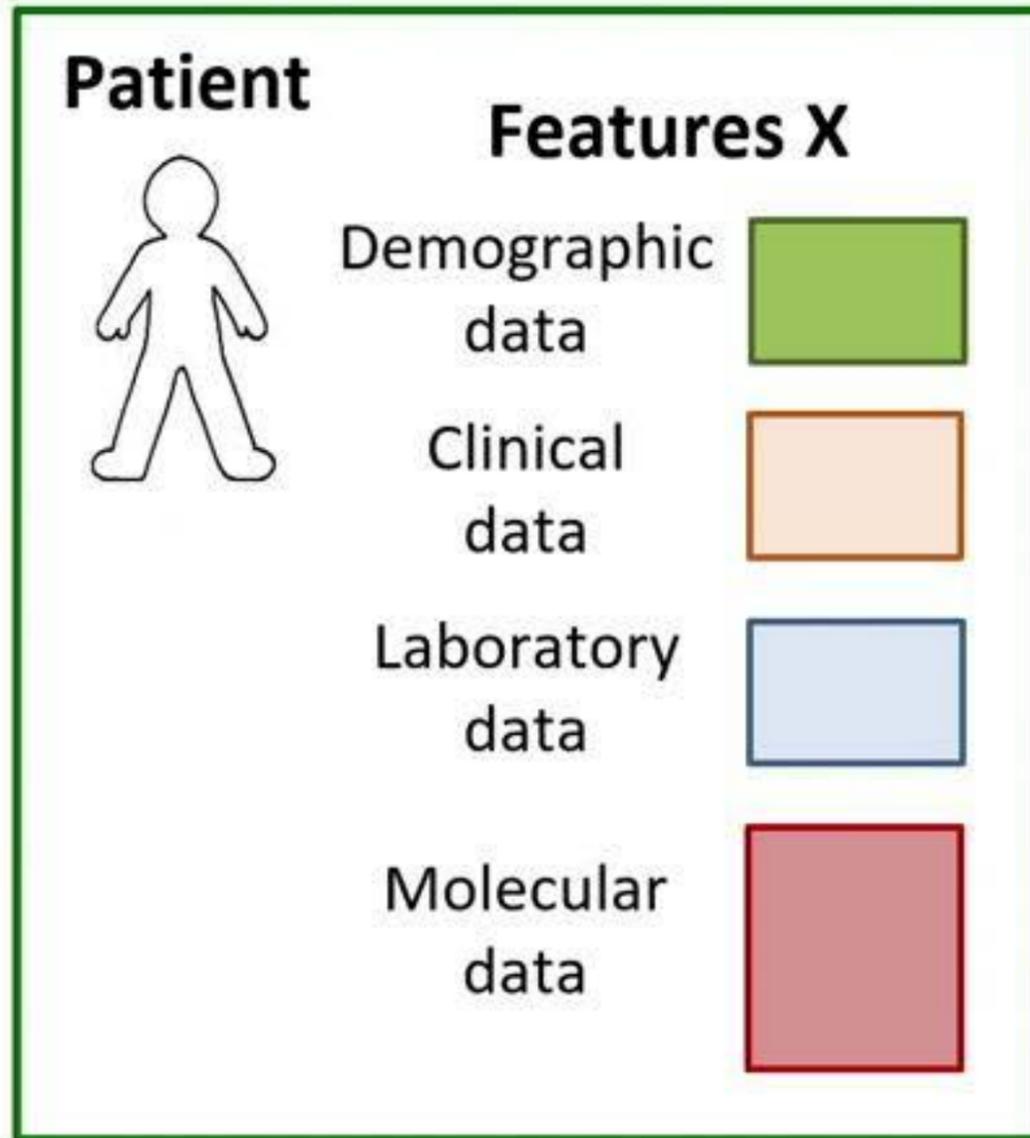
University of Washington, Seattle

What current machine learning (ML) *can* do for precision medicine

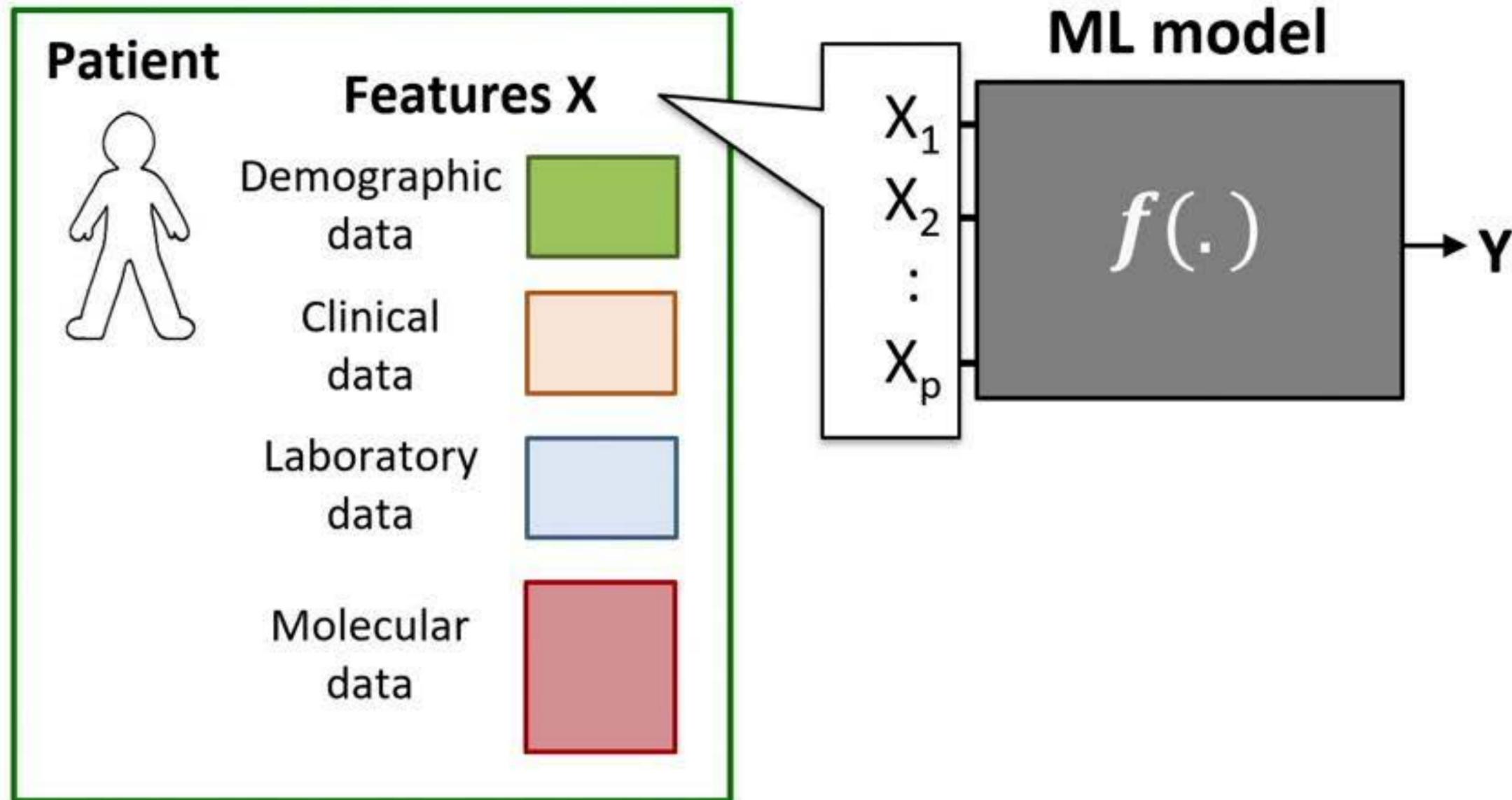
Patient



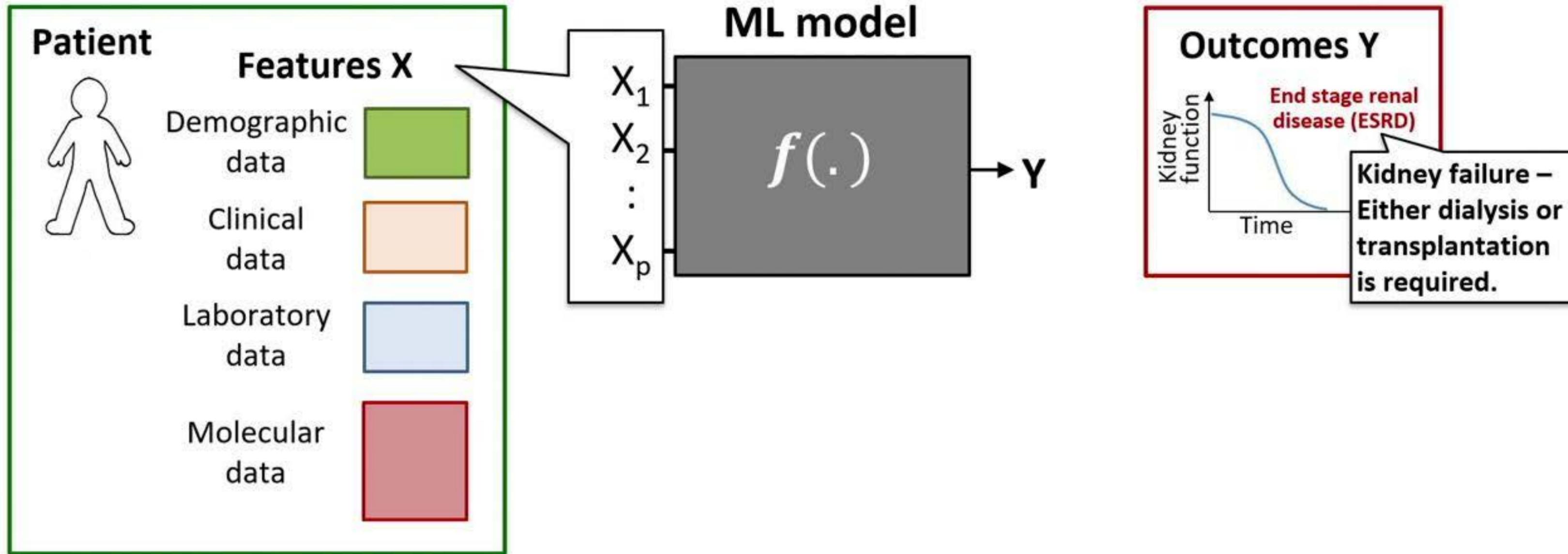
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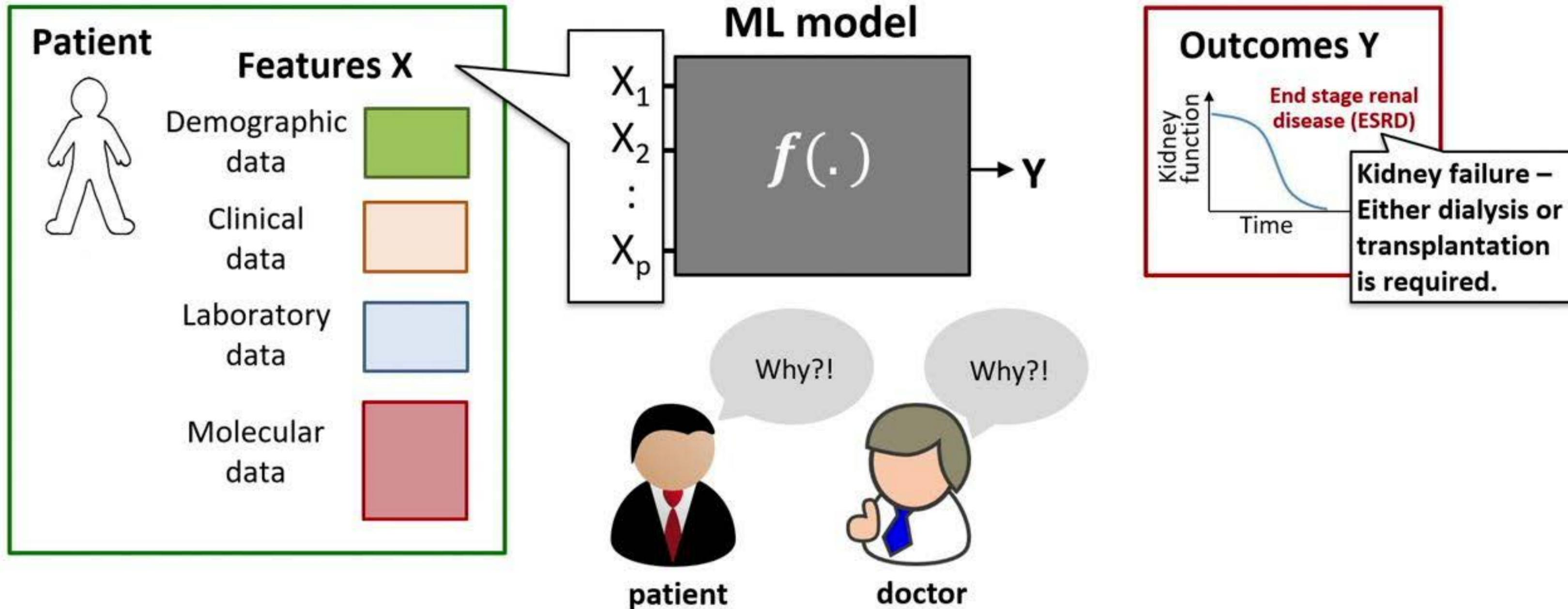
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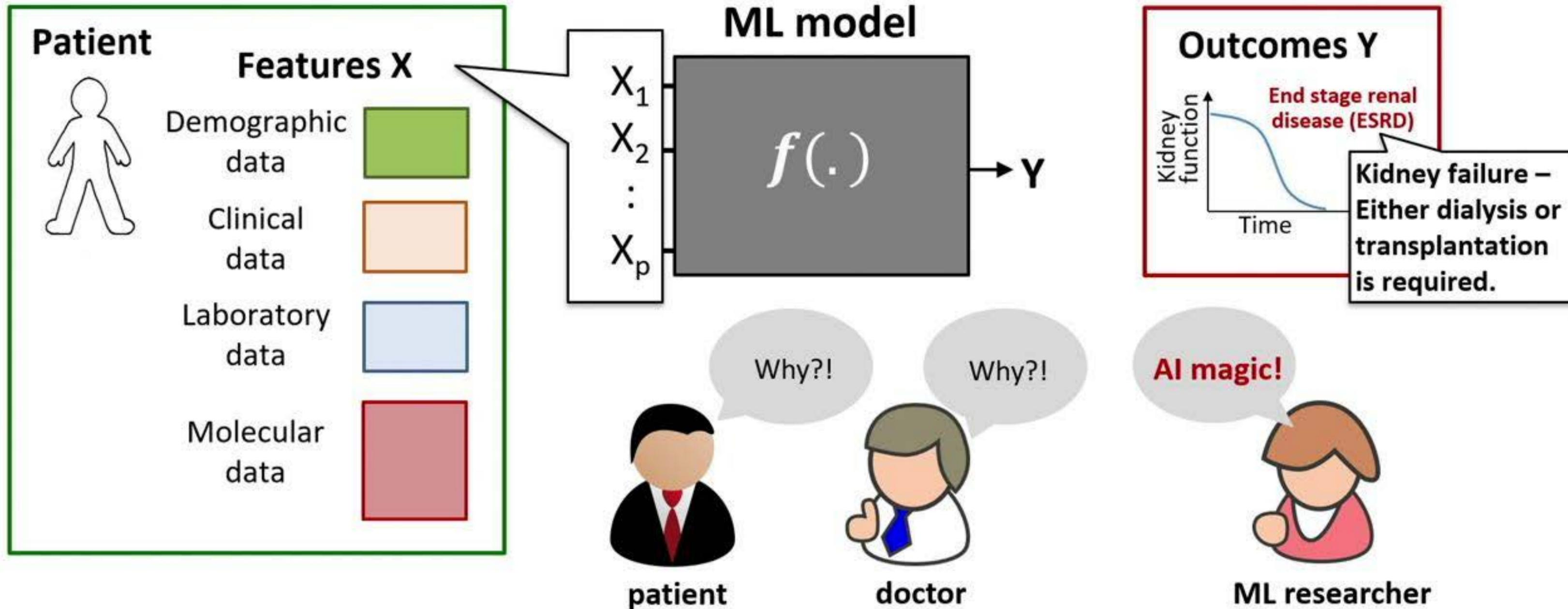
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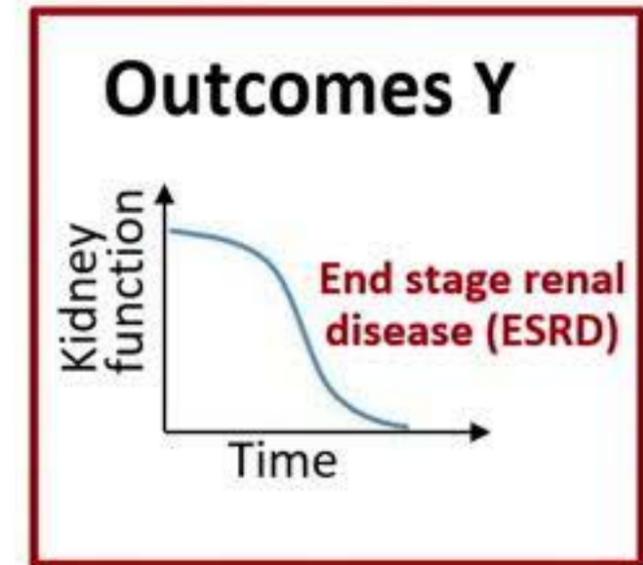
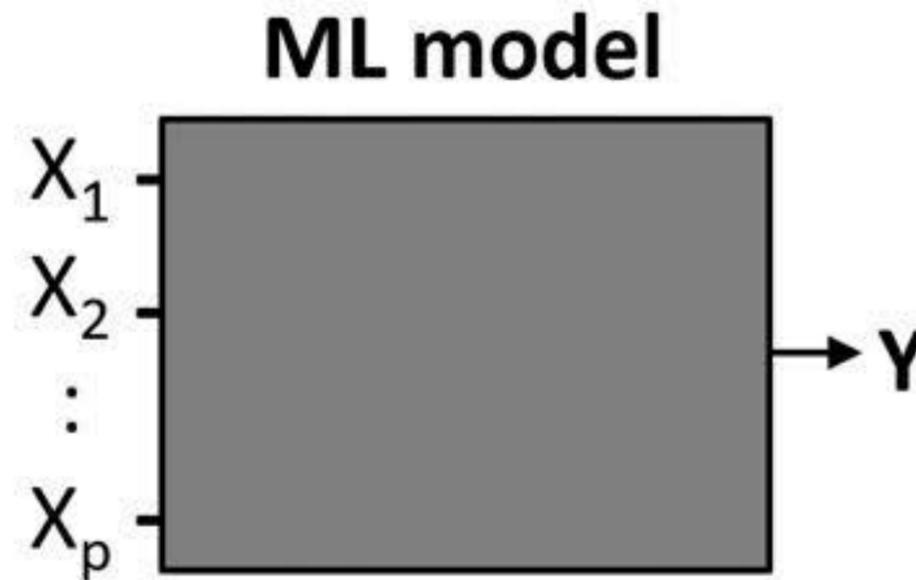
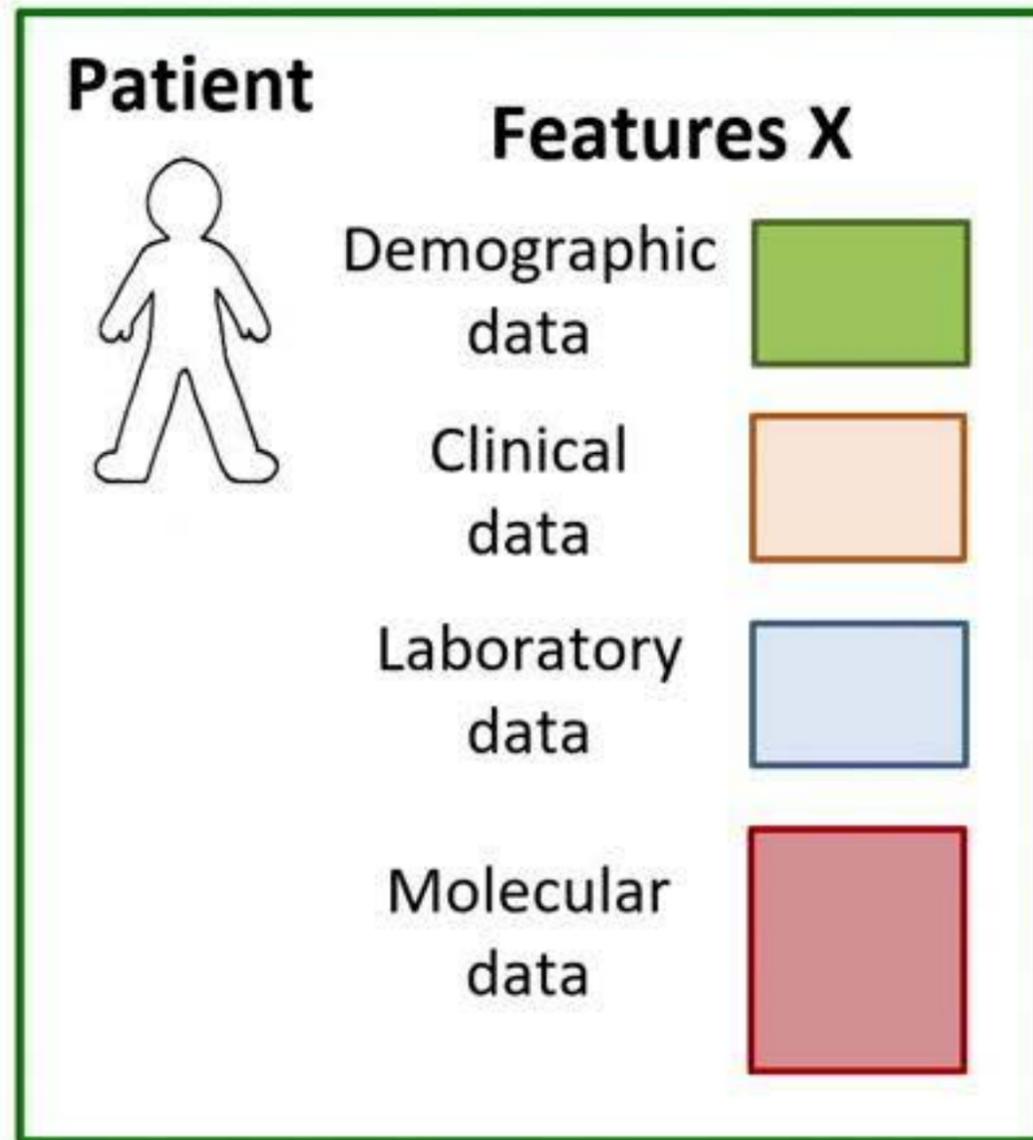
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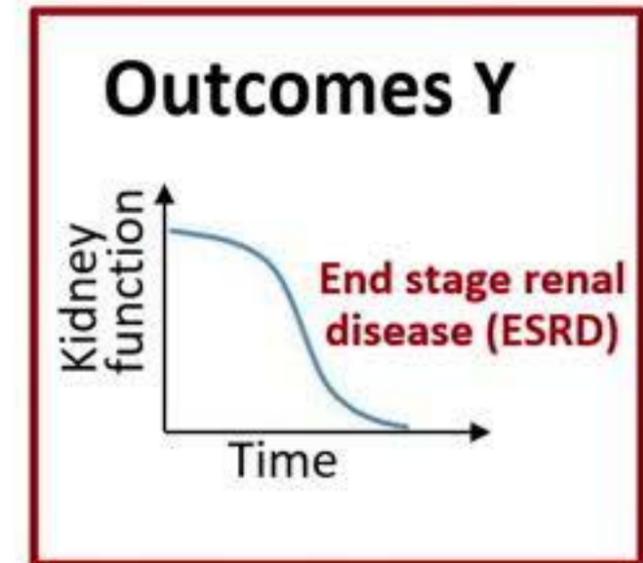
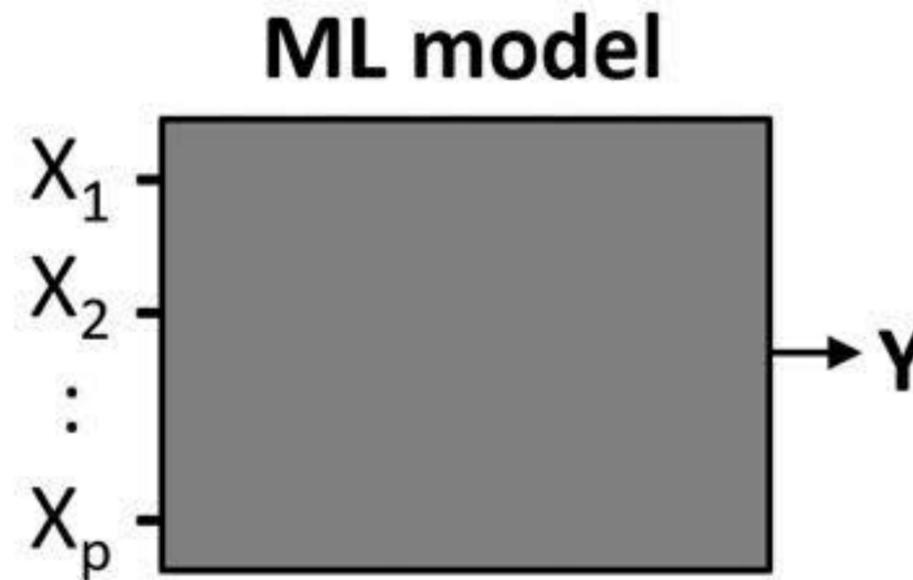
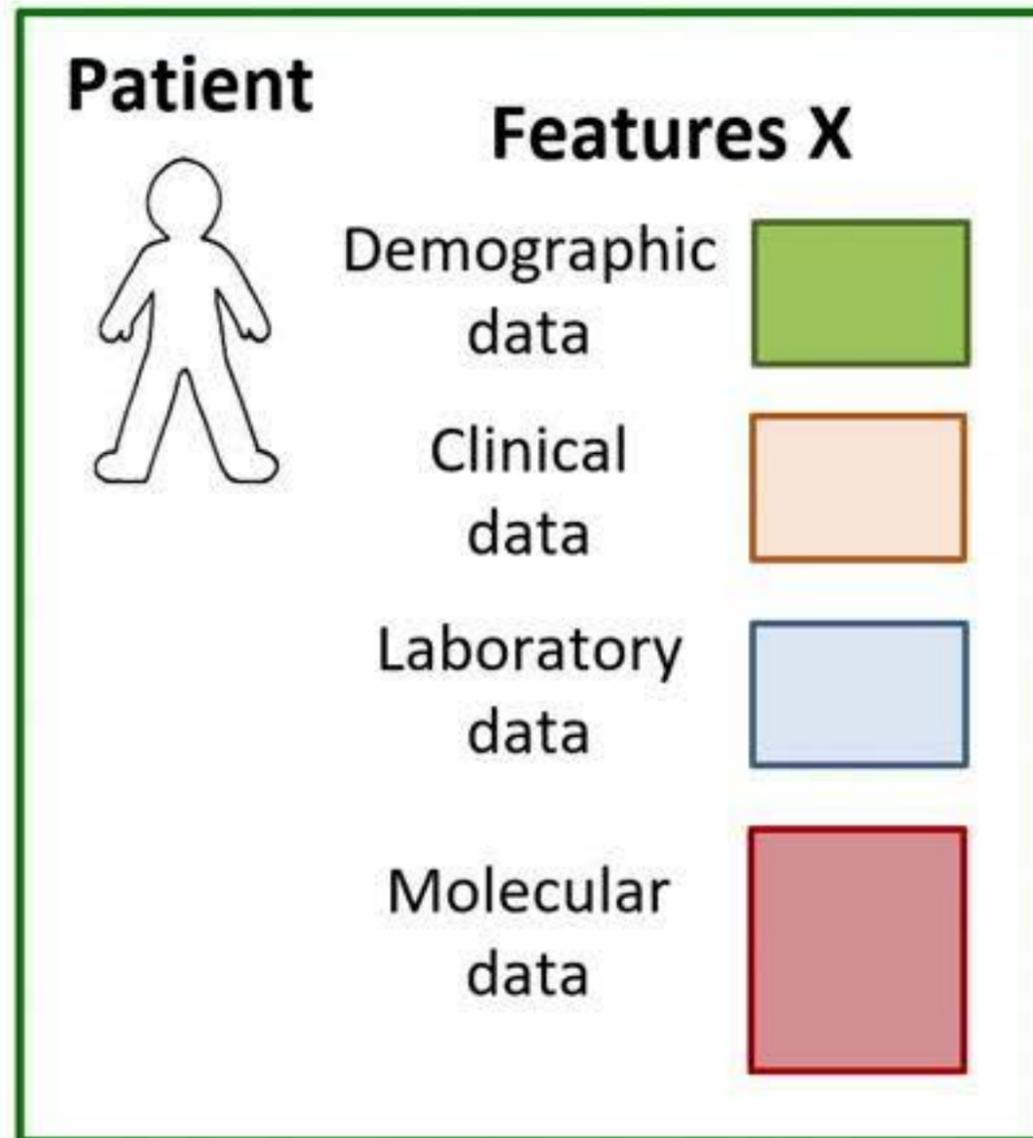


What current ML *cannot* do for precision medicine



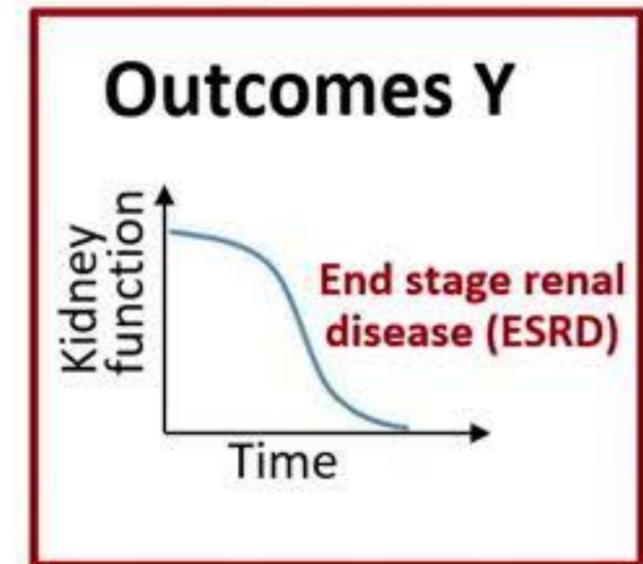
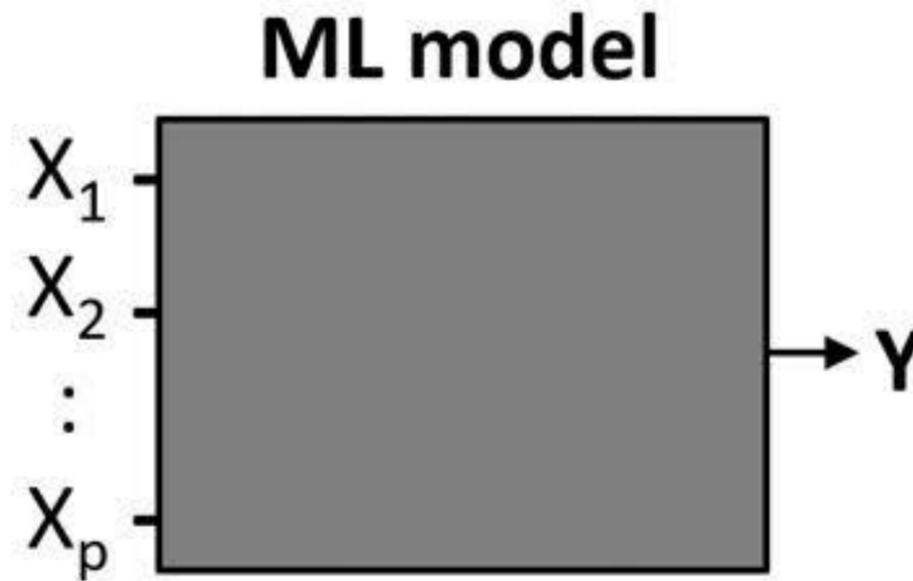
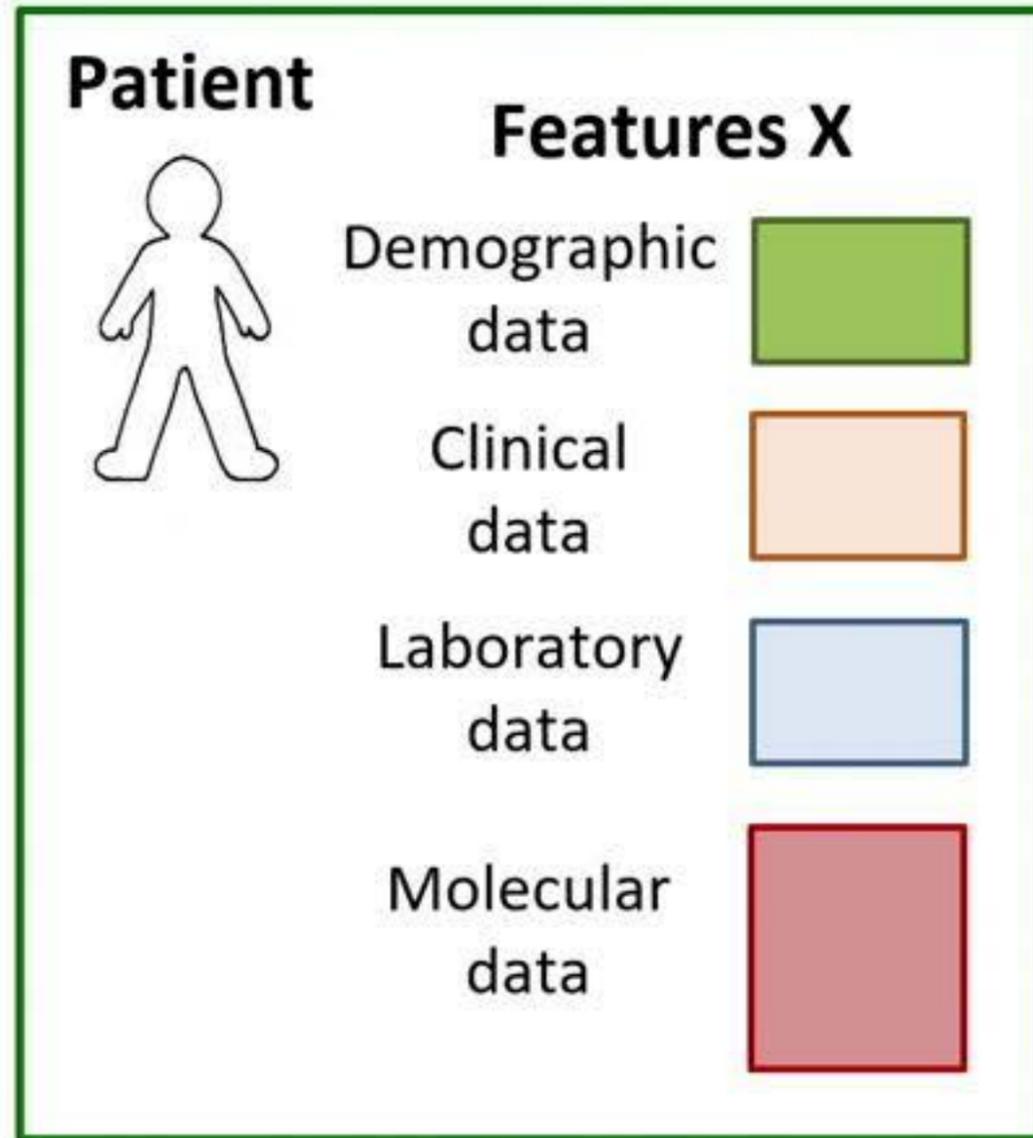
- **Interpretability** is sometimes more important than accuracy.
 - Why selected features make sense?
 - Which features contributed to the prediction and how?

What current ML *cannot* do for precision medicine

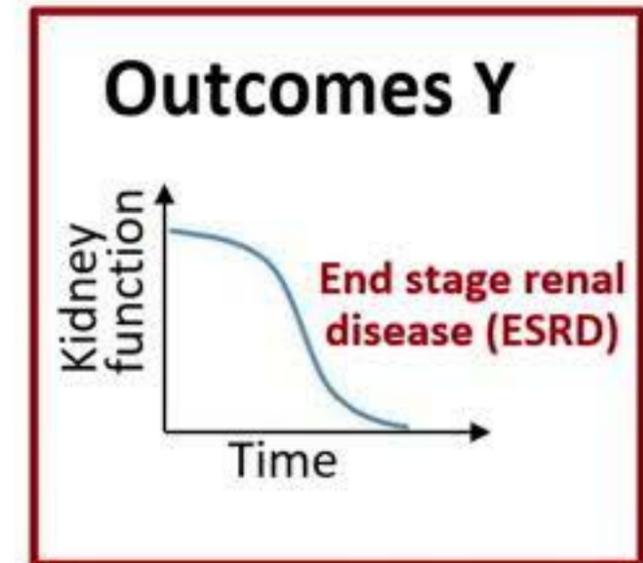
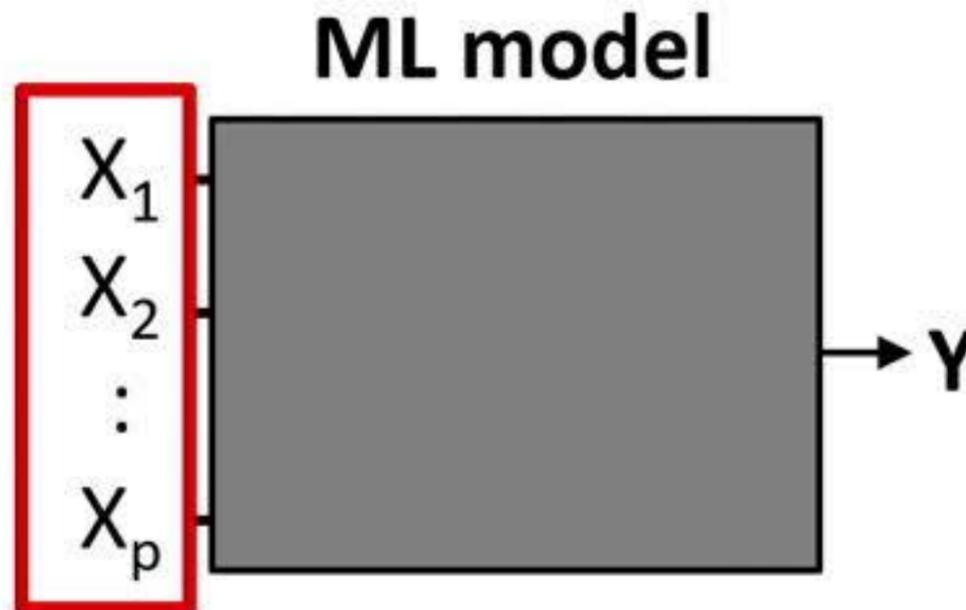
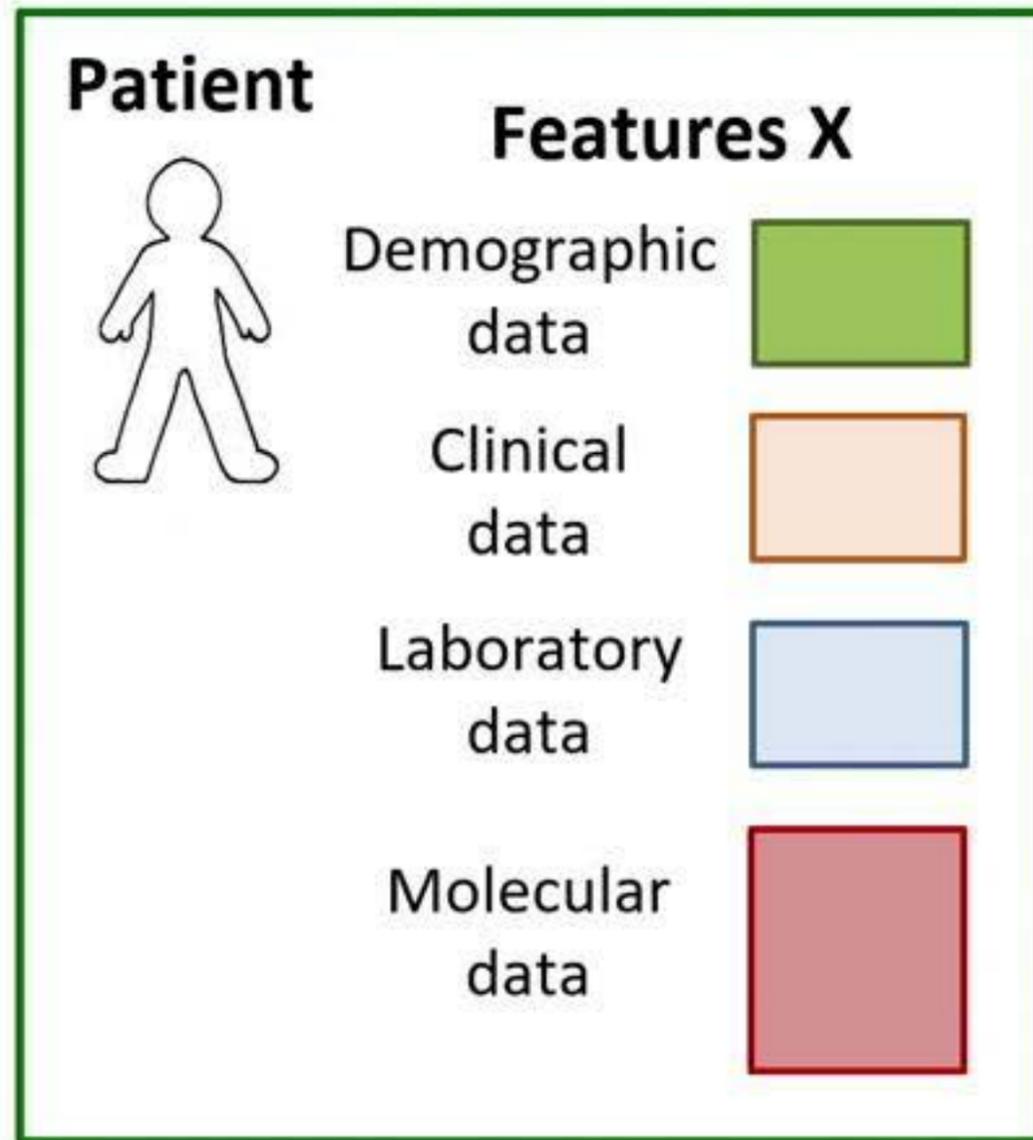


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Interpretable ML for precision medicine

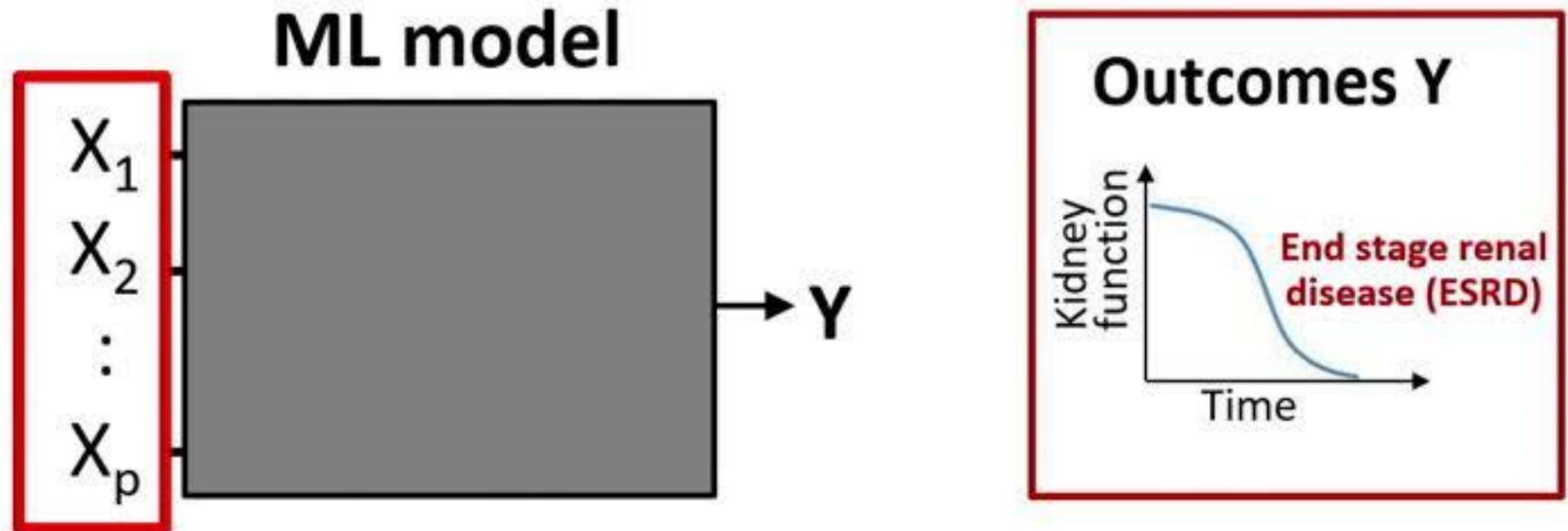
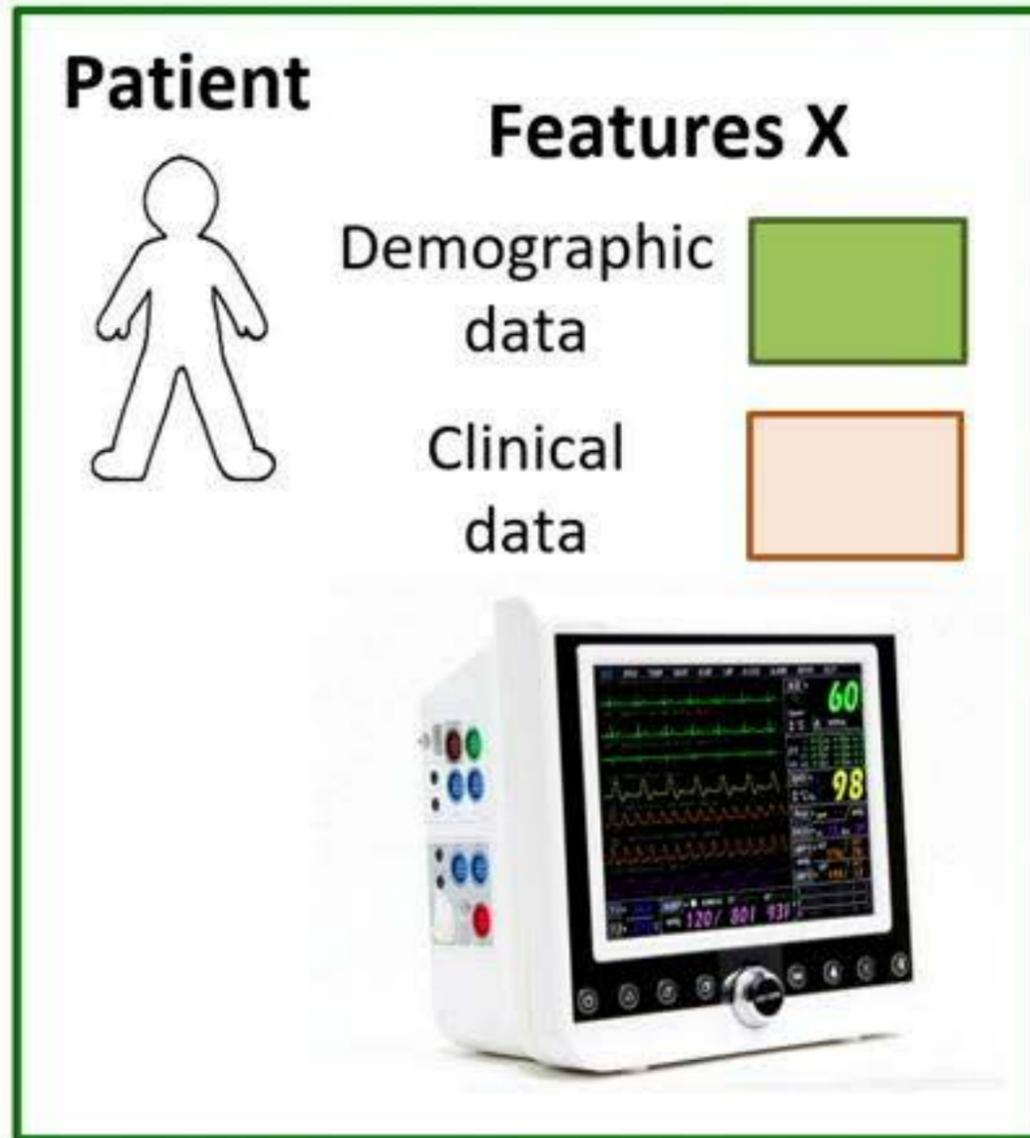


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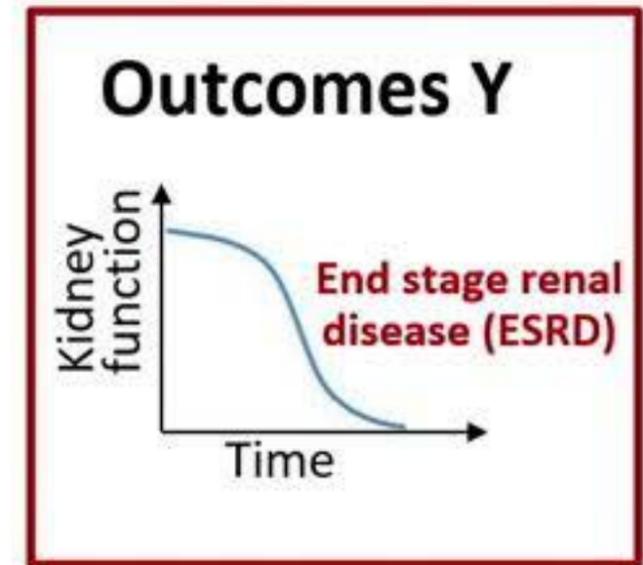
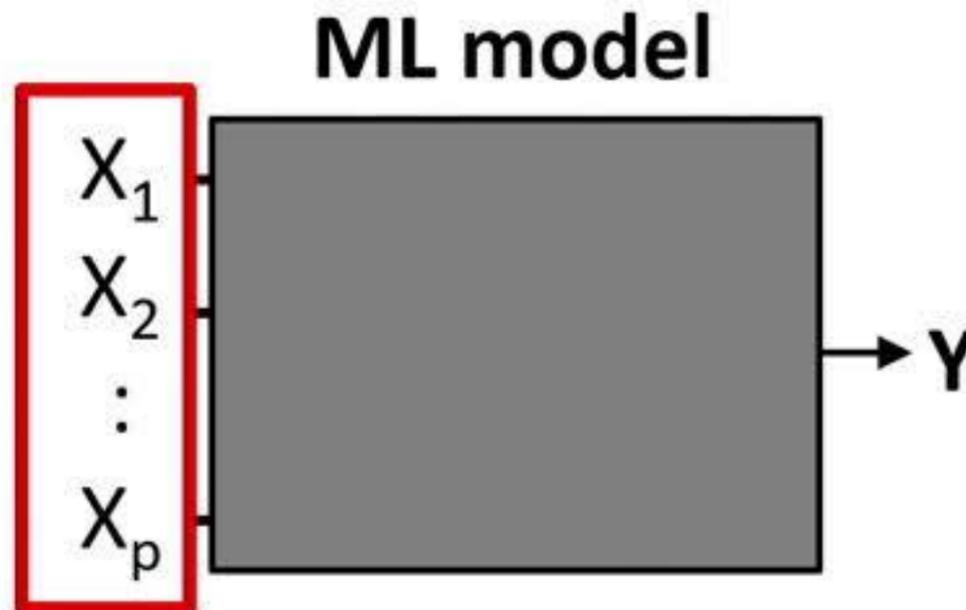
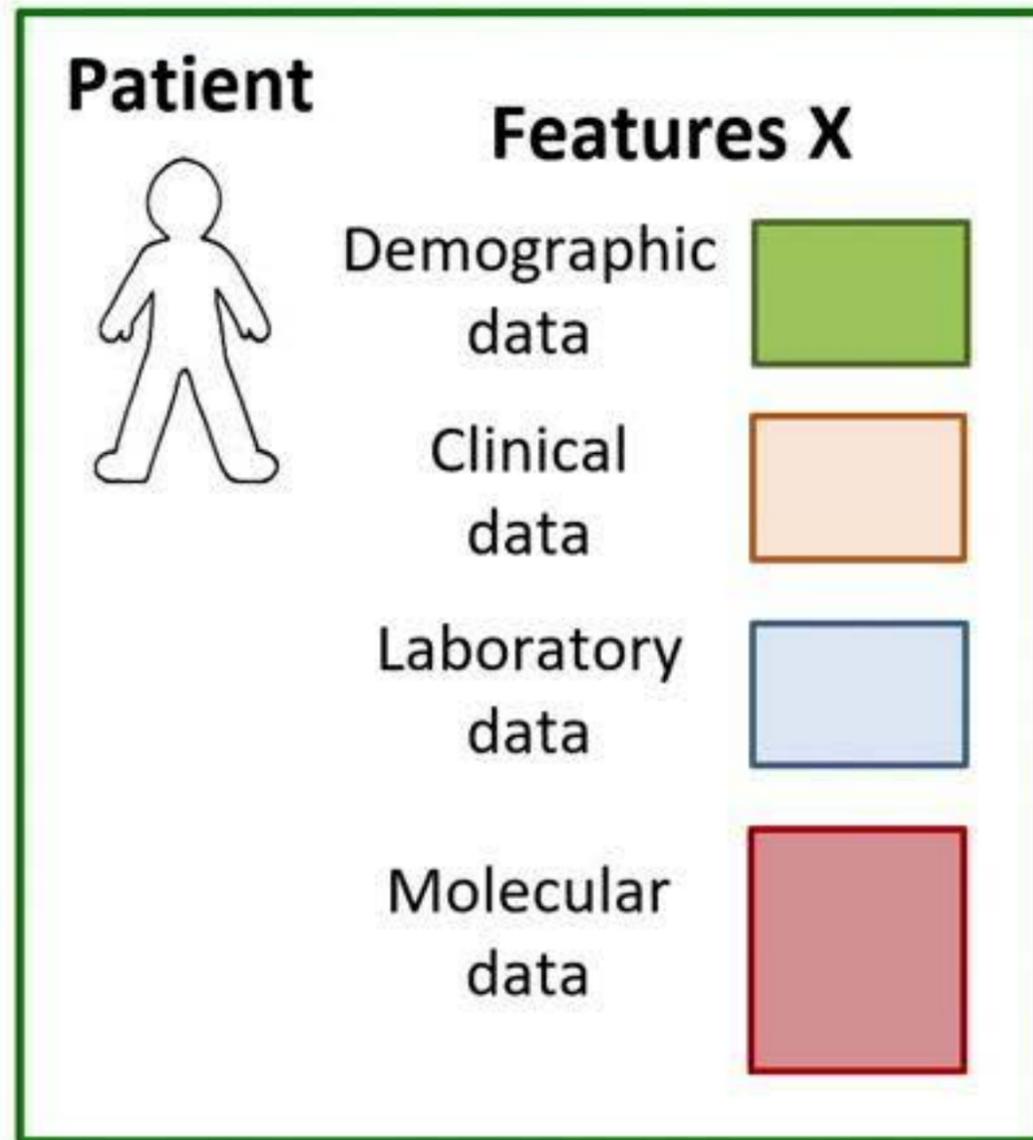
- **1. Learn interpretable feature representation.**
 - Pre-select or learn features likely relevant to Y.

Interpretable ML for precision medicine



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 - Extract meaningful patterns from physiological signals.

Interpretable ML for precision medicine



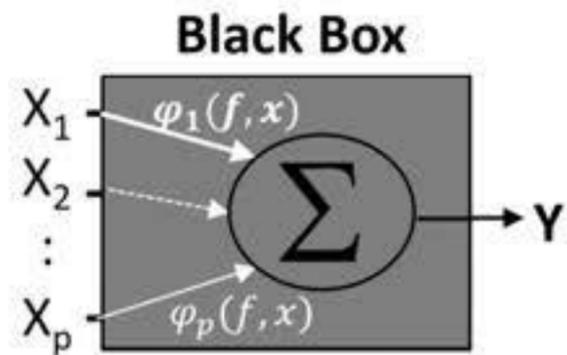
- **1. Learn interpretable feature representation.**
 - Pre-select or learn features likely relevant to Y.
 - Extract meaningful patterns from physiological signals.
 - Enable interactive prediction for time-sensitive diagnosis.

Interpretable ML can transform important areas of medicine

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Prediction & decision support systems in hospitals

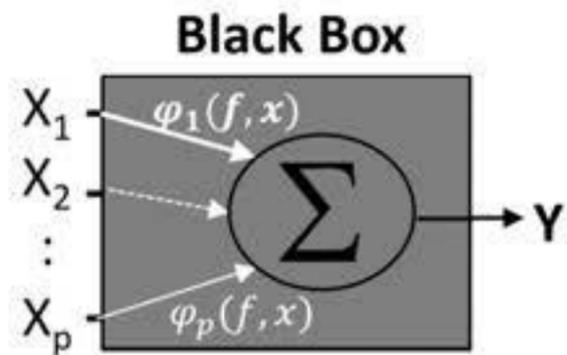
- Make interpretable predictions from complex models.



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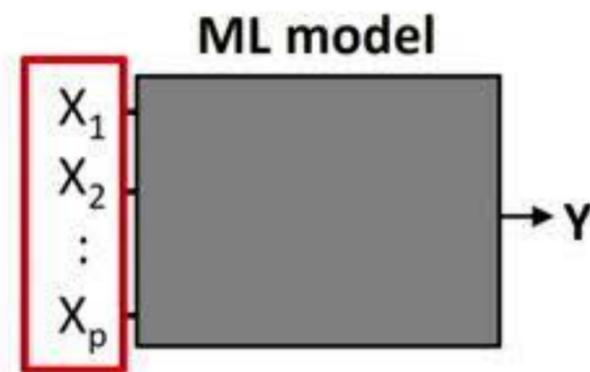
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Cancer precision medicine

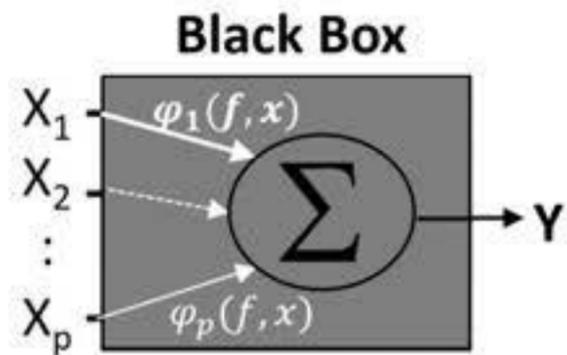
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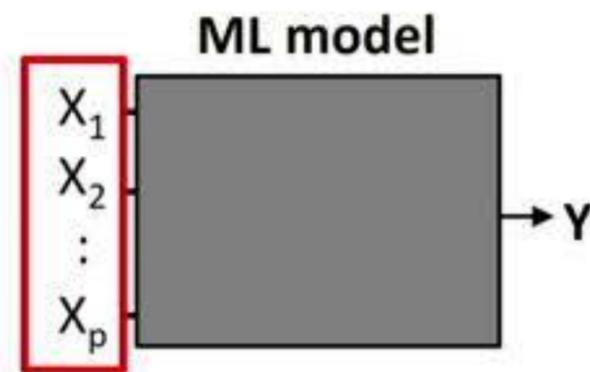
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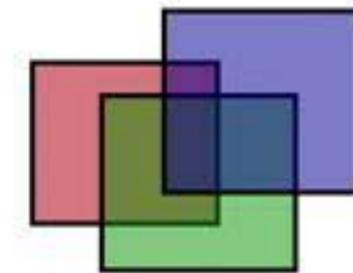
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Alzheimer's disease therapeutic target discovery

- Integrate data sets for statistical power and interpretability.

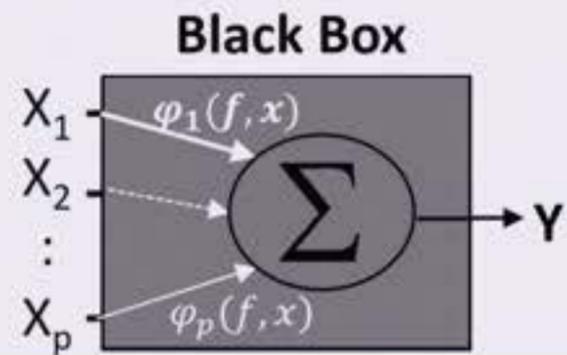
Data integration



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Prediction & decision support systems in hospitals

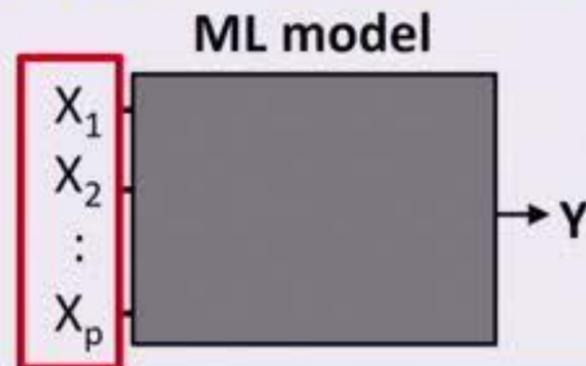
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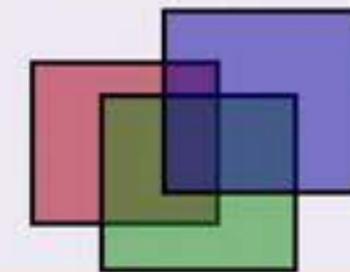
General ML techniques



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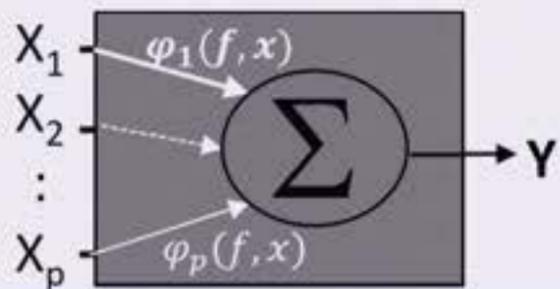
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Black Box

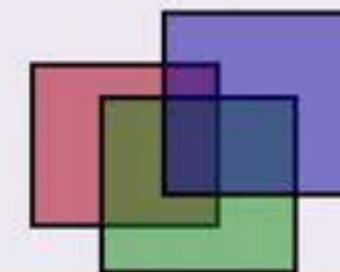


General ML techniques

ML model



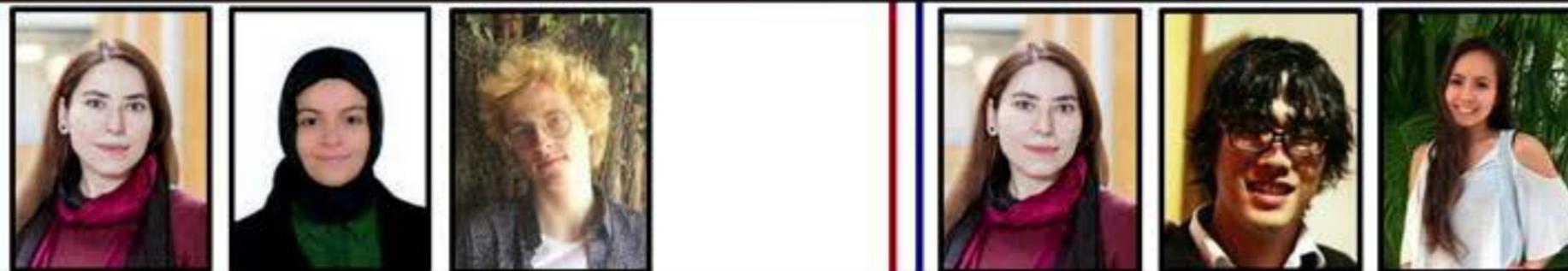
Data integration



Bedside applications



Basic science



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Prediction & decision support systems in hospitals

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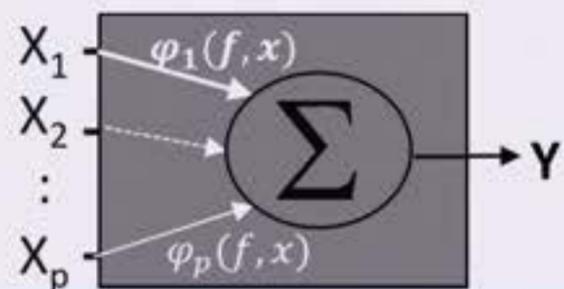
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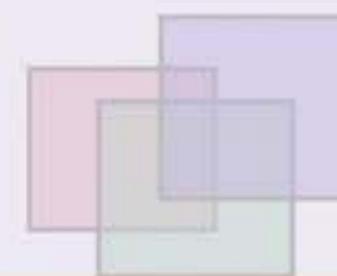
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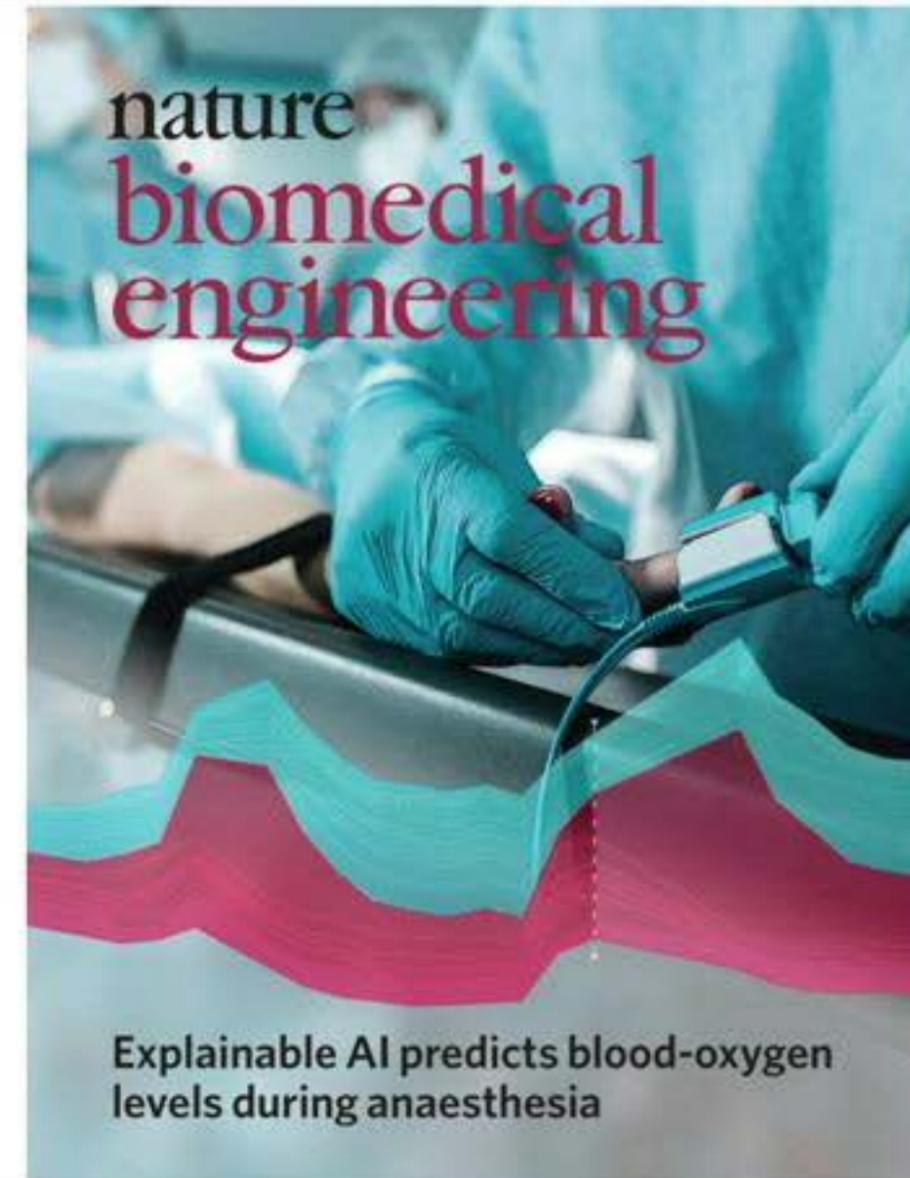


Basic science



The operating room is a data-rich environment

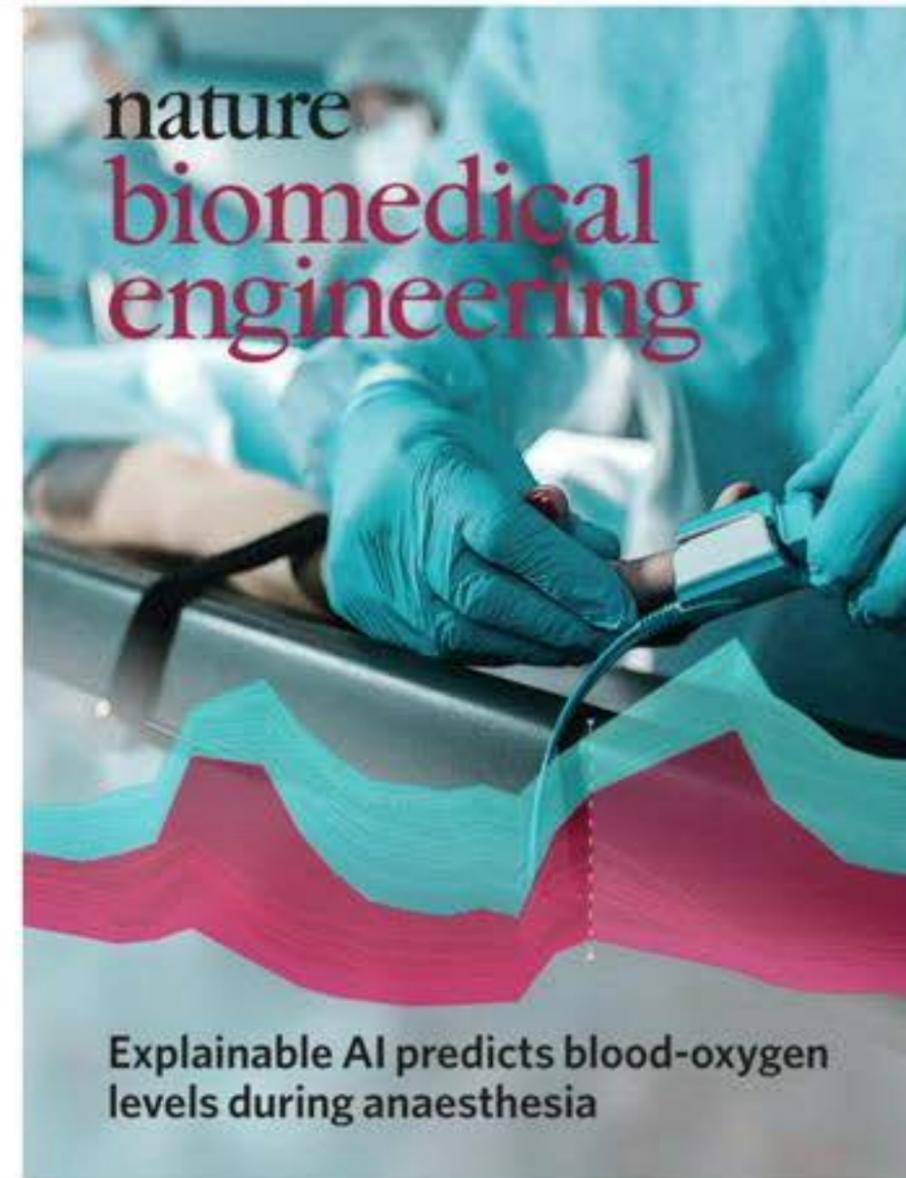
- Over 200 million surgeries every year



Scott M. Lundberg, Bala Nair, Monica S. Vavilala, Mayumi Horibe, Michael J. Eisses, Trevor Adams, David E. Liston, Daniel King-Wai Low, Shu-Fang Newman, Jerry Kim, and Su-In Lee. **Explainable machine-learning predictions for the prevention of hypoxaemia during surgery.** *Nature BME* 2, 749–760 (2018) - **Featured on the Cover**

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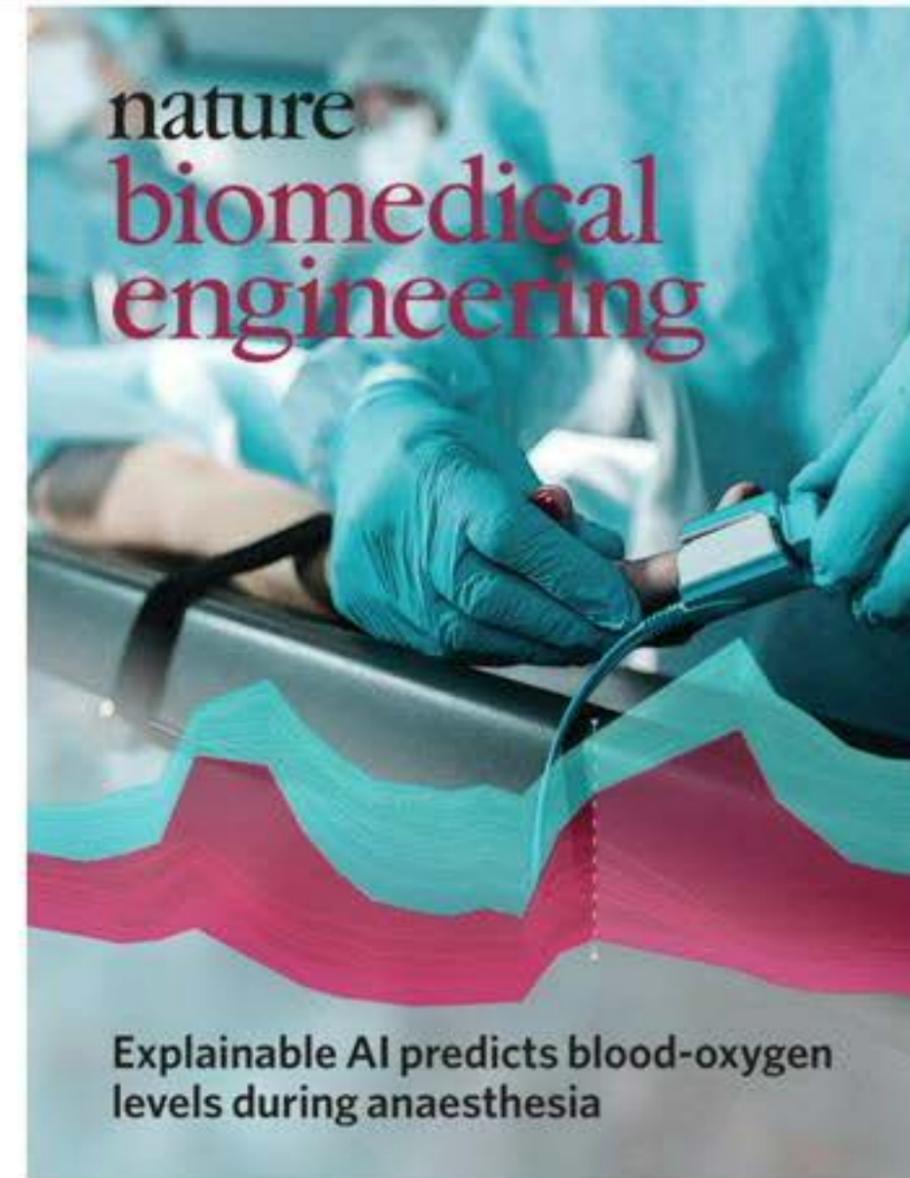
- Over 200 million surgeries every year
- Hypoxemia (i.e., low arterial blood oxygen tension)
 - The drop in SpO_2 , i.e., arterial blood oxygen saturation as measured by pulse oximetry, to 92% or lower



Scott M. Lundberg, Bala Nair, Monica S. Vavilala, Mayumi Horibe, Michael J. Eisses, Trevor Adams, David E. Liston, Daniel King-Wai Low, Shu-Fang Newman, Jerry Kim, and Su-In Lee. **Explainable machine-learning predictions for the prevention of hypoxaemia during surgery.** *Nature BME* 2, 749–760 (2018) - **Featured on the Cover**

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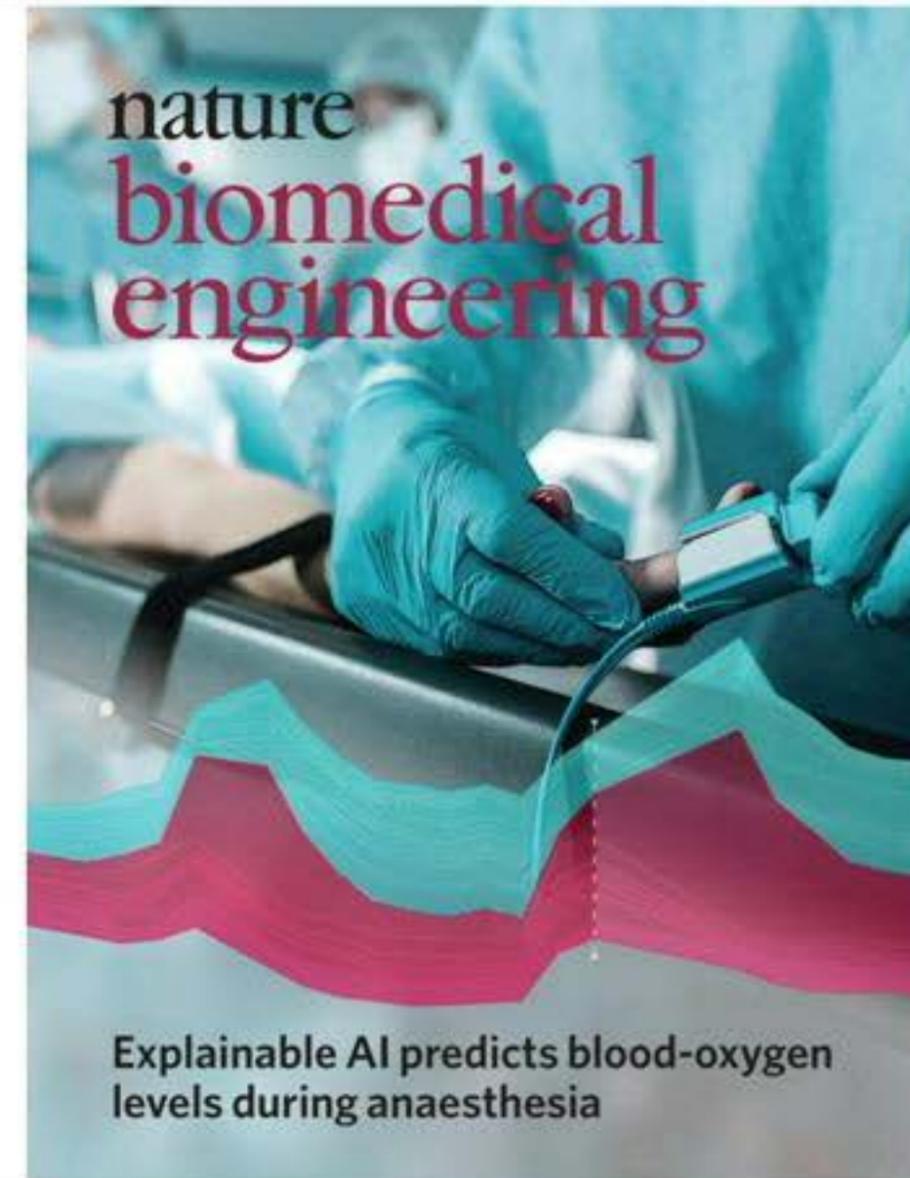
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- Hypoxemia (i.e., low arterial blood oxygen tension)
 - The drop in SpO_2 , i.e., arterial blood oxygen saturation as measured by pulse oximetry, to 92% or lower
- Predicting hypoxemia events in advance would allow proactive intervention.



Scott M. Lundberg, Bala Nair, Monica S. Vavilala, Mayumi Horibe, Michael J. Eisses, Trevor Adams, David E. Liston, Daniel King-Wai Low, Shu-Fang Newman, Jerry Kim, and Su-In Lee. **Explainable machine-learning predictions for the prevention of hypoxaemia during surgery.** *Nature BME* 2, 749–760 (2018) - **Featured on the Cover**

The operating room is a data-rich environment

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 - The drop in SpO₂, i.e., arterial blood oxygen saturation as measured by pulse oximetry, to 92% or lower
- Predicting hypoxemia events in advance would allow proactive intervention.
- We developed the *Prescience* system that can predict hypoxemia in the next 5 minutes in real time.



Scott M. Lundberg, Bala Nair, Monica S. Vavilala, Mayumi Horibe, Michael J. Eisses, Trevor Adams, David E. Liston, Daniel King-Wai Low, Shu-Fang Newman, Jerry Kim, and Su-In Lee. **Explainable machine-learning predictions for the prevention of hypoxaemia during surgery.** *Nature BME* 2, 749–760 (2018) - **Featured on the Cover**

Prescience predicts hypoxemia and explains why



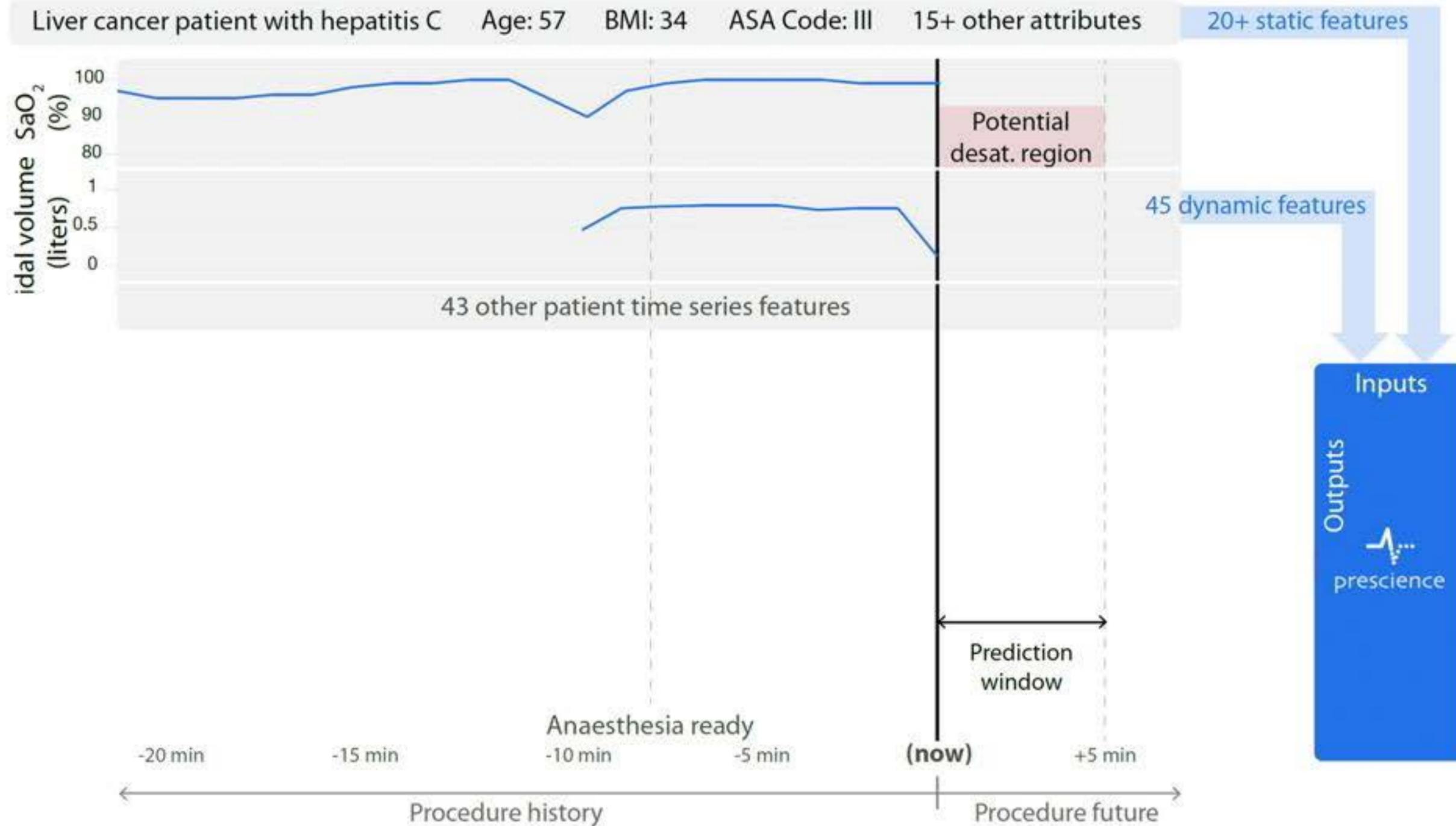
Prescience predicts hypoxemia and explains why

Liver cancer patient with hepatitis C Age: 57 BMI: 34 ASA Code: III 15+ other attributes

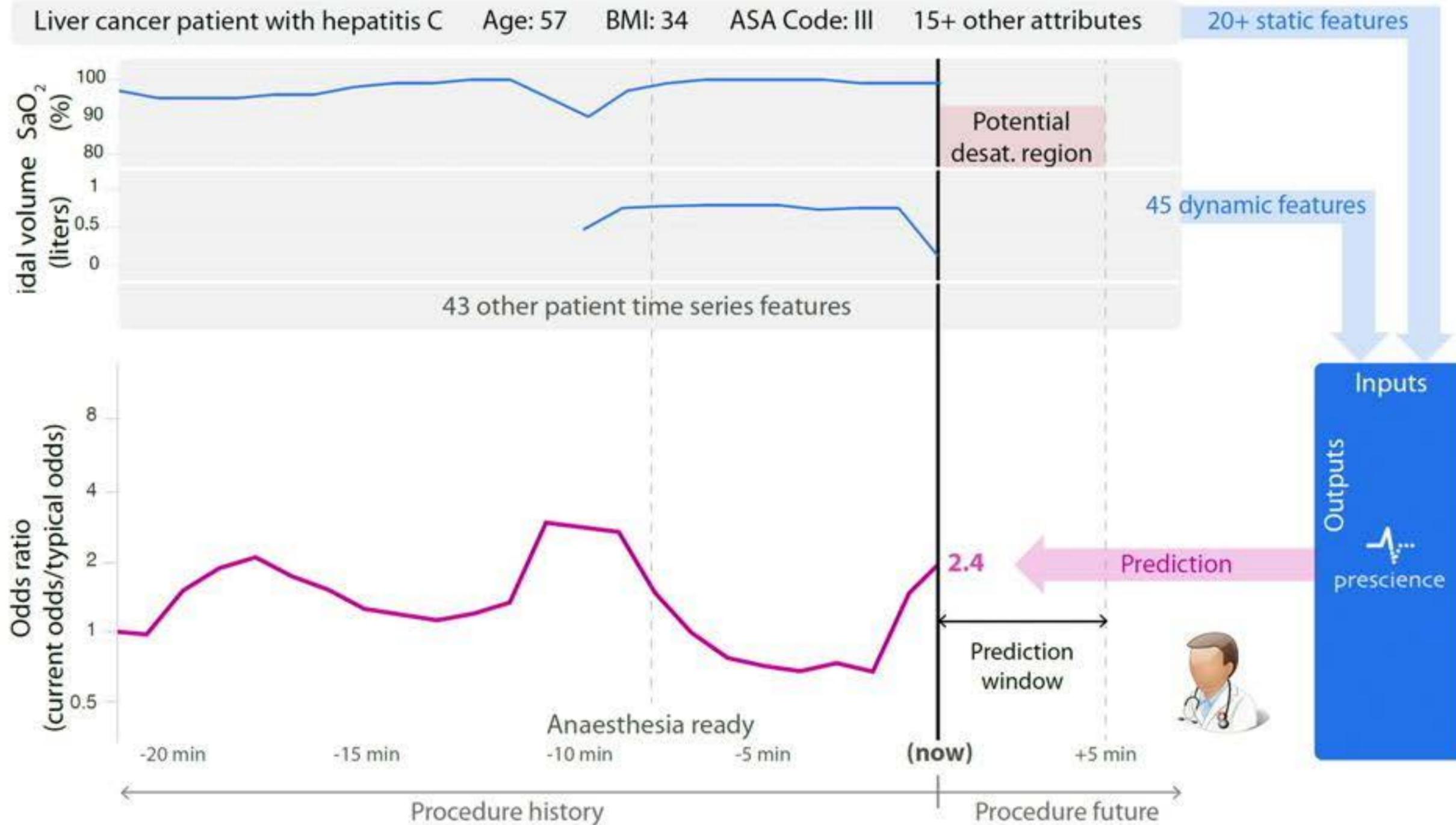
20+ static features



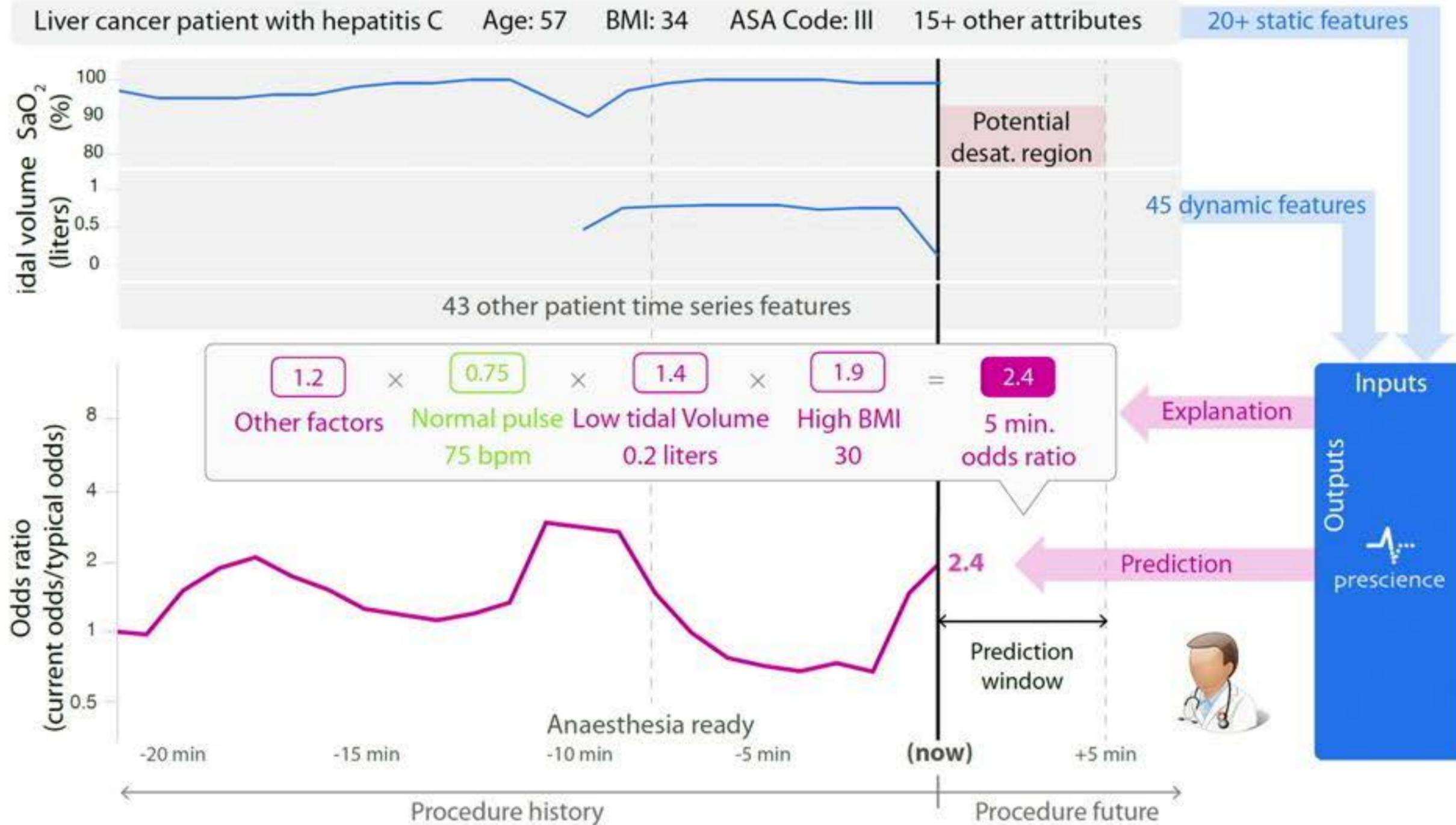
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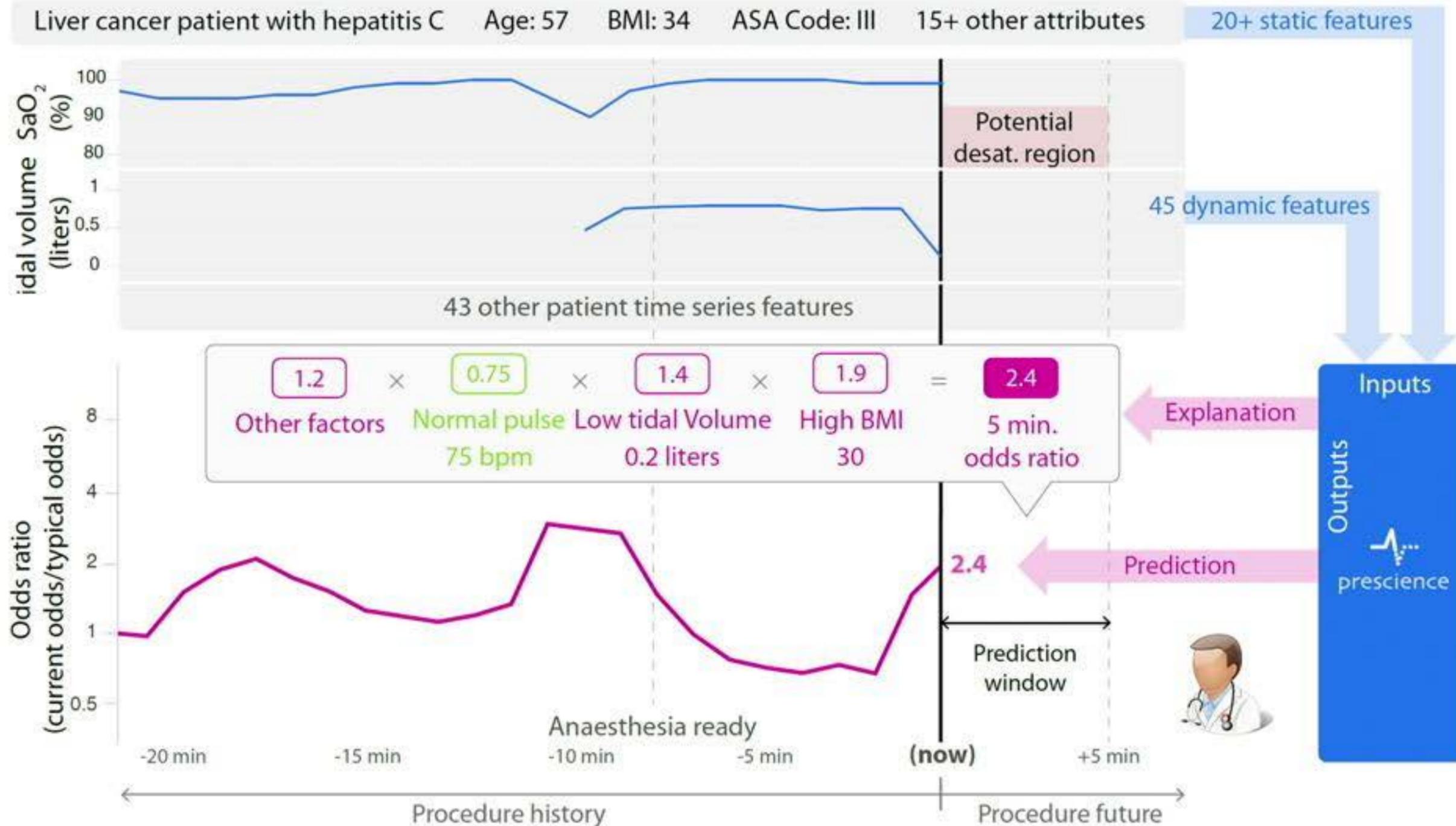
Prescience predicts hypoxemia and explains why



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Prescience predicts hypoxemia and explains why



- Training data
 - Anesthesia Information Management System (AIMS) data
 - 50,000 surgeries from UW Medical Center and Harborview Medical Center

Anesthesiology & Pain Medicine



Bala Nair



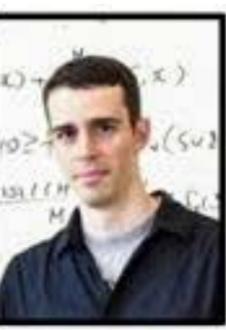
Jerry Kim

Different prediction models result in different prediction performance



Scott

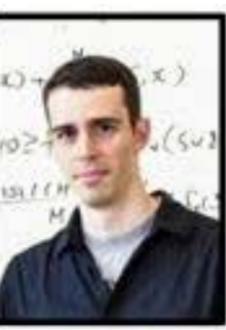
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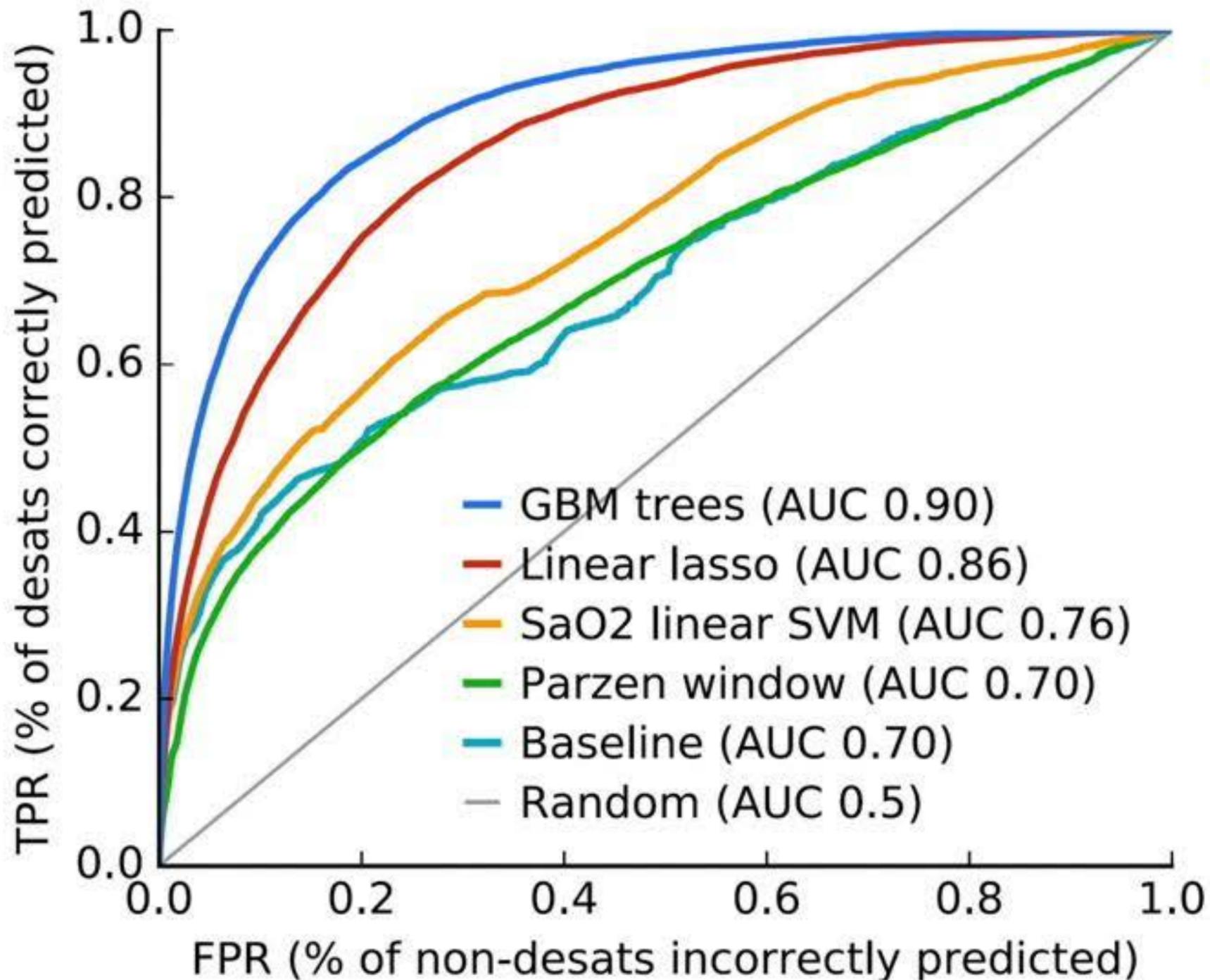
Scott

- Receiver operating characteristic (ROC) curve from 10-fold cross validation tests.

Different prediction models result in different prediction performance

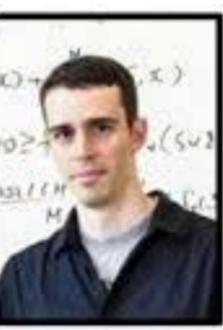


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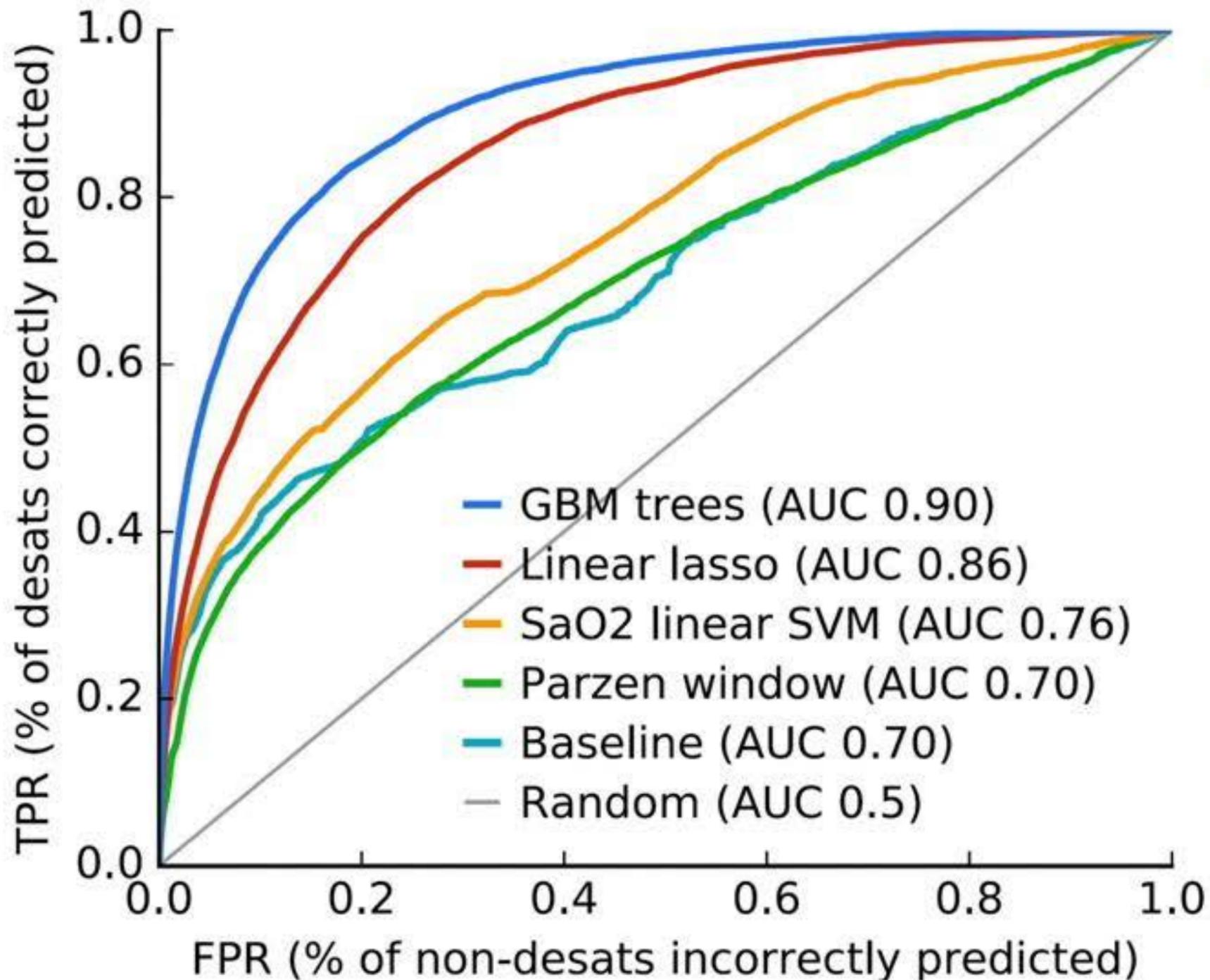


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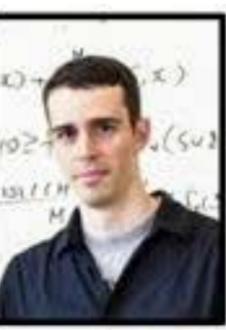


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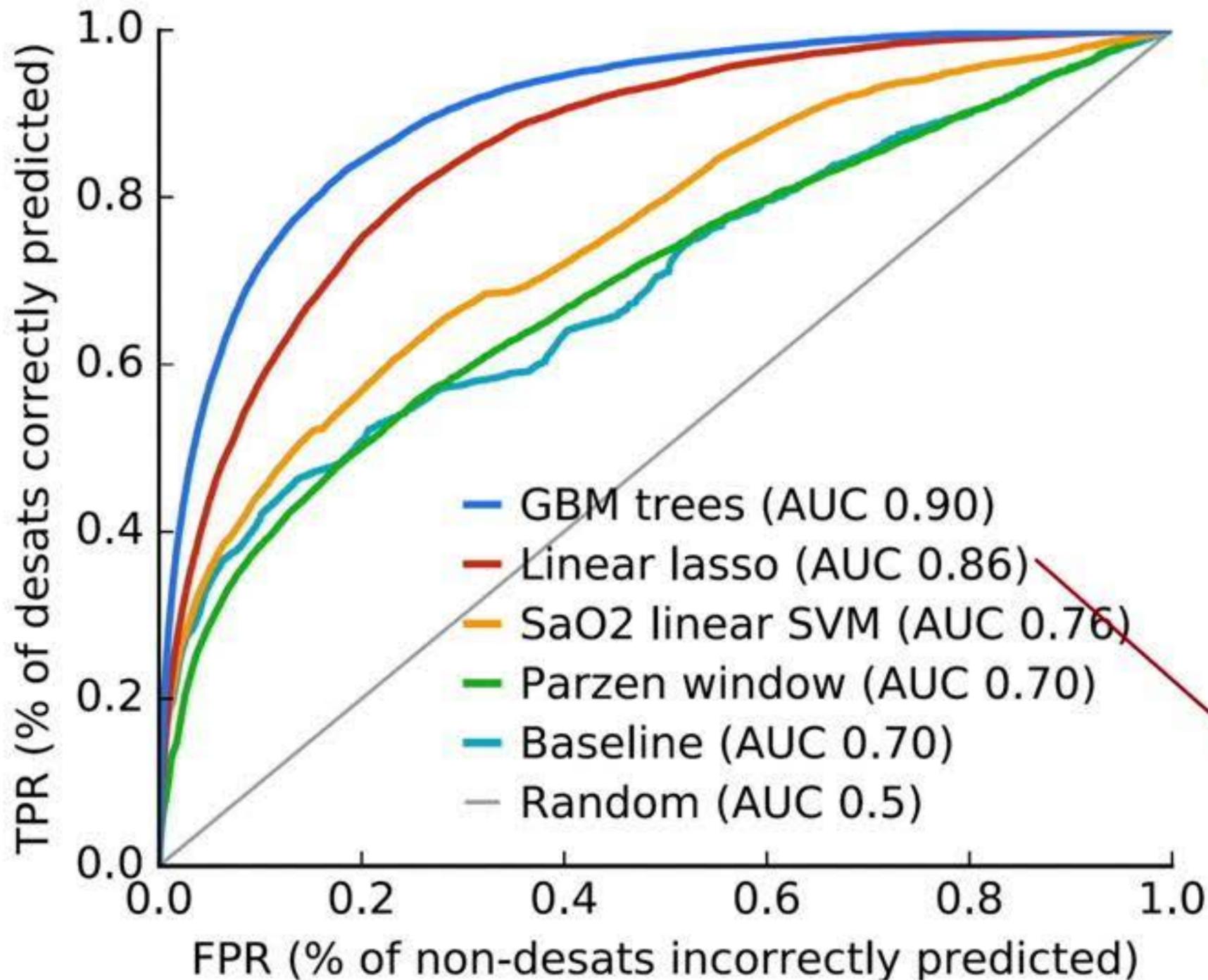


- Receiver operating characteristic (ROC) curve from 10-fold cross validation tests.
 - Simple vs. complex models

Different prediction models result in different prediction performance



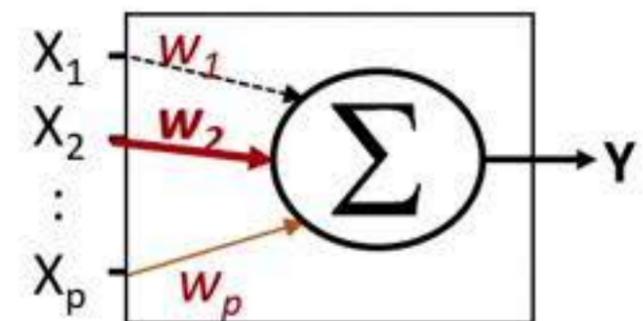
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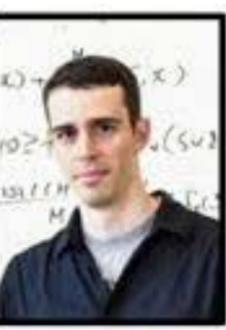
- Receiver operating characteristic (ROC) curve from 10-fold cross validation tests.
 - Simple vs. complex models

Generalized linear model

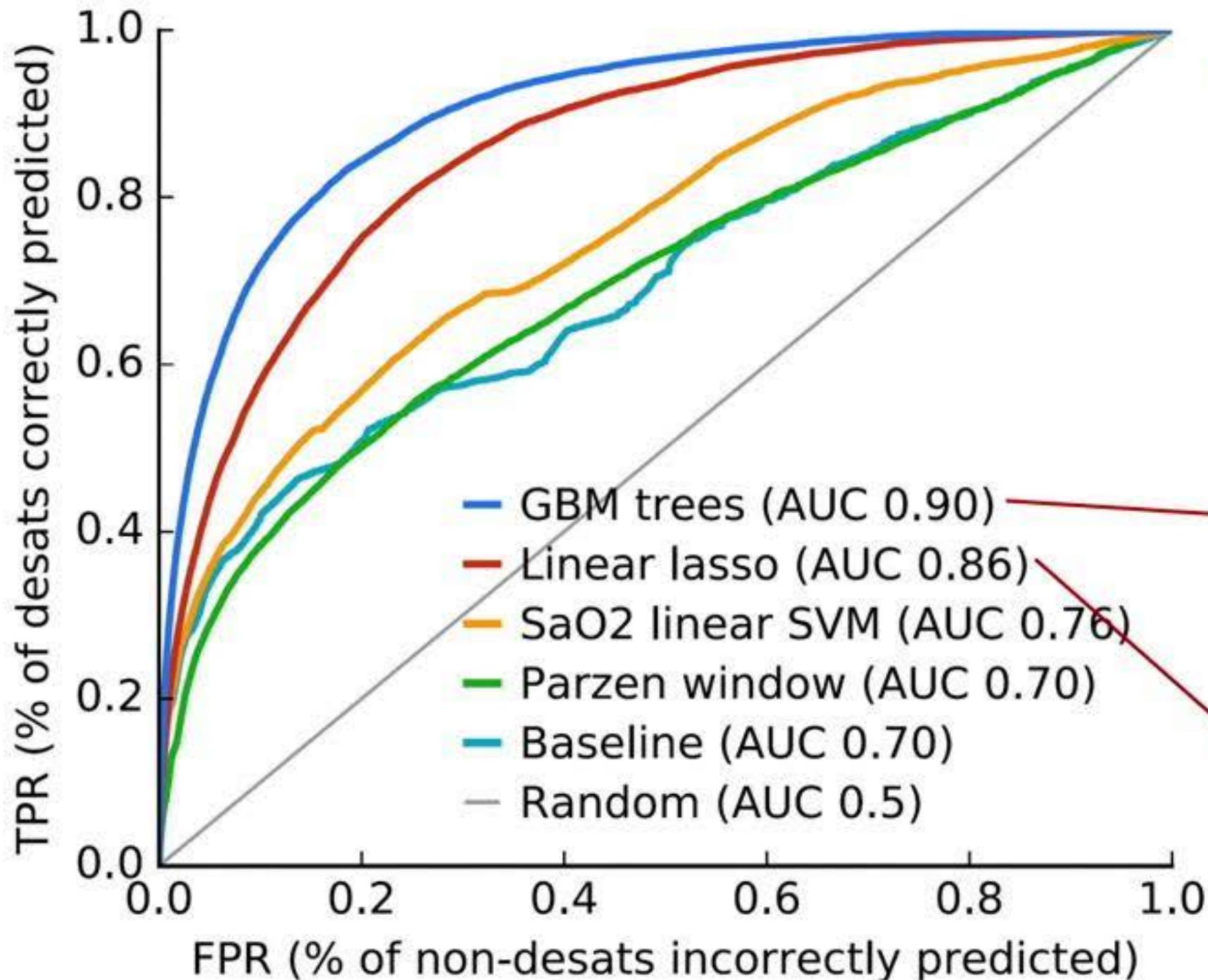
X: Features Y: Outcome



Different prediction models result in different prediction performance



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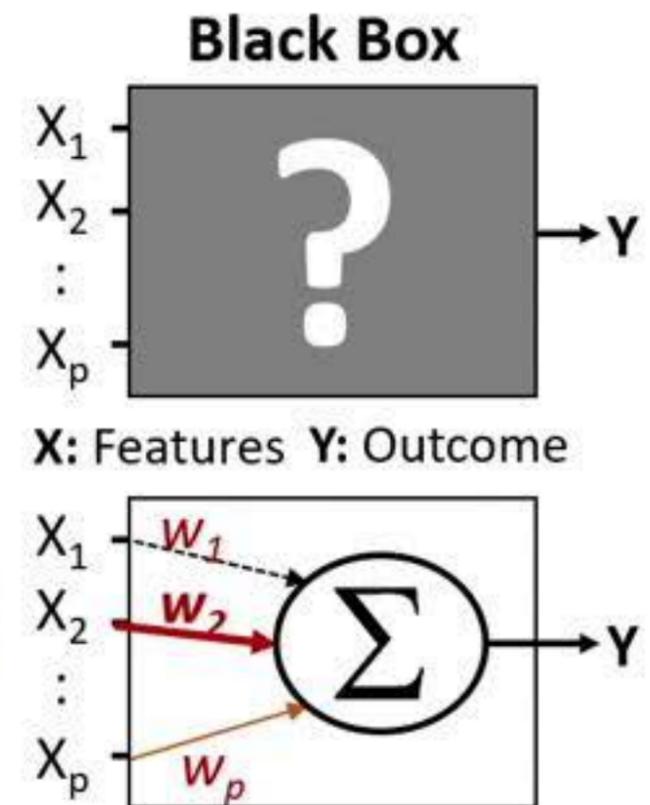


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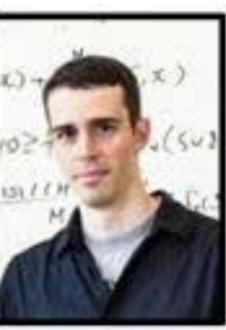
- Simple vs. complex models

Complex model $f(.)$

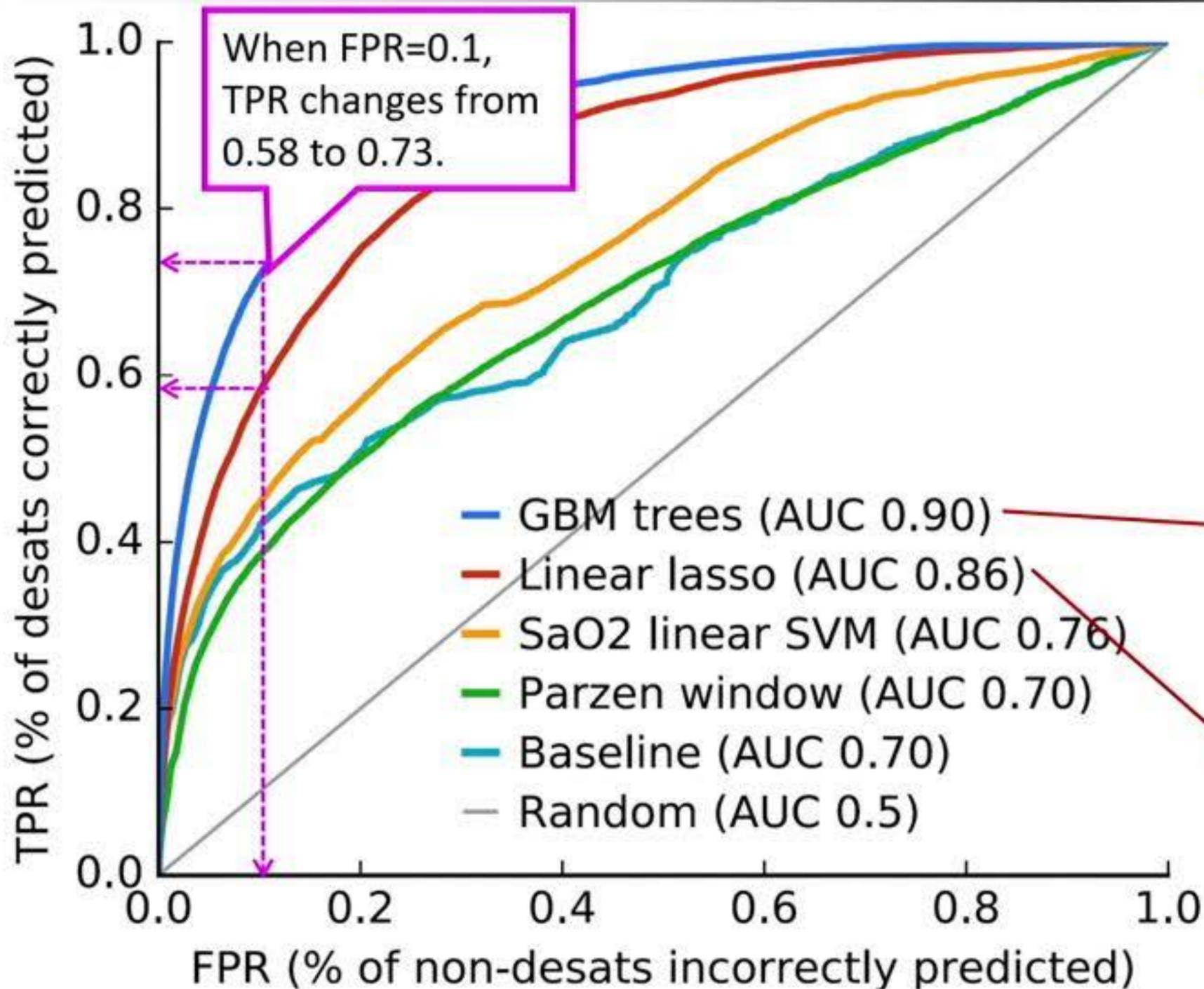
Generalized linear model



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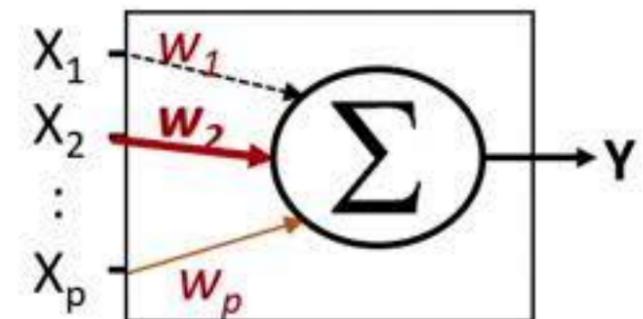
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Black Box



X: Features Y: Outcome



Complex model $f(.)$

Generalized linear model

Our solution is to make a prediction with explanations



Scott

- Accuracy vs. interpretability

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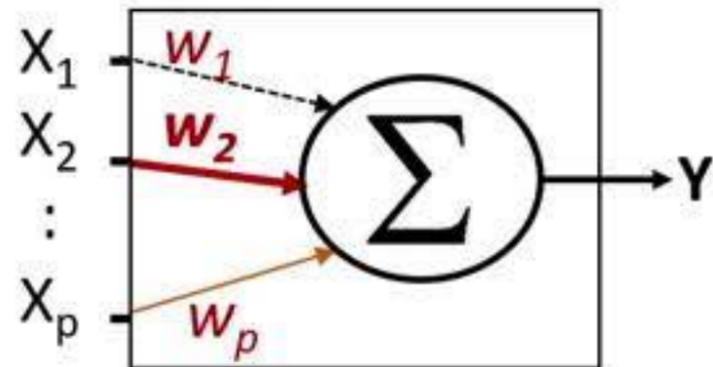


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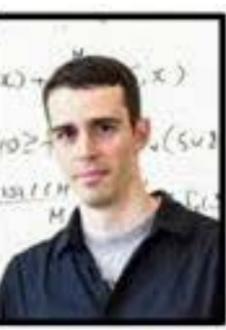
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 - Simple models often lead to lower performance.

Linear model

X: Features **Y:** Outcome



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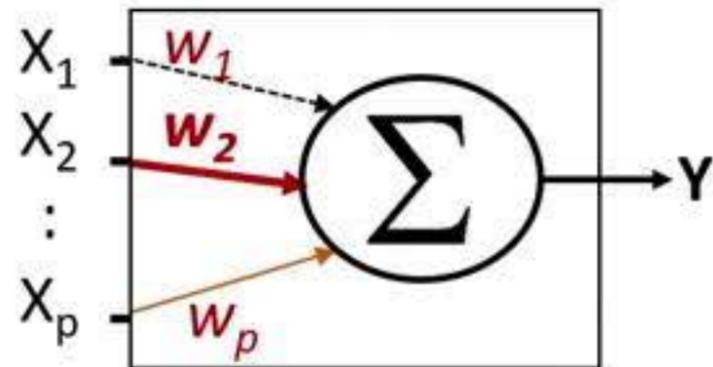


Scott

- Accuracy vs. interpretability
 - Simple models often lead to lower performance.
 - Complex models are often considered to be a black box.

Linear model

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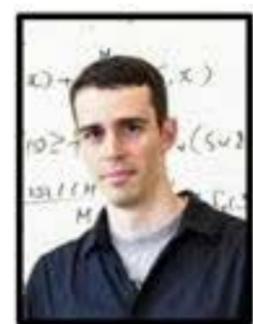


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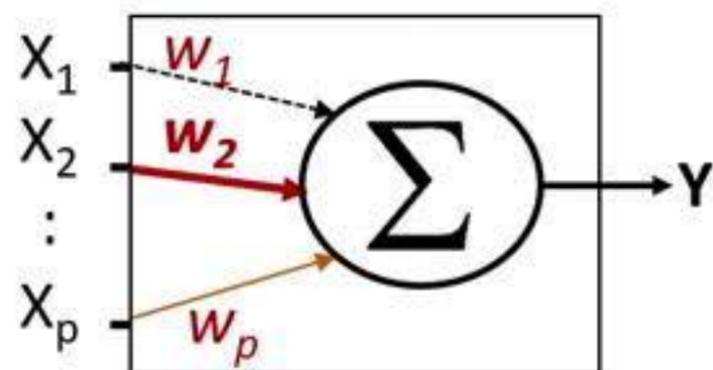


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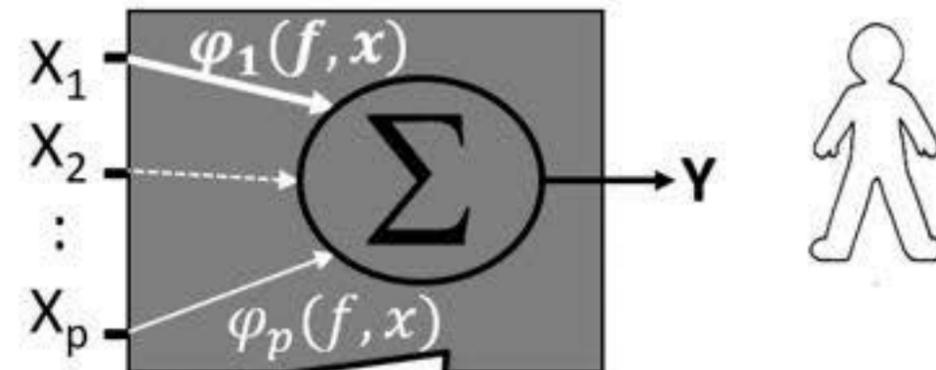
Complex model $f(\cdot)$

Black Box



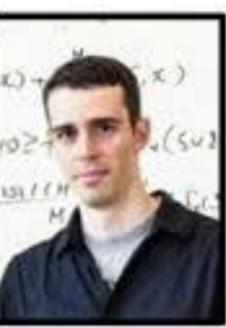
Our approach, SHAP

For a particular prediction



- SHAP can estimate feature importance for a particular prediction for any model.

Our solution is to make a prediction with explanations



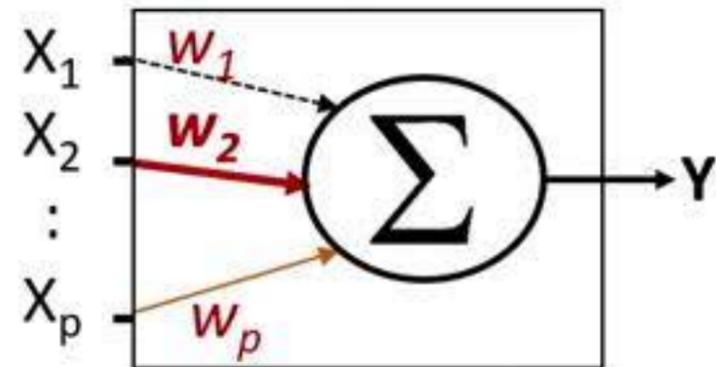
Scott

Eliminating the accuracy vs. interpretability tradeoff
⇒ Broader applicability of ML to medicine

- Accuracy vs. interpretability
 - Simple models often lead to lower performance.
 - Complex models are often considered to be a black box.

Linear model

X: Features Y: Outcome



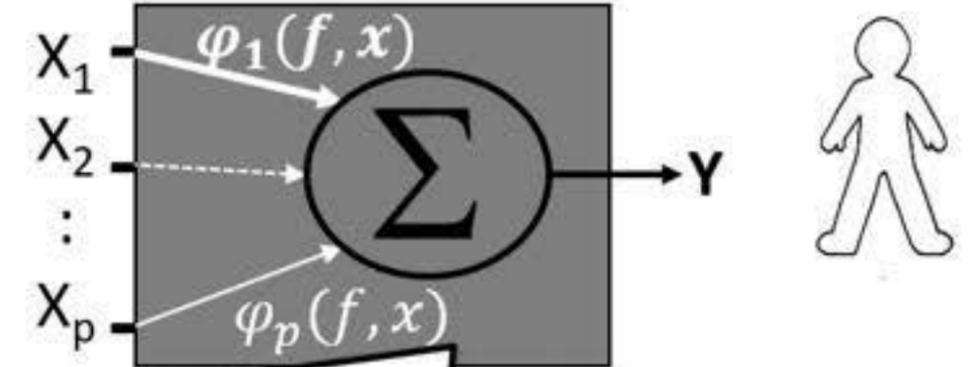
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Our approach, SHAP

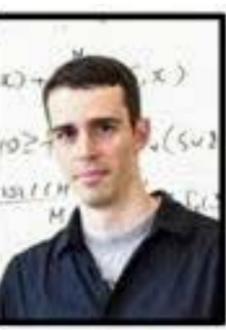
For a particular prediction



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How exactly can we estimate feature importance?

- SHapley Additive exPlanation (SHAP) values



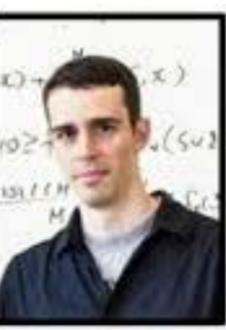
Scott



John, a bank customer

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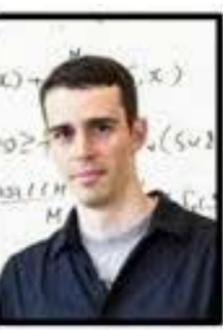
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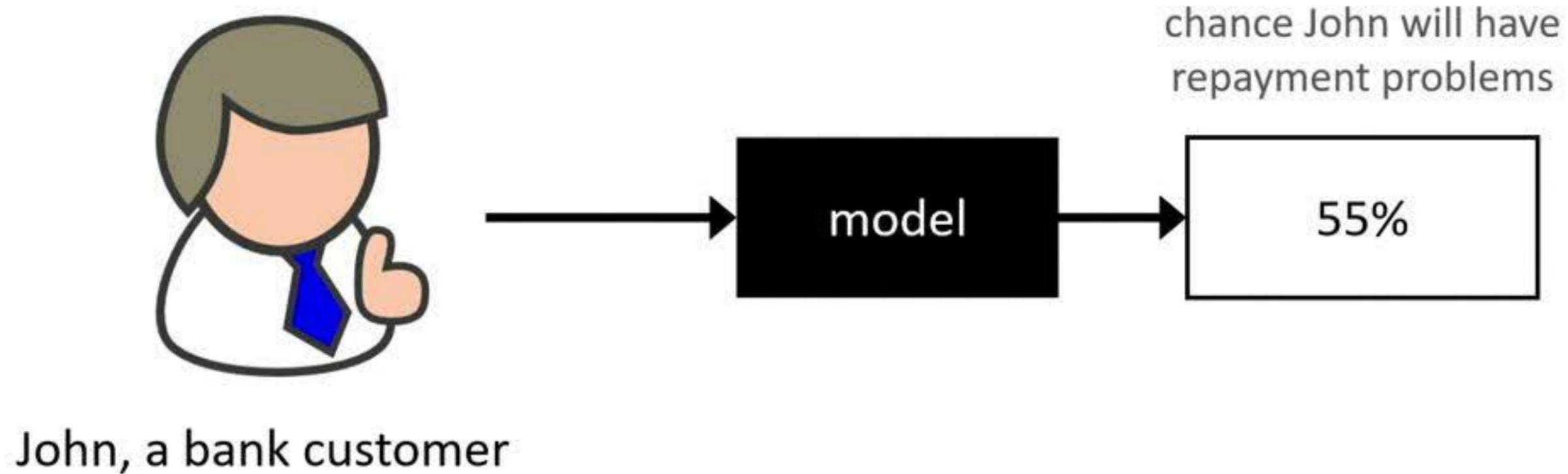
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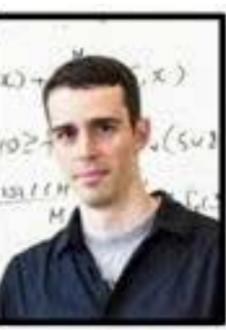


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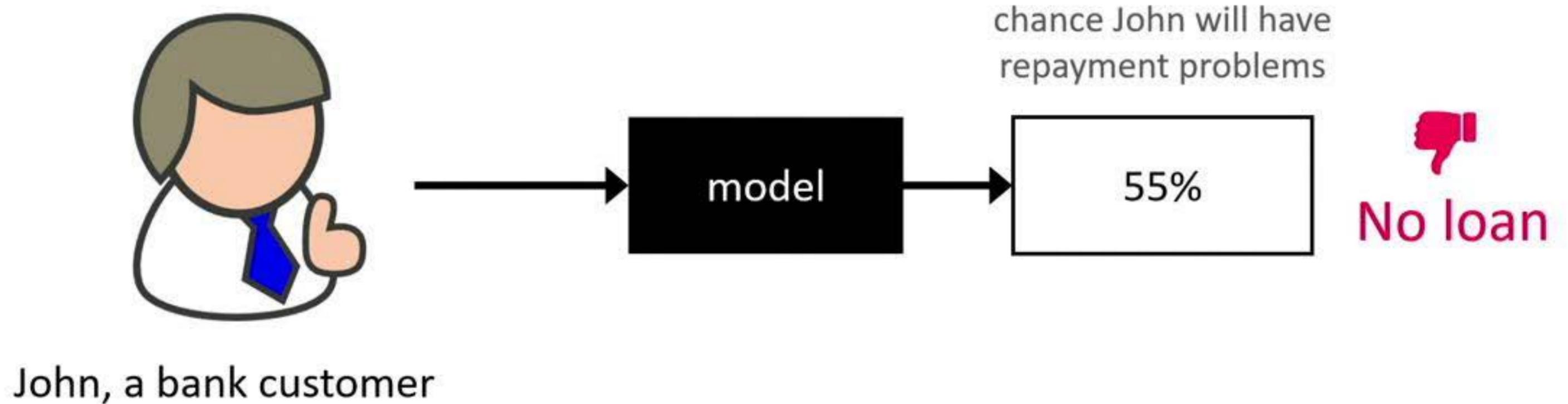


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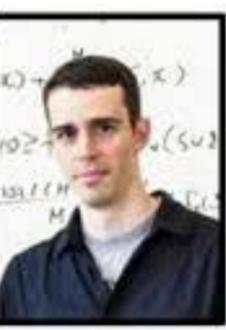


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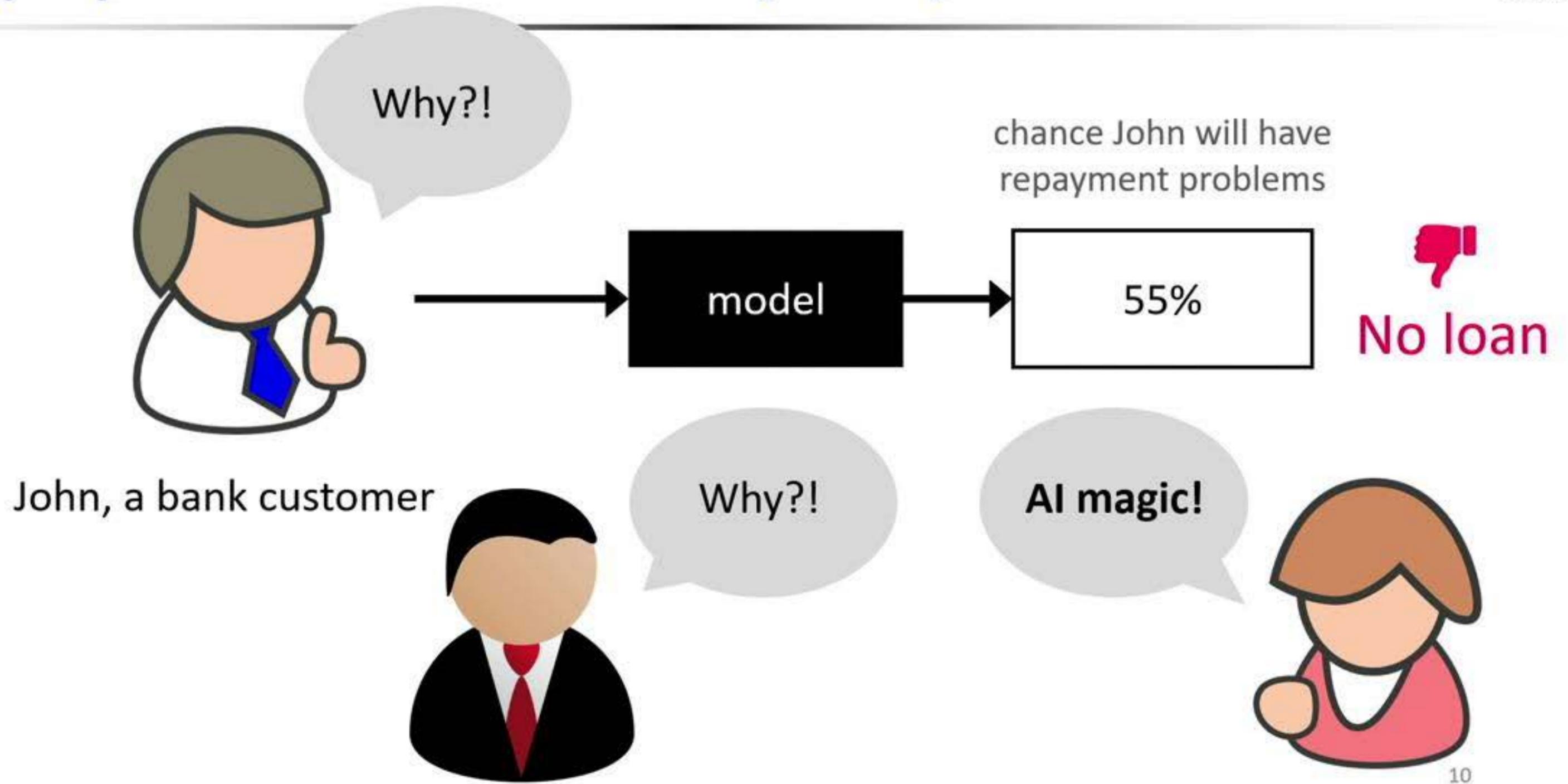


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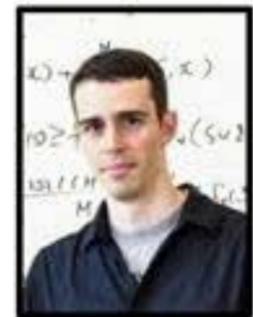


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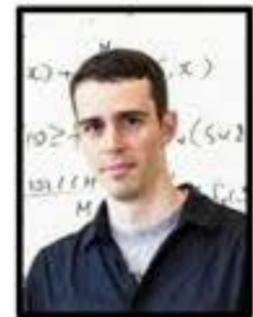
Scott



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Scott



Base rate

20%

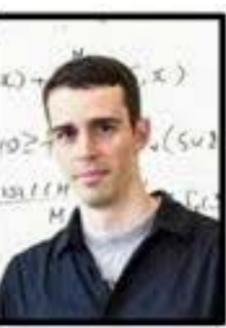
$E[f(x)]$

0



How exactly can we estimate feature importance?

— SHapley Additive exPlanation (SHAP) values



Scott



Base rate

Prediction for John

20%

55%

0

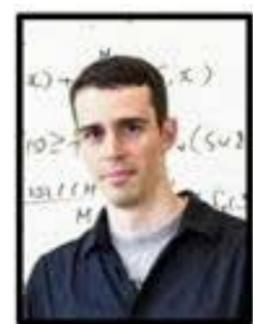
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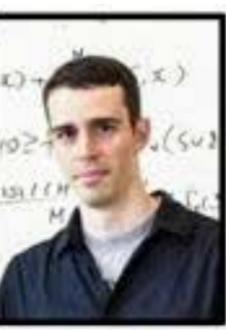
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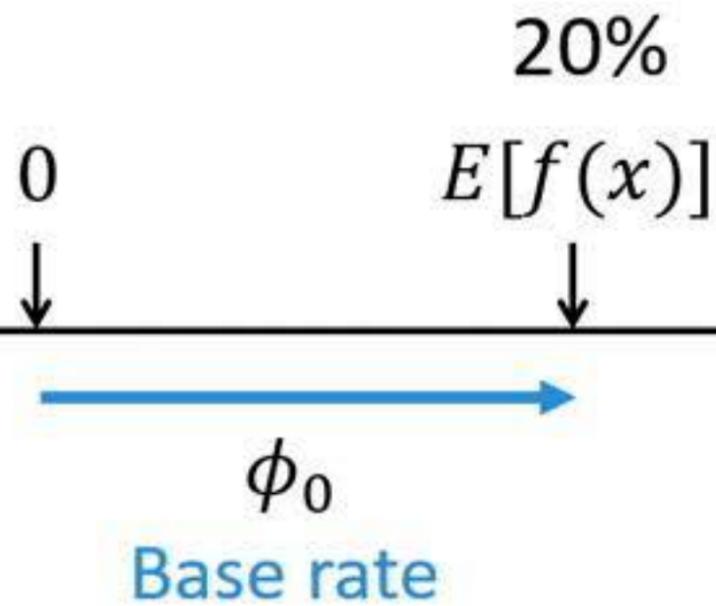
How did we get here?

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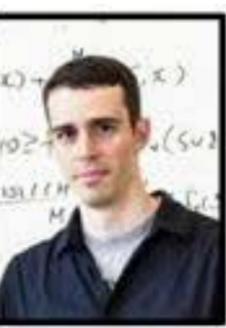


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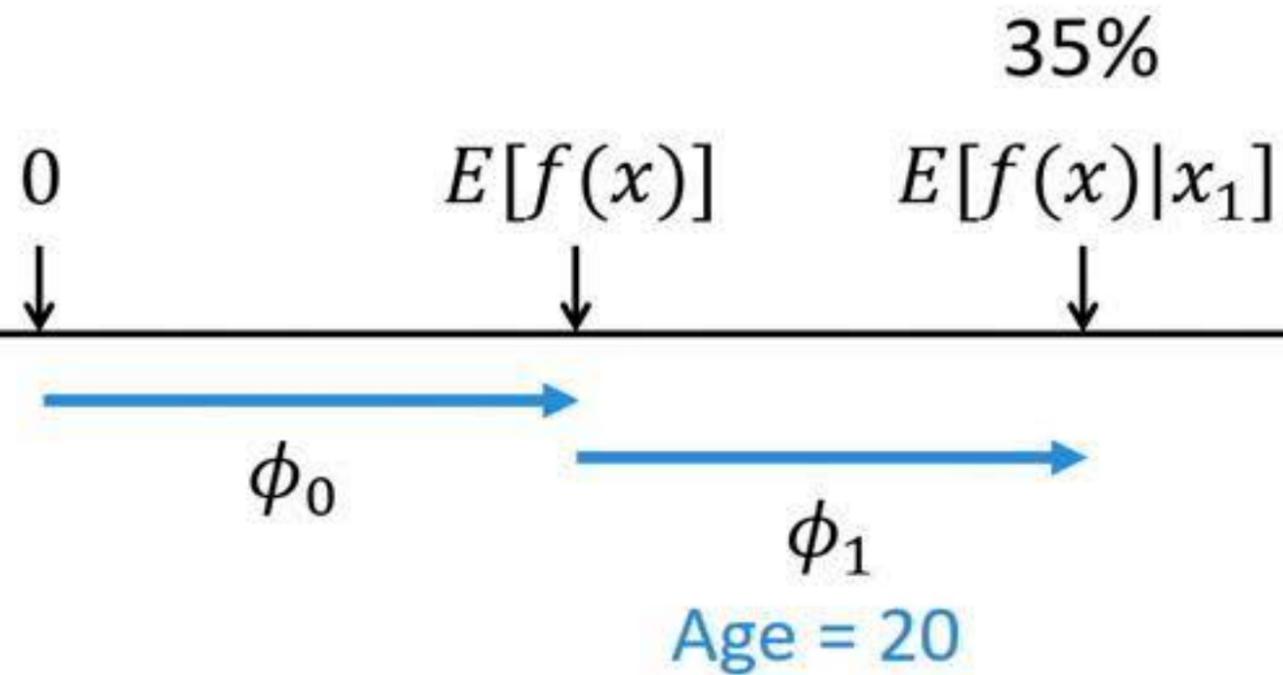


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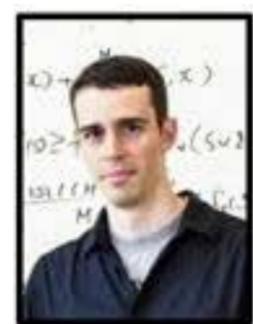


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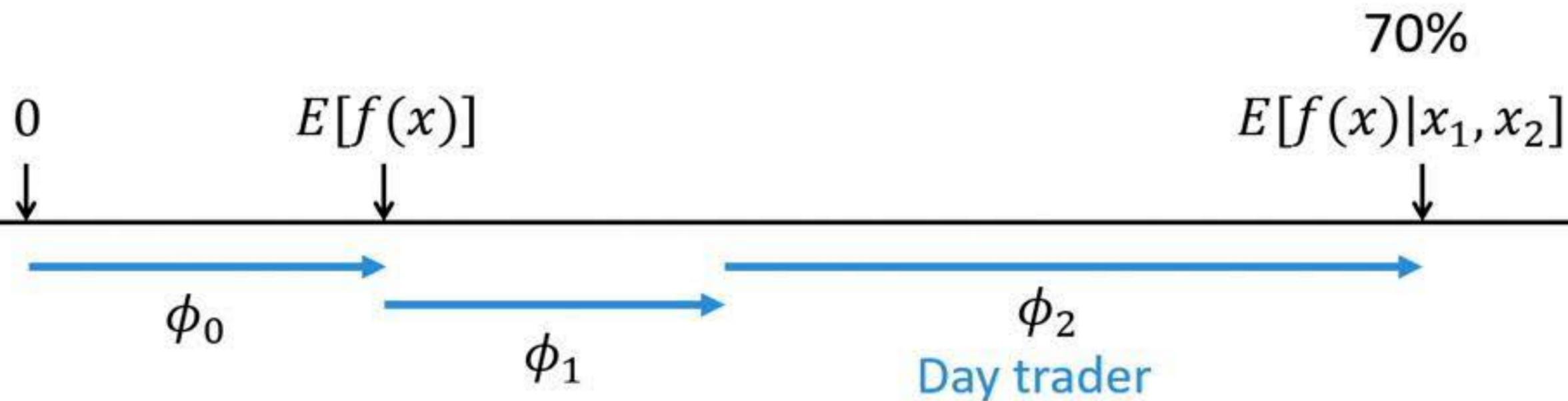


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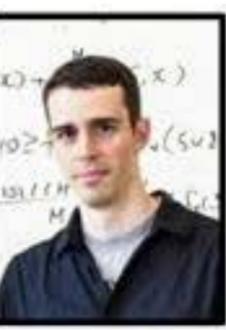


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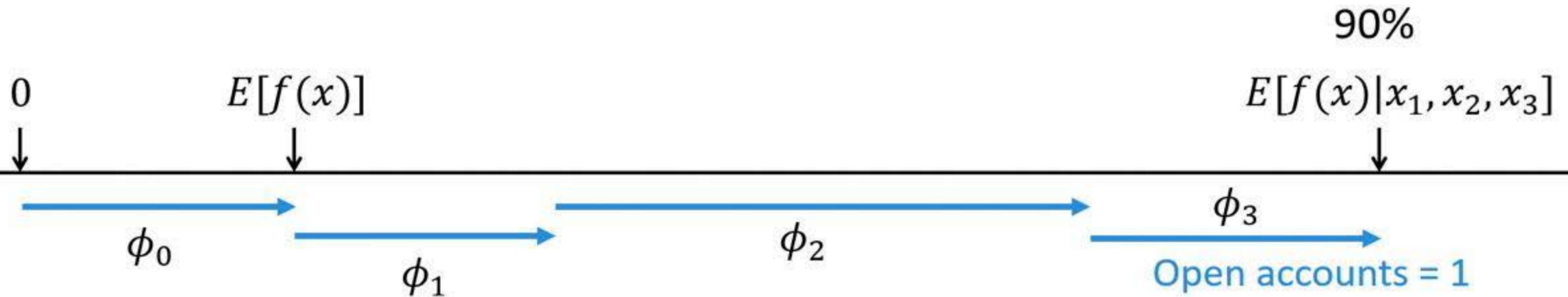


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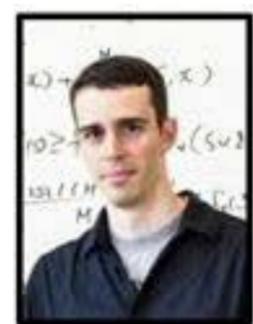


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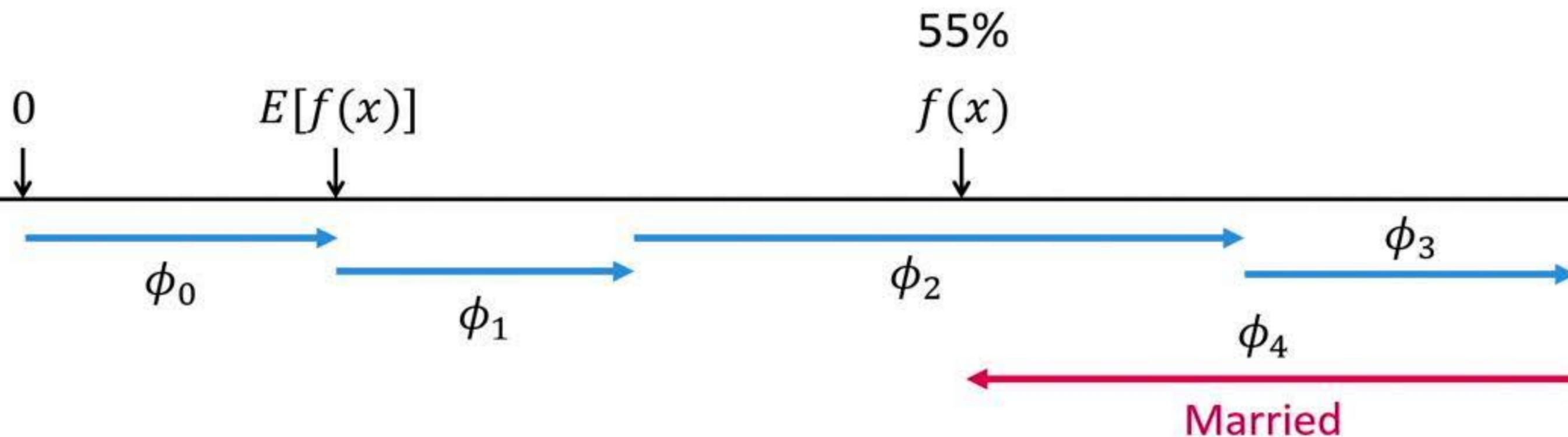


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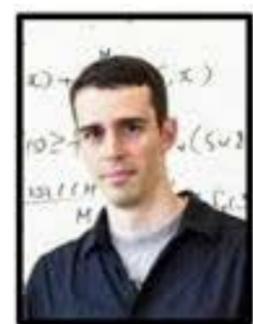


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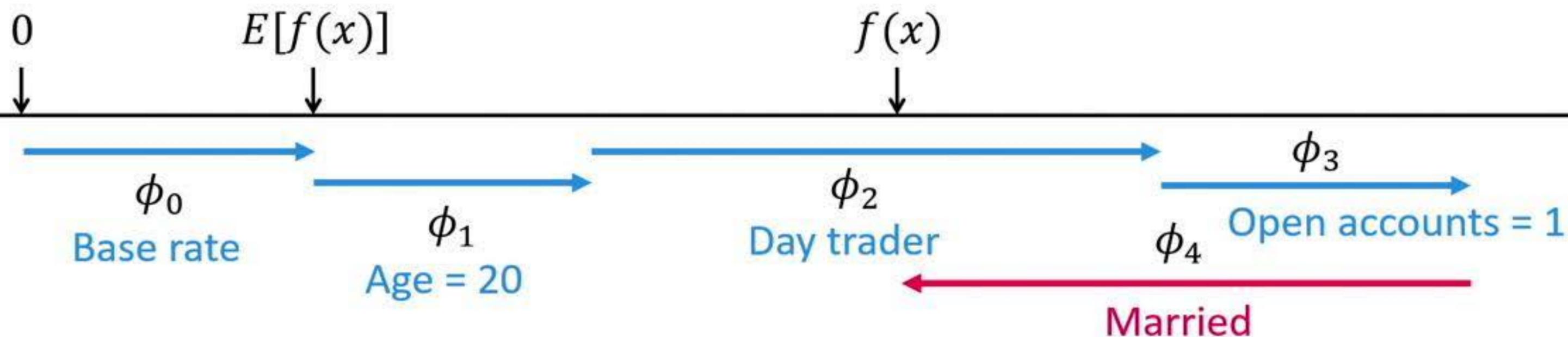
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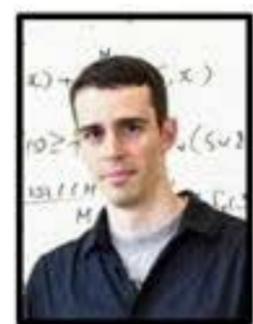
Scott

The order matters!



How exactly can we estimate feature importance?

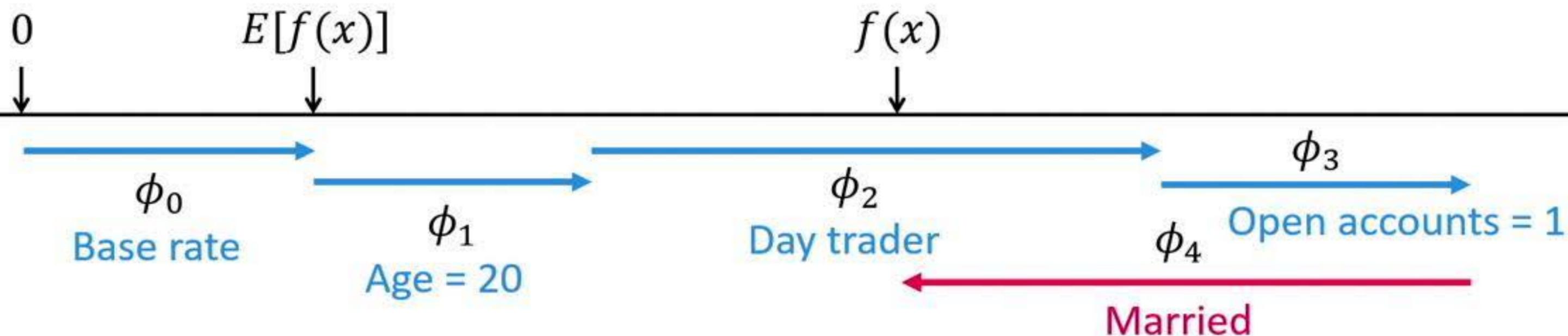
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The order matters!

SHAP values result from averaging over all $N!$ possible orderings



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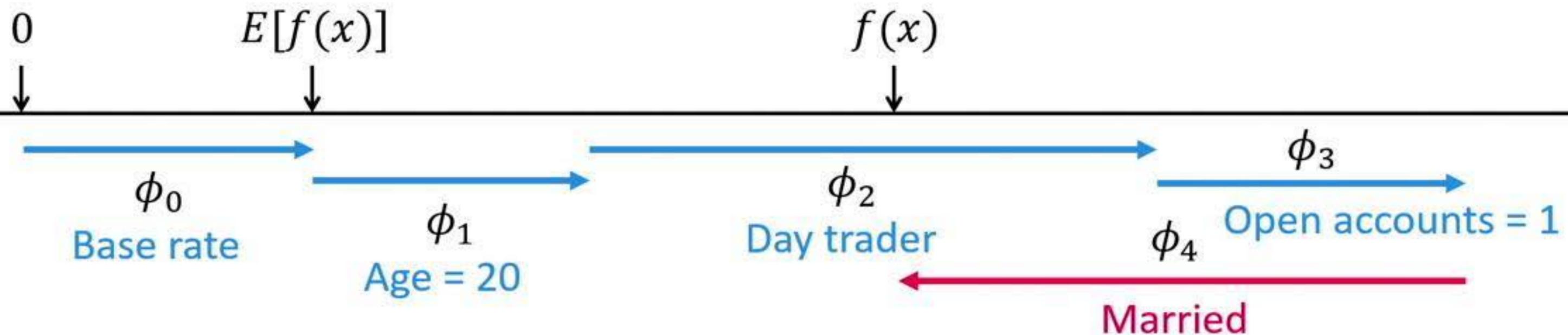
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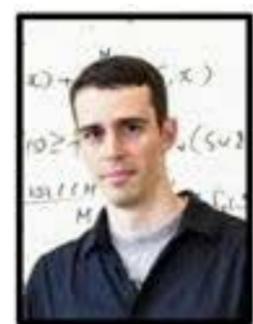
The order matters!

SHAP values result from averaging over all $N!$ possible orderings
They are the only solution that satisfies three important properties



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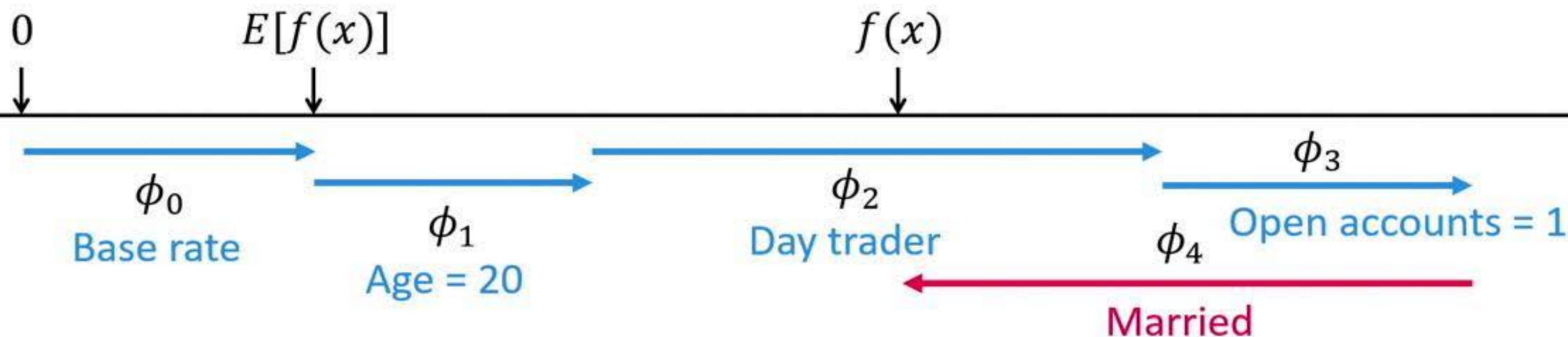
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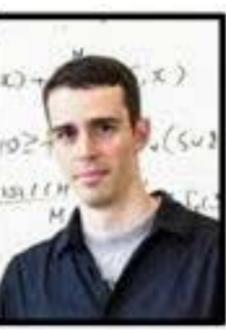
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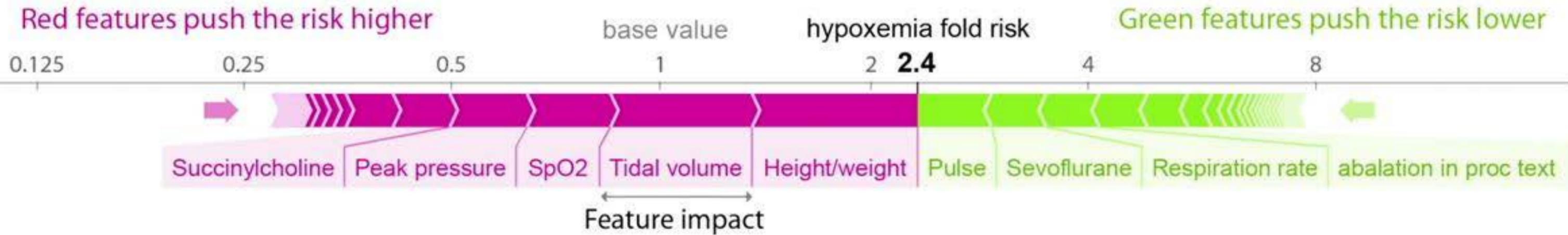
We need to develop efficient methods to estimate or compute exact SHAP values.



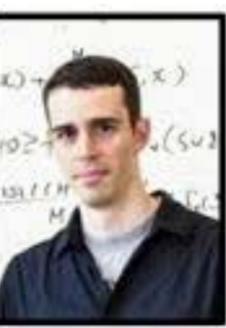
Prescience efficiently computes SHAP values on a predict made on a single time point for a particular patient.



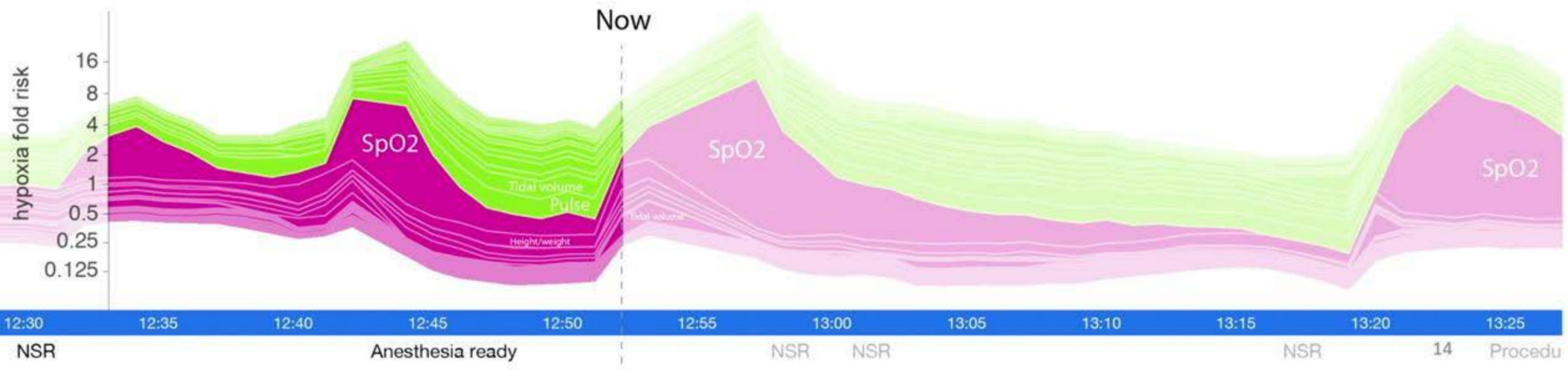
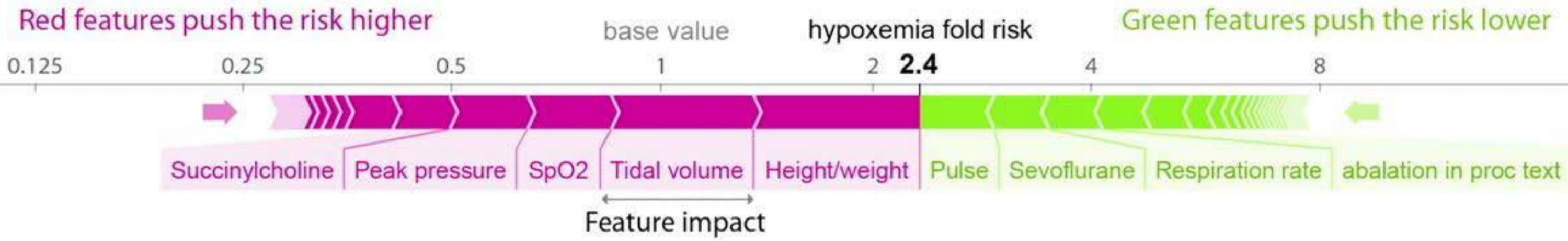
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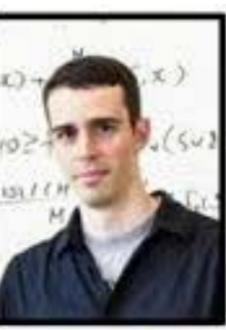
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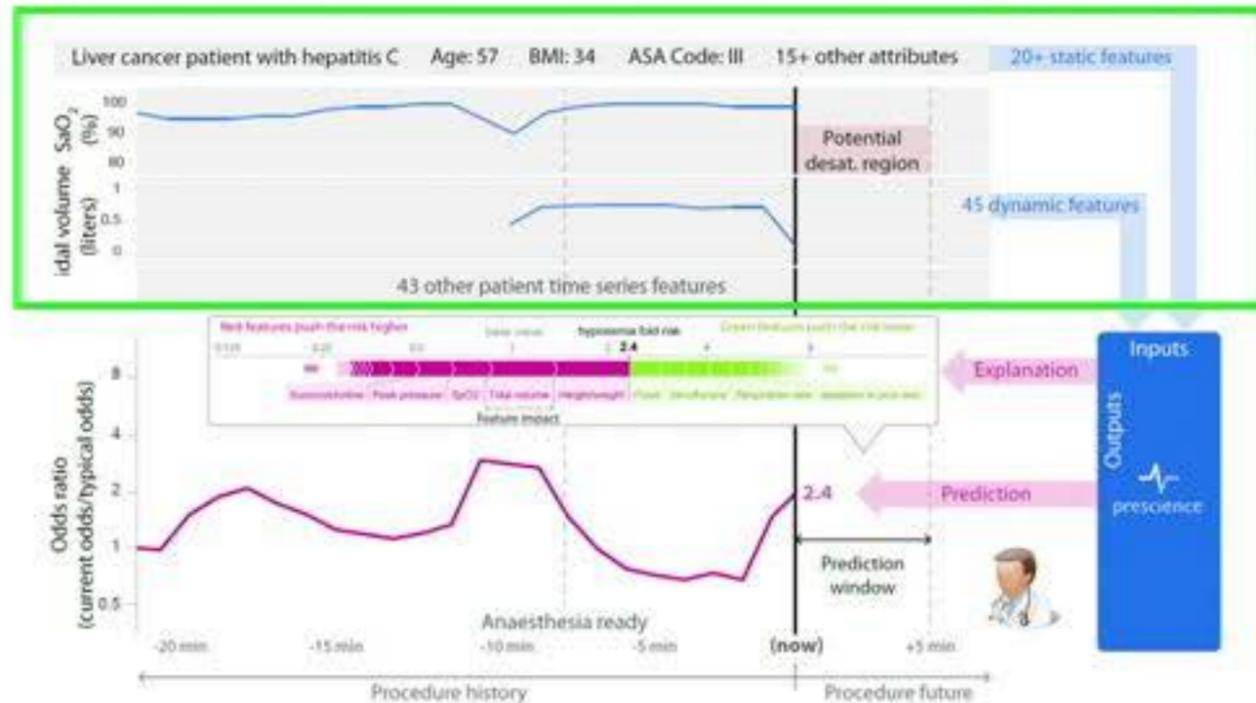


Prescience improves anesthesiologist's ability to predict hypoxemia

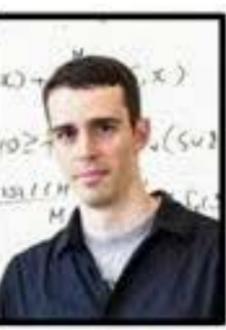


Scott

- We replayed prerecorded surgery data in a web-based visualization to 5 anesthesiologists.

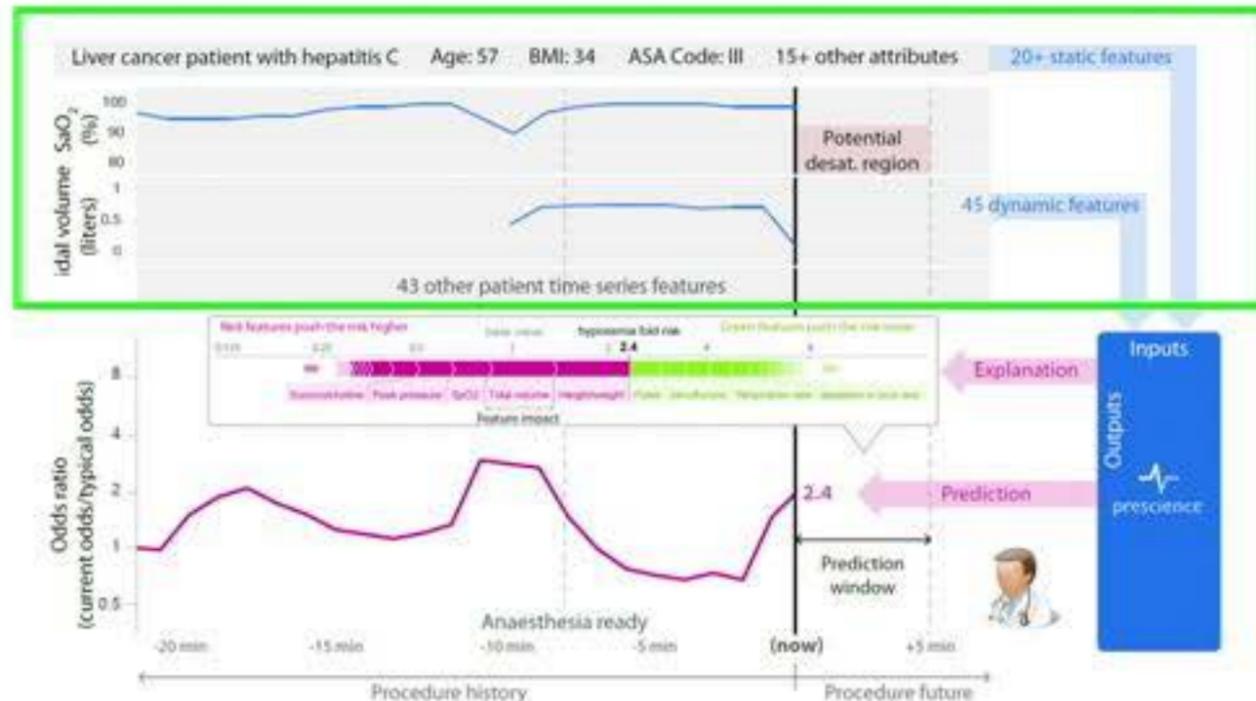


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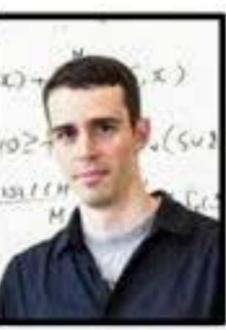


Scott

- We replayed prerecorded surgery data in a web-based visualization to 5 anesthesiologists.
- Each anesthesiologist provided a relative risk of hypoxemia for ~270 cases **without** or **with** the aid of Prescience.

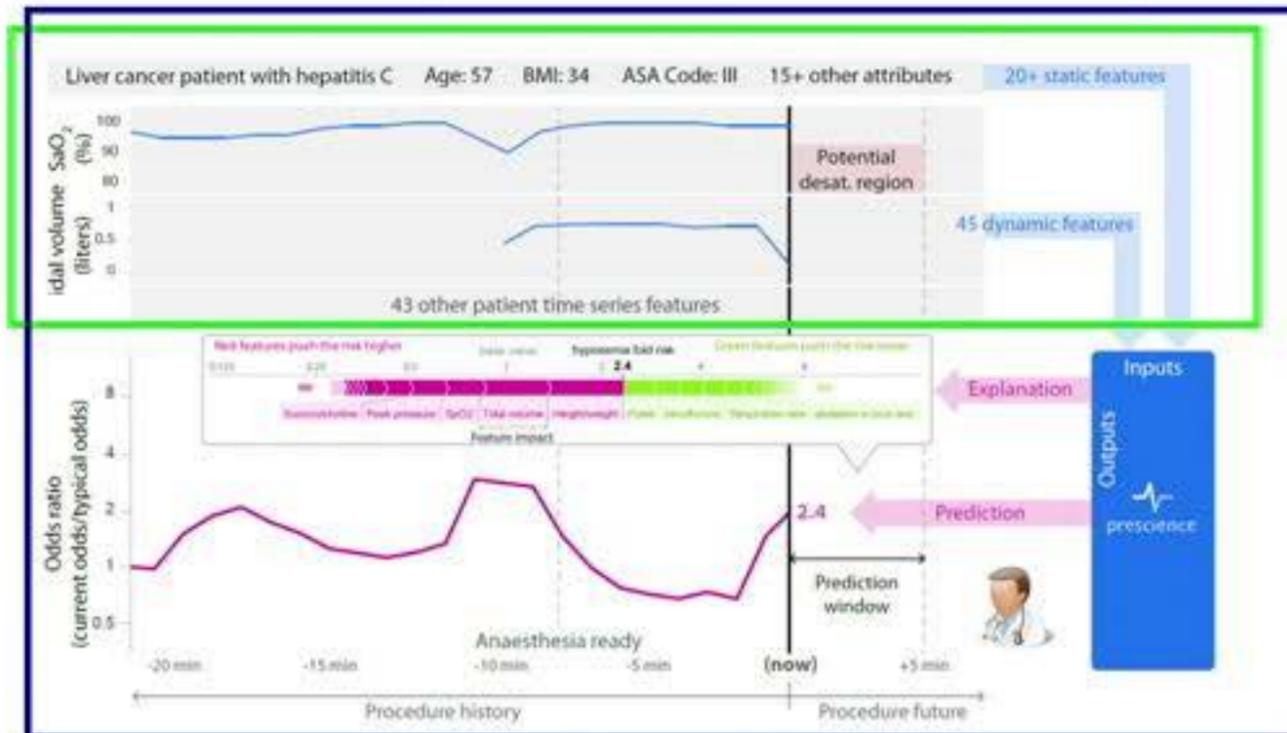


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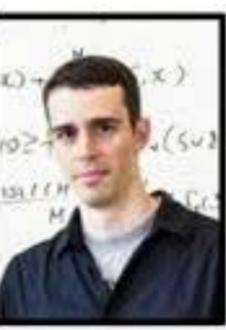


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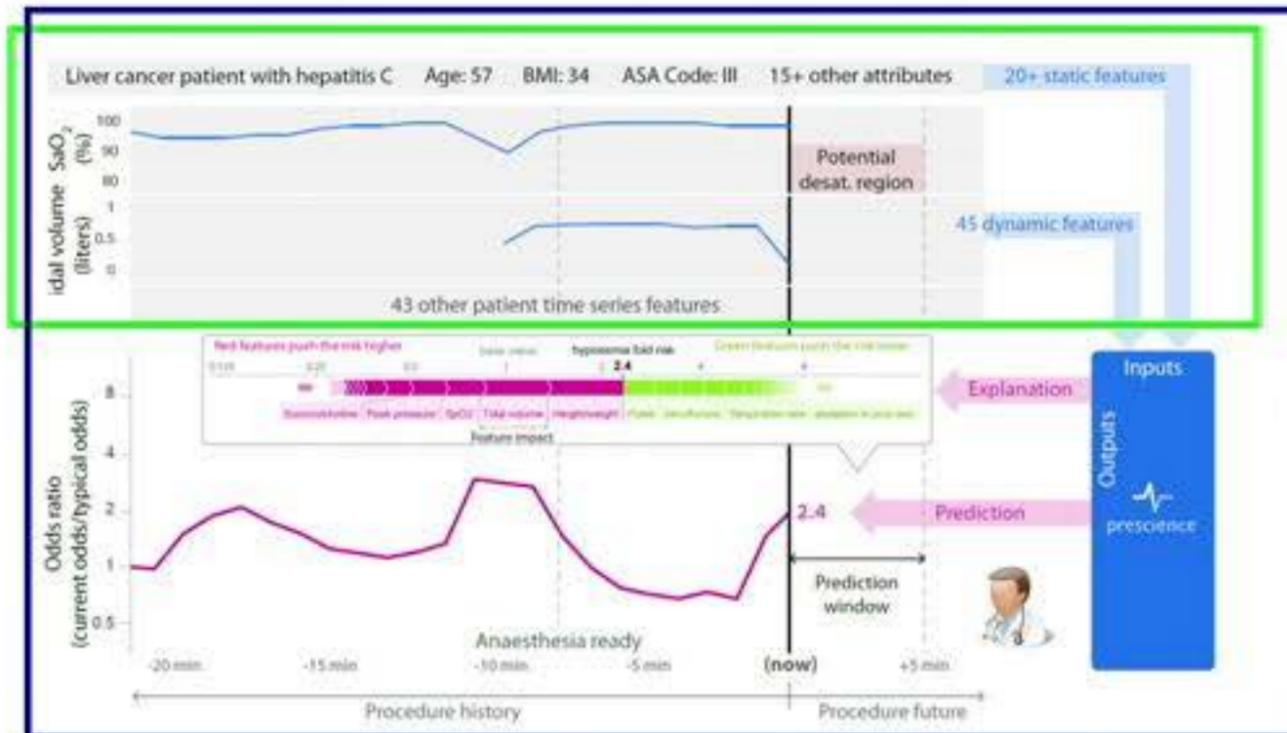
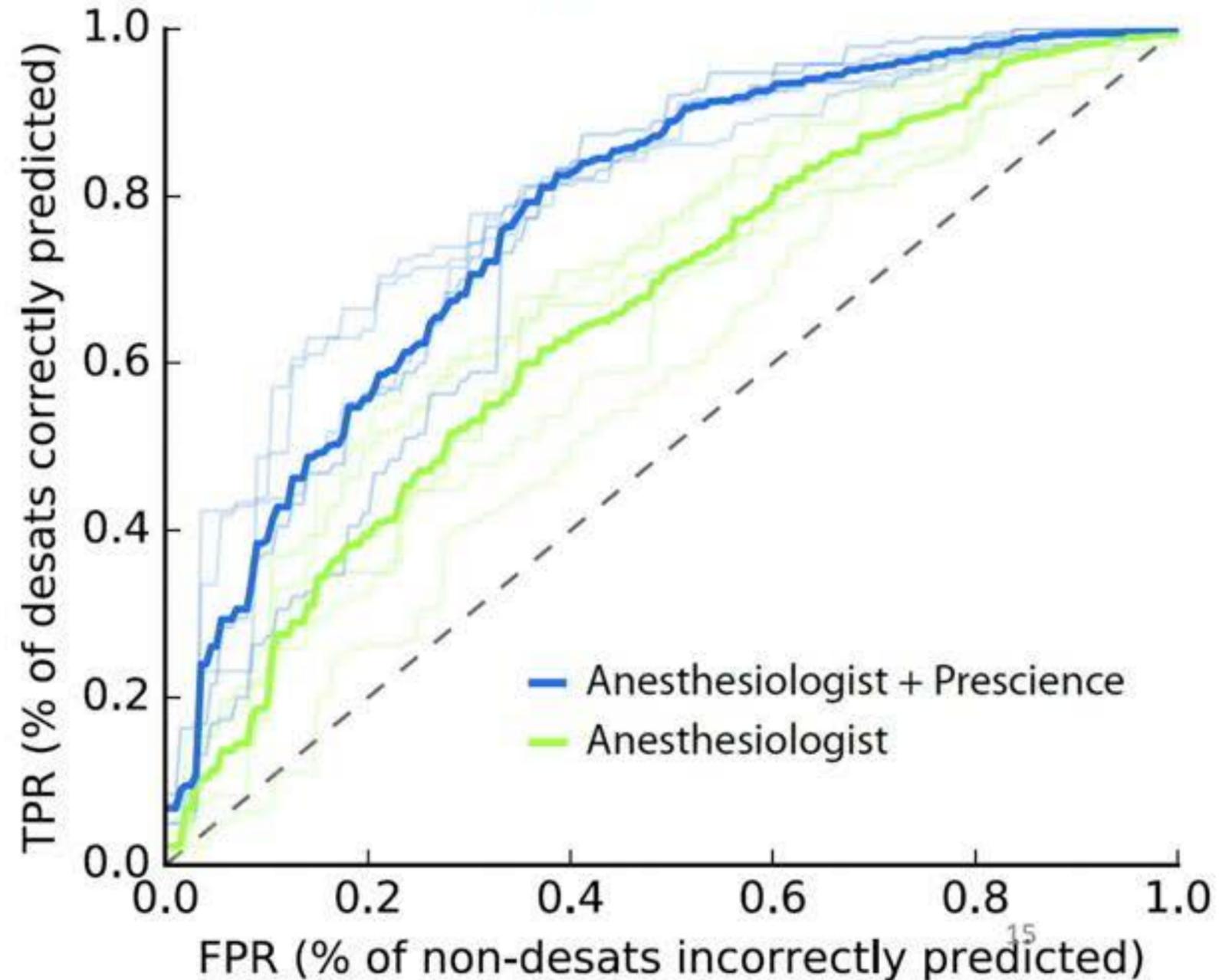
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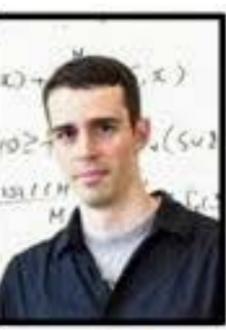
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Real-time hypoxemia prediction

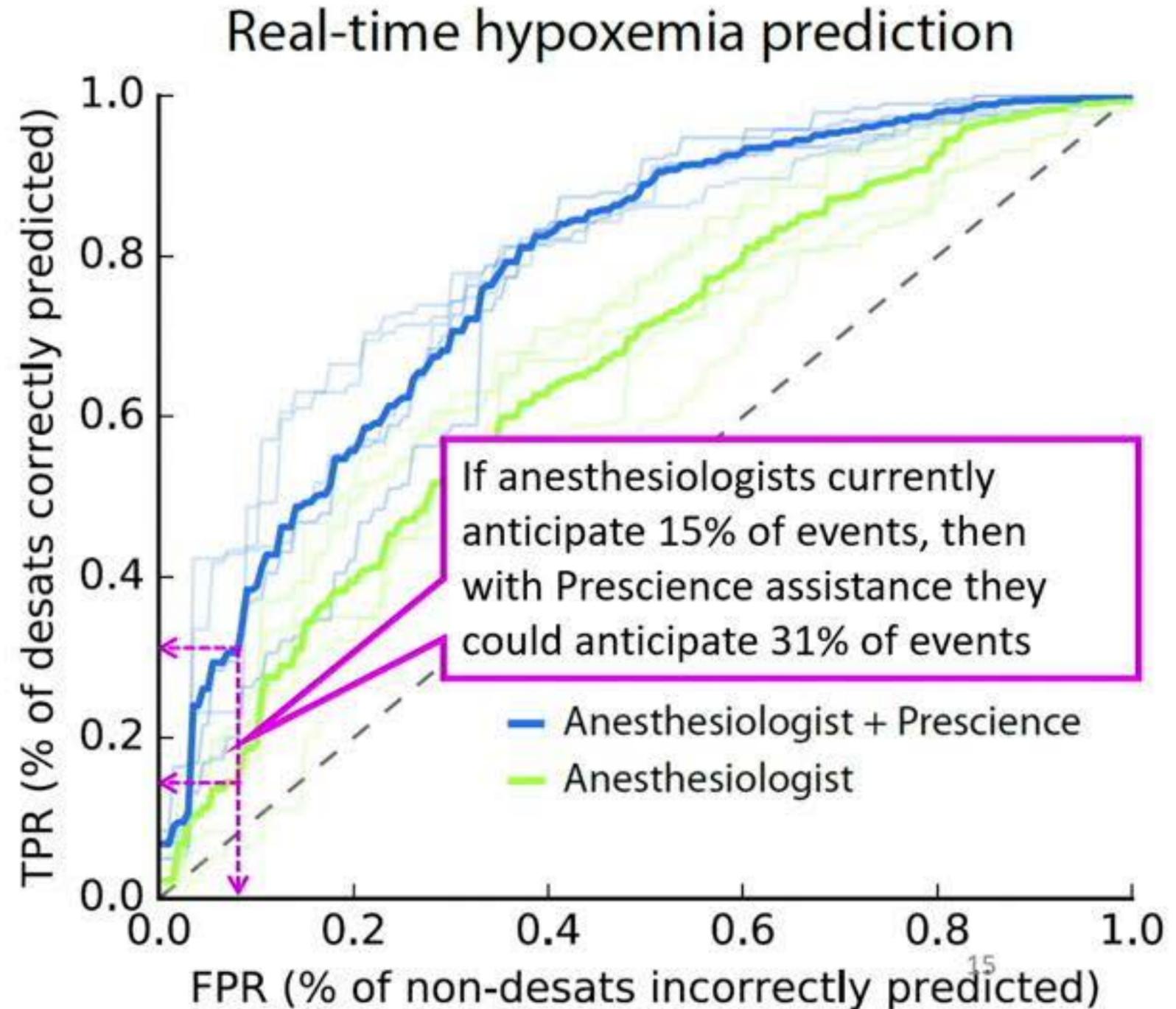


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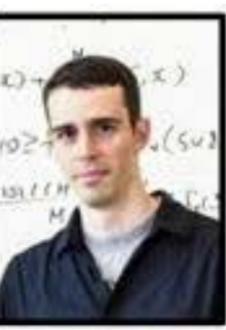


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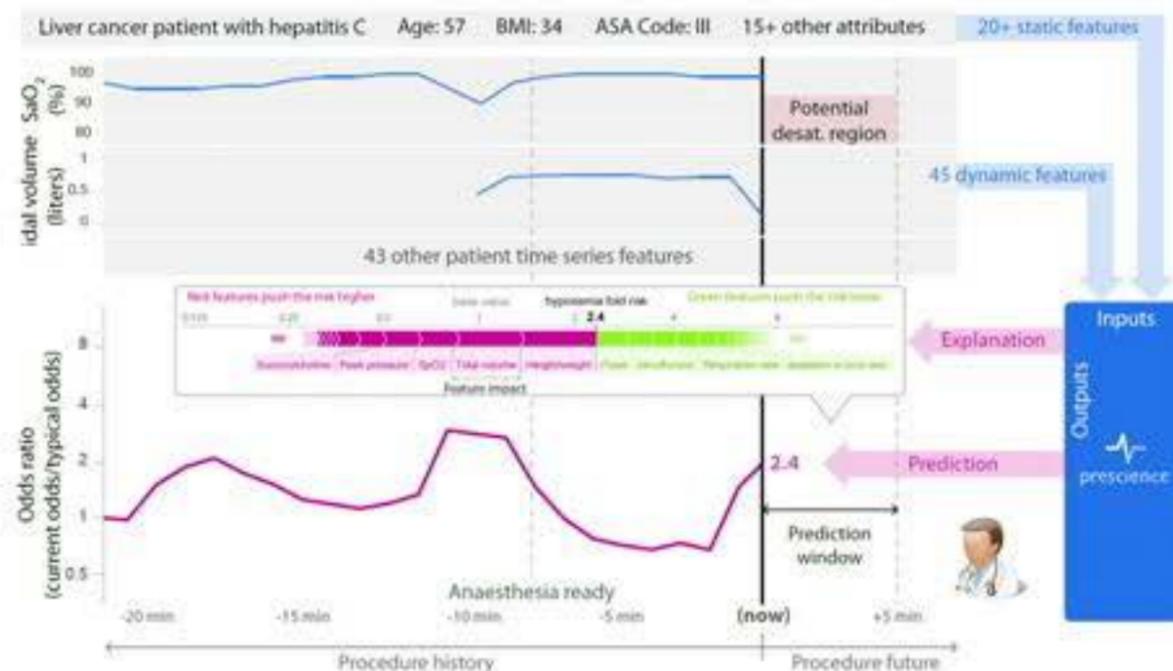


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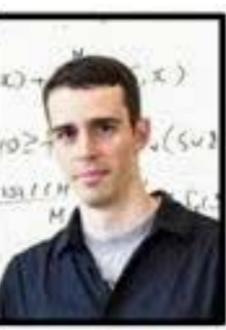


Scott

- What if we just let Prescience predict the hypoxemia risk?

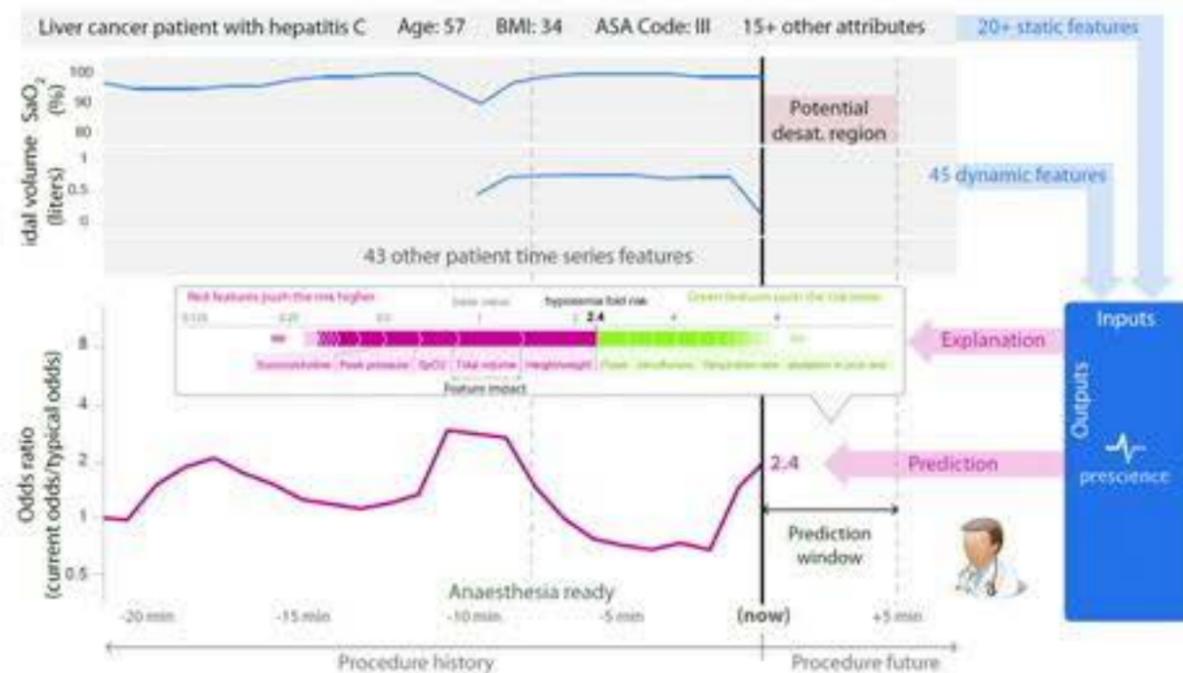


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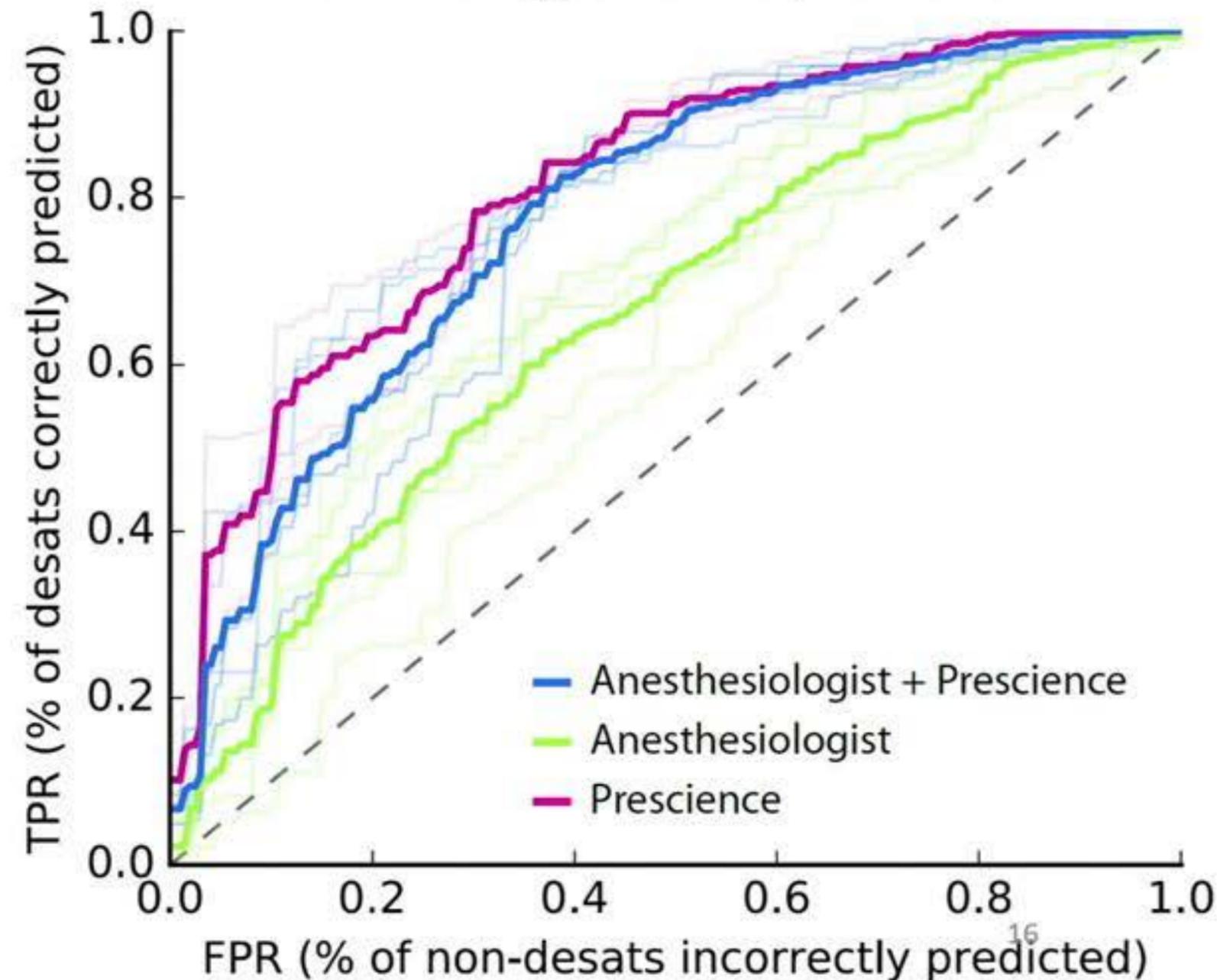


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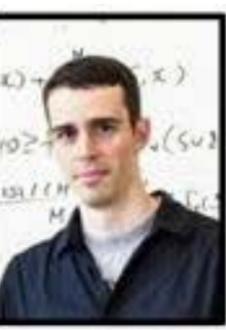
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Real-time hypoxemia prediction

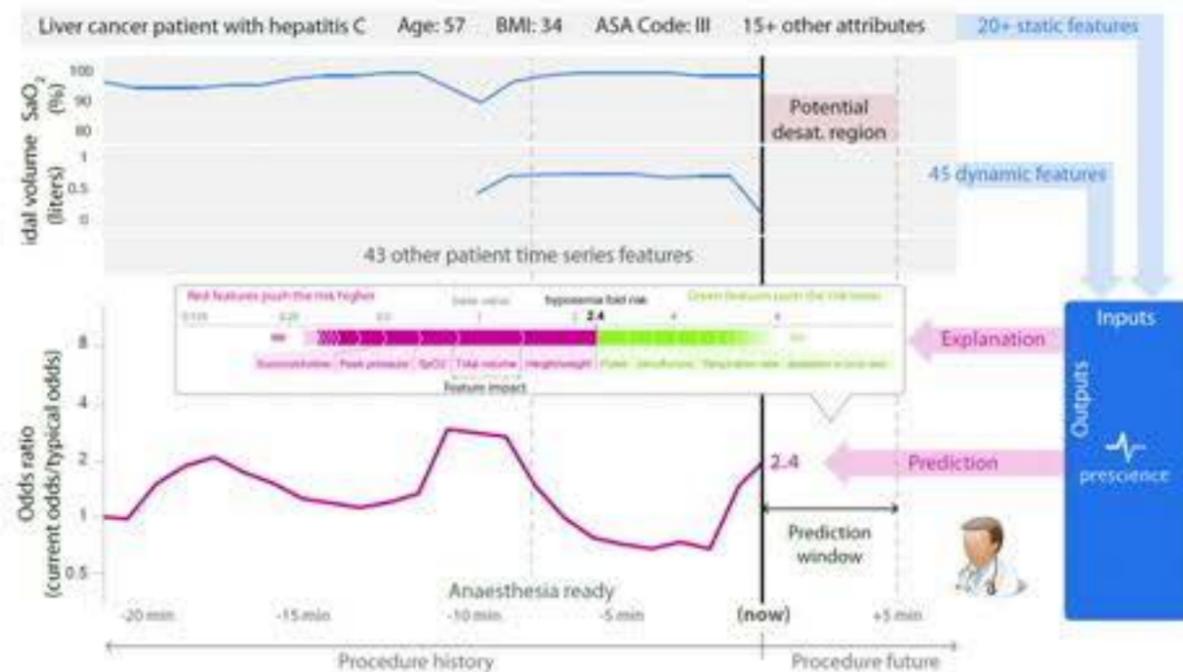


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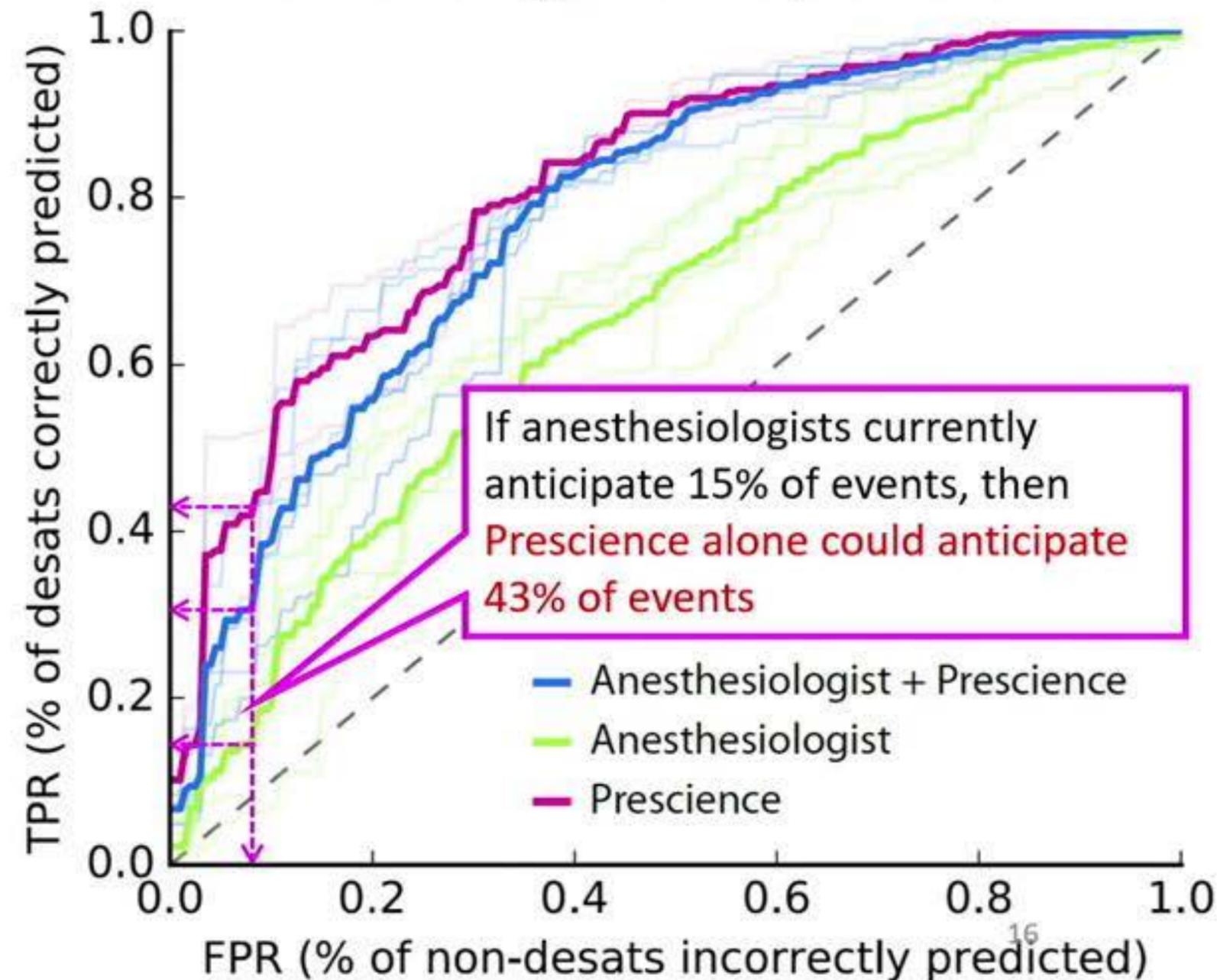


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Real-time hypoxemia prediction



We are improving prediction accuracy further by developing PHASE (PHysiologicalAI Signal Embedding)



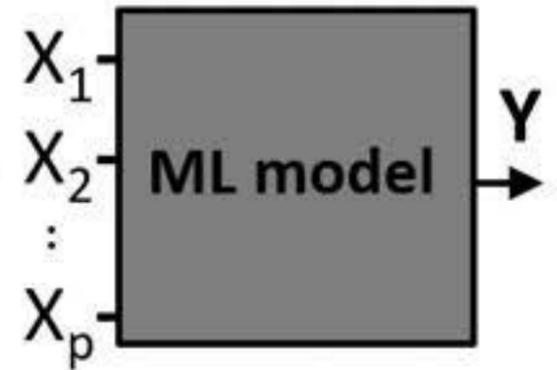
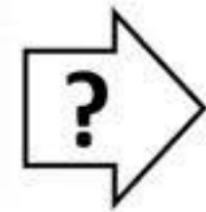
Hugh

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Hugh

- Embedding model for time-series data:

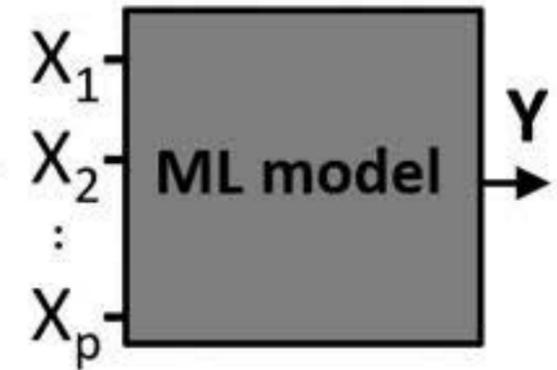
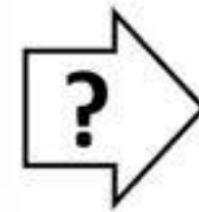


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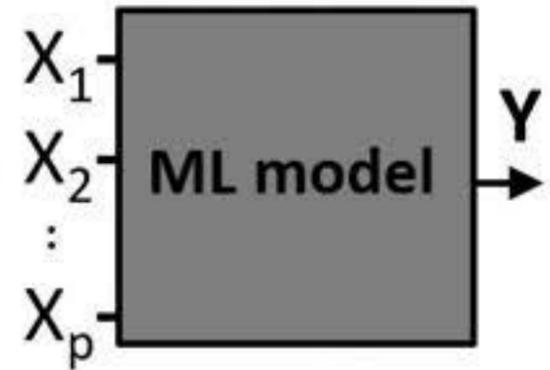
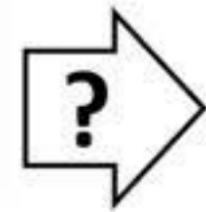


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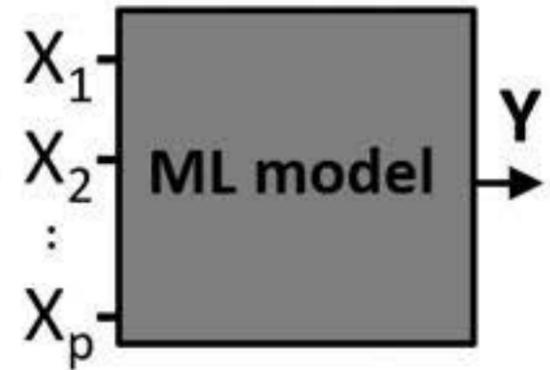
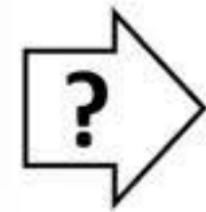


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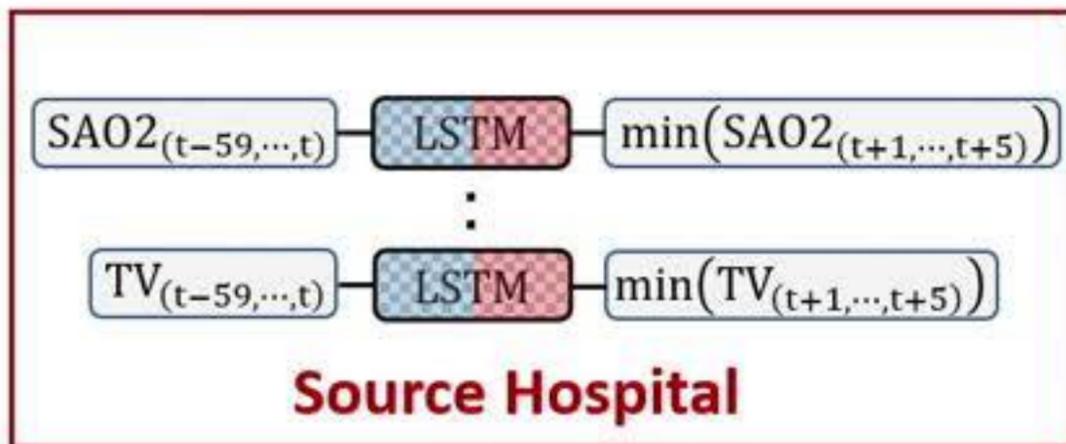
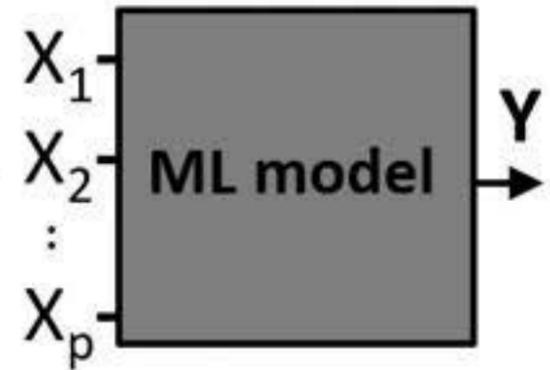
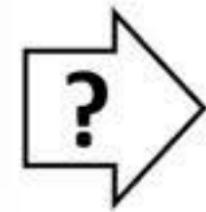


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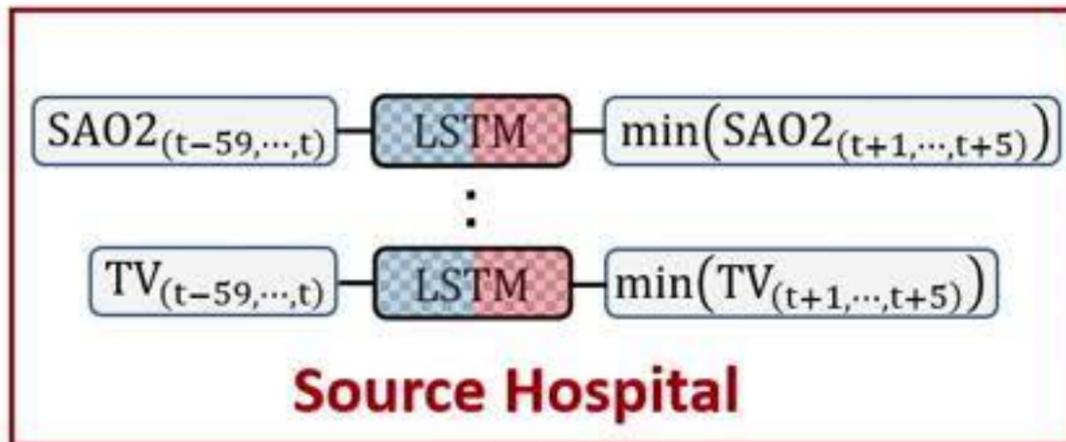
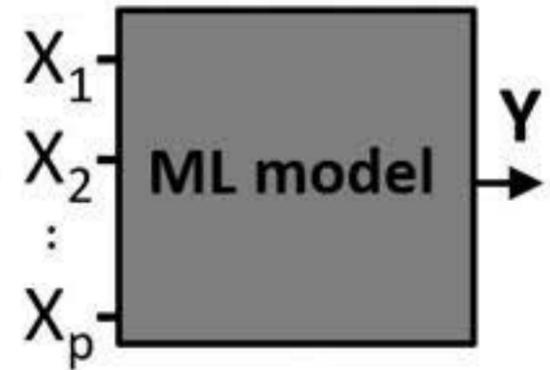
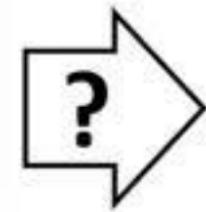


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 - Transfer the embedding model between hospitals without sharing data

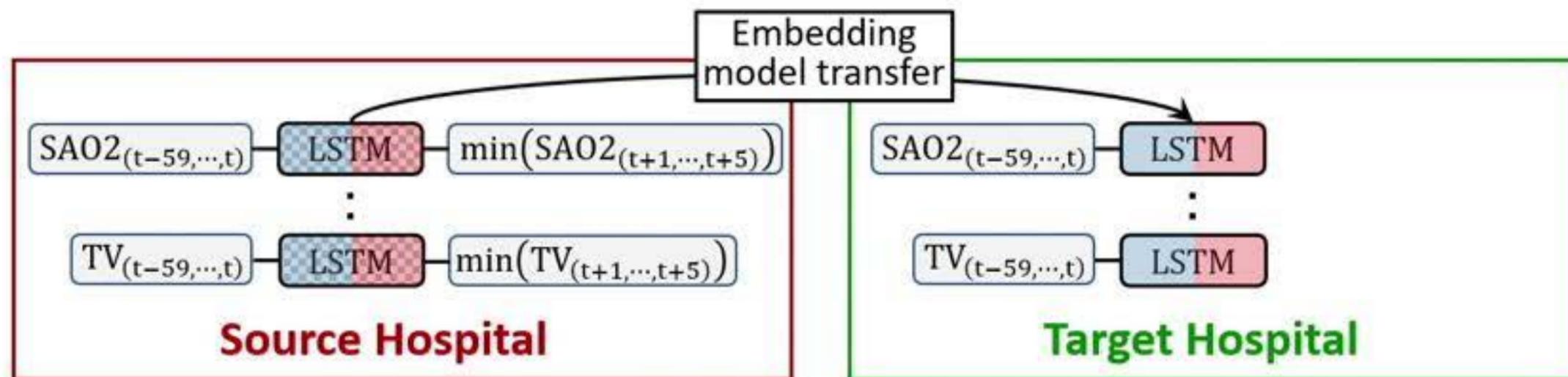
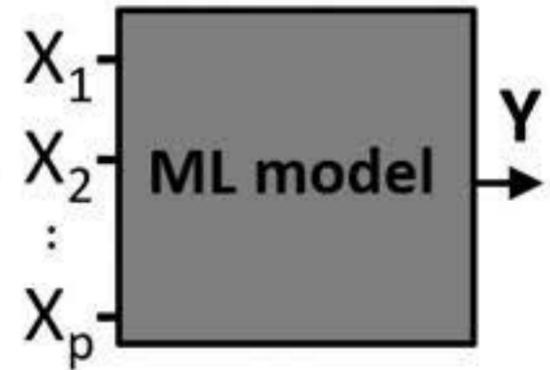
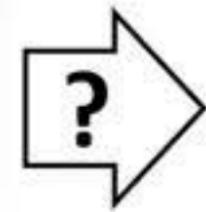


We are improving prediction accuracy further by developing PHASE (PHysiologicalAI Signal Embedding)



Hugh

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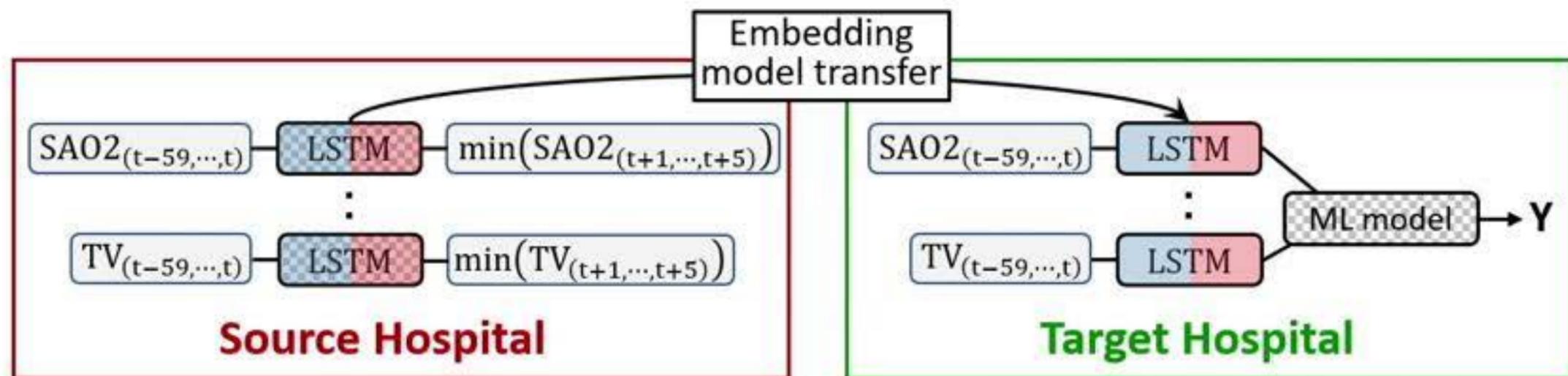
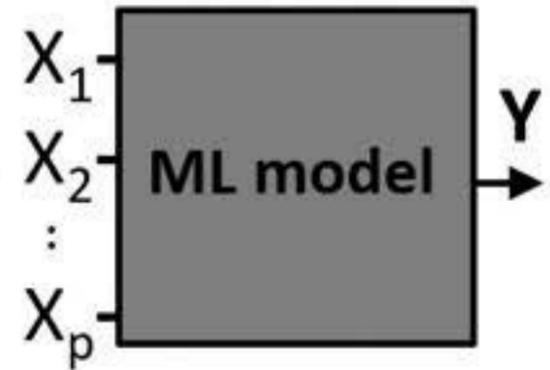
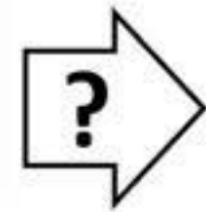


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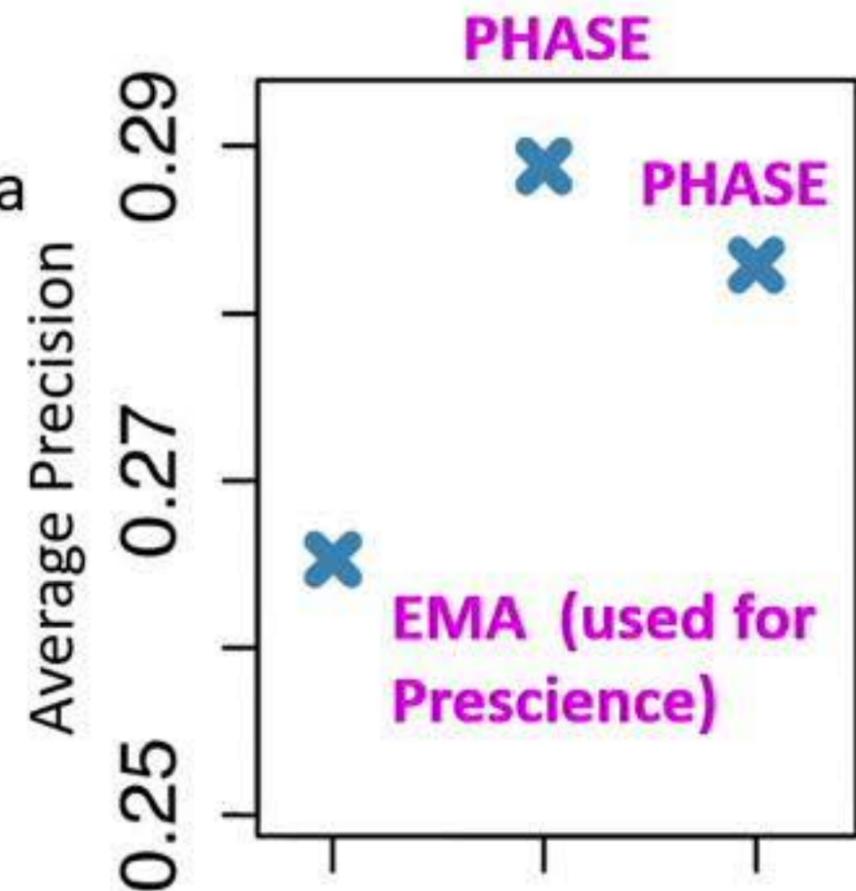
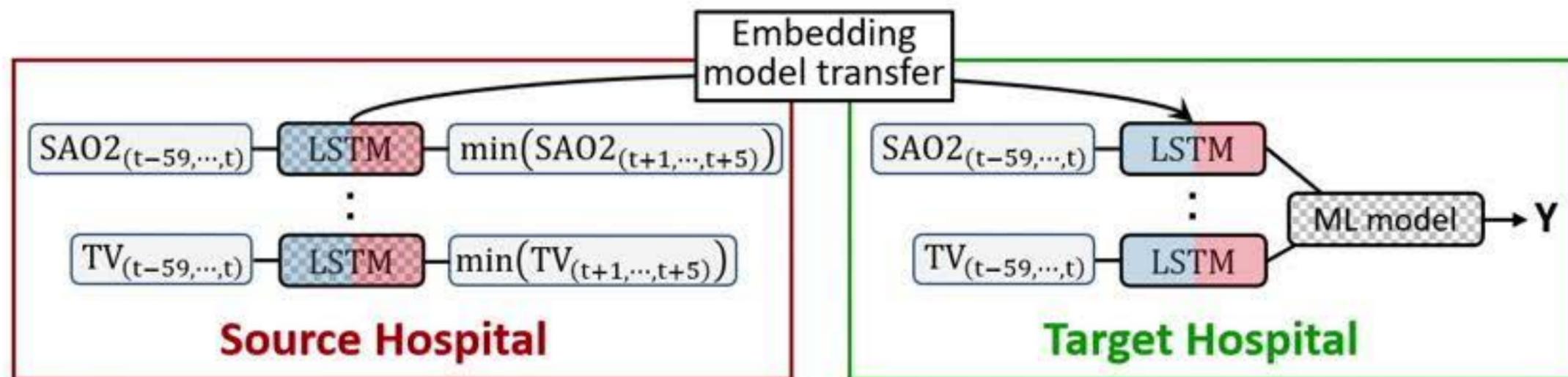
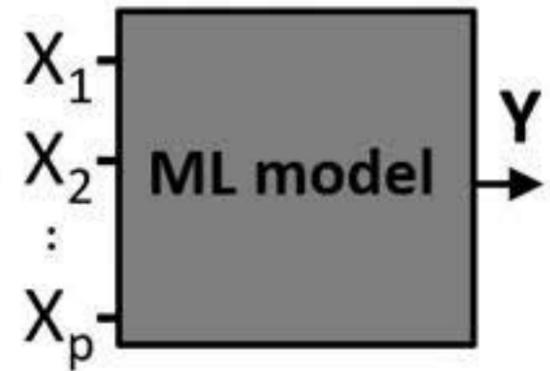
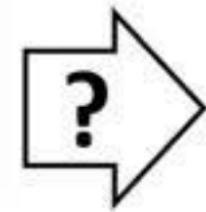


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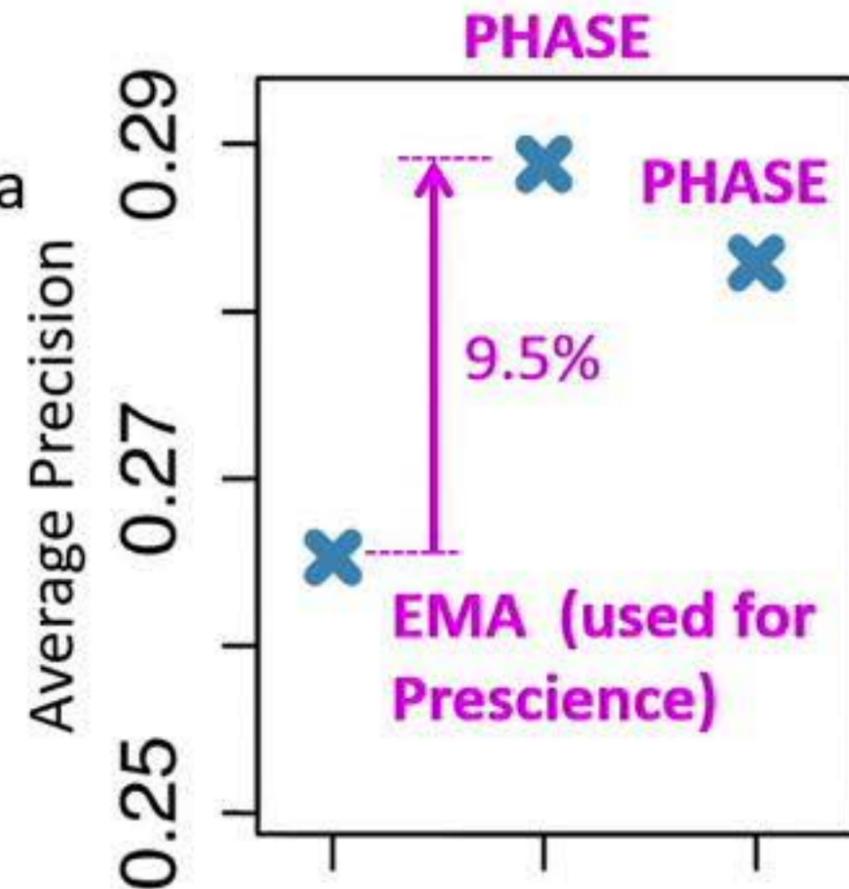
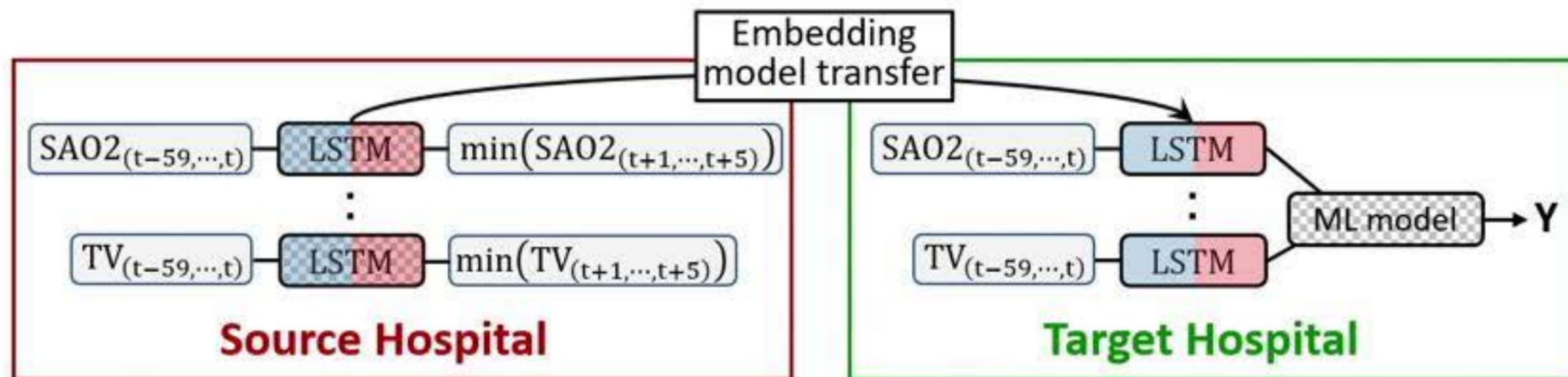
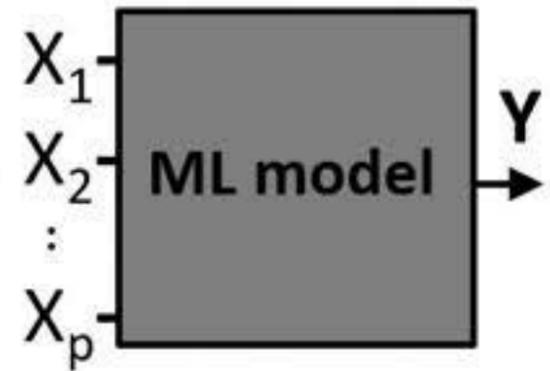
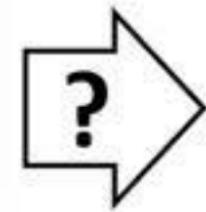


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Making tree ensembles interpretable



Scott

Gabe

Hugh

- Why tree ensembles?



Making tree ensembles interpretable



Scott

Gabe

Hugh

- Why tree ensembles? 
 - Gradient Boosted Trees and Random Forests are widely used state-of-the-art models.
 - Over half (17/29) of all Kaggle competition winners in 2015 used XGBoost (Chen and Guestrin).

Making tree ensembles interpretable



Scott

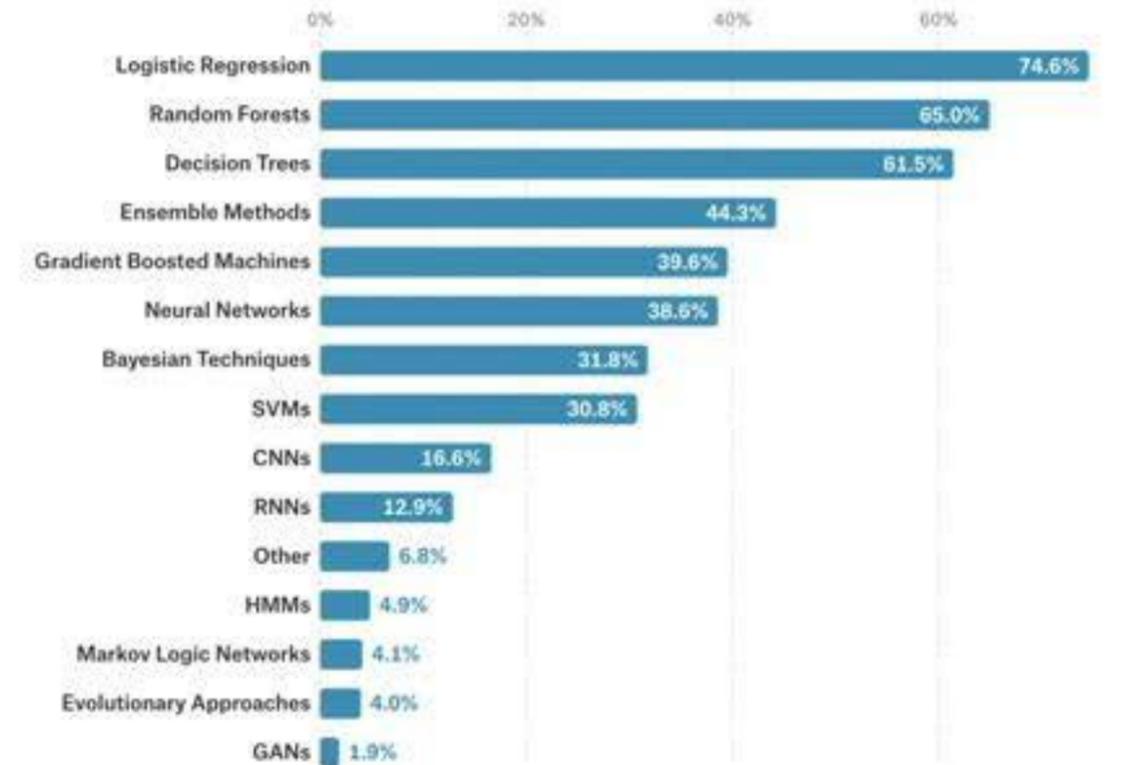
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2,039 responses

Making tree ensembles interpretable



Scott

Gabe

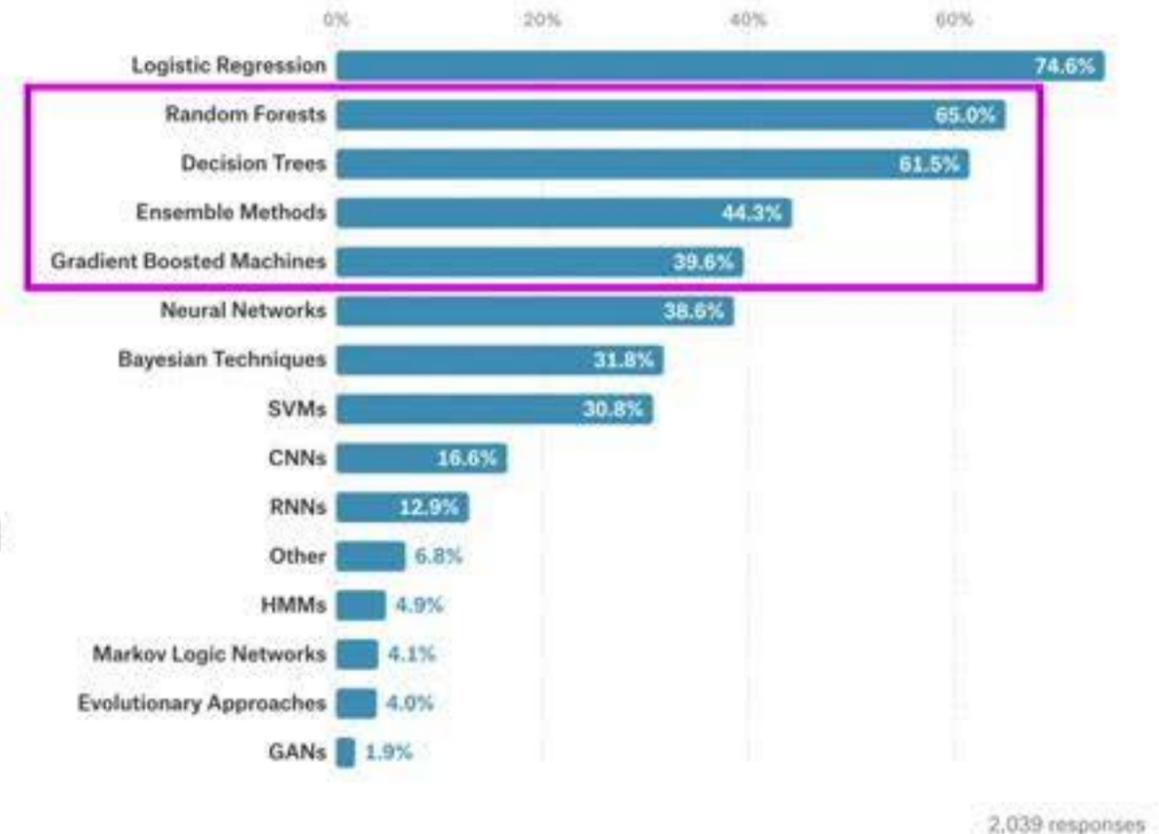
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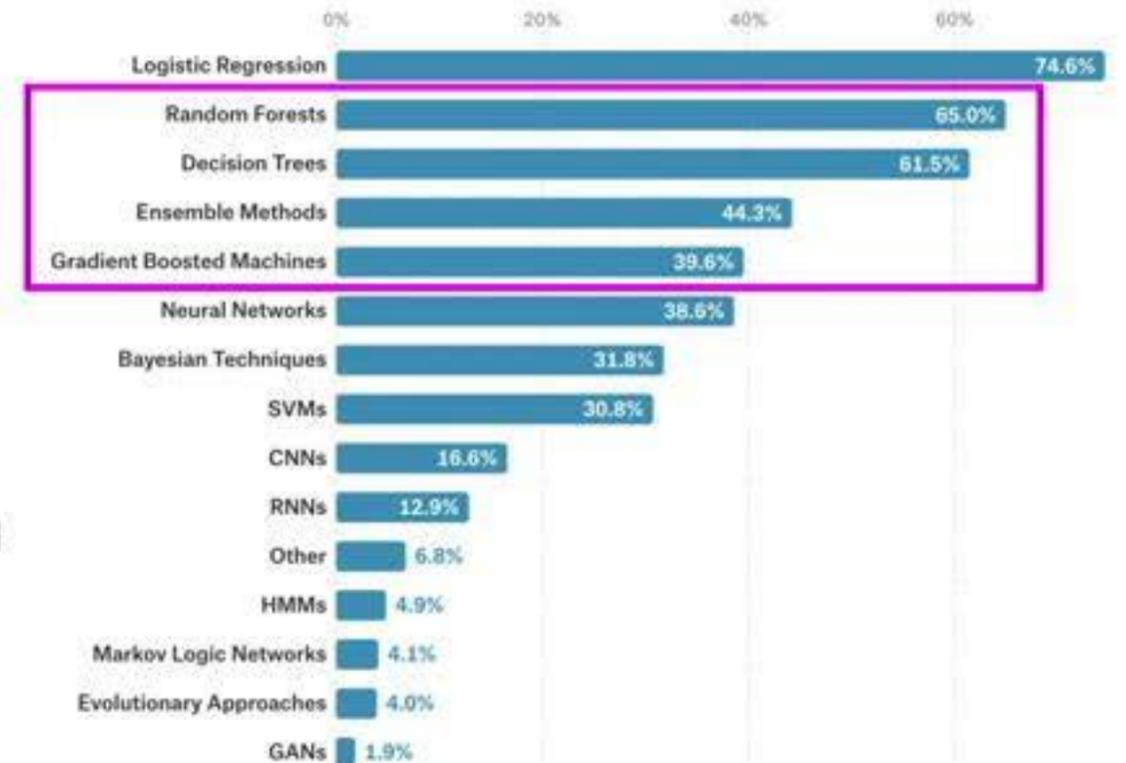
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Making tree ensembles interpretable



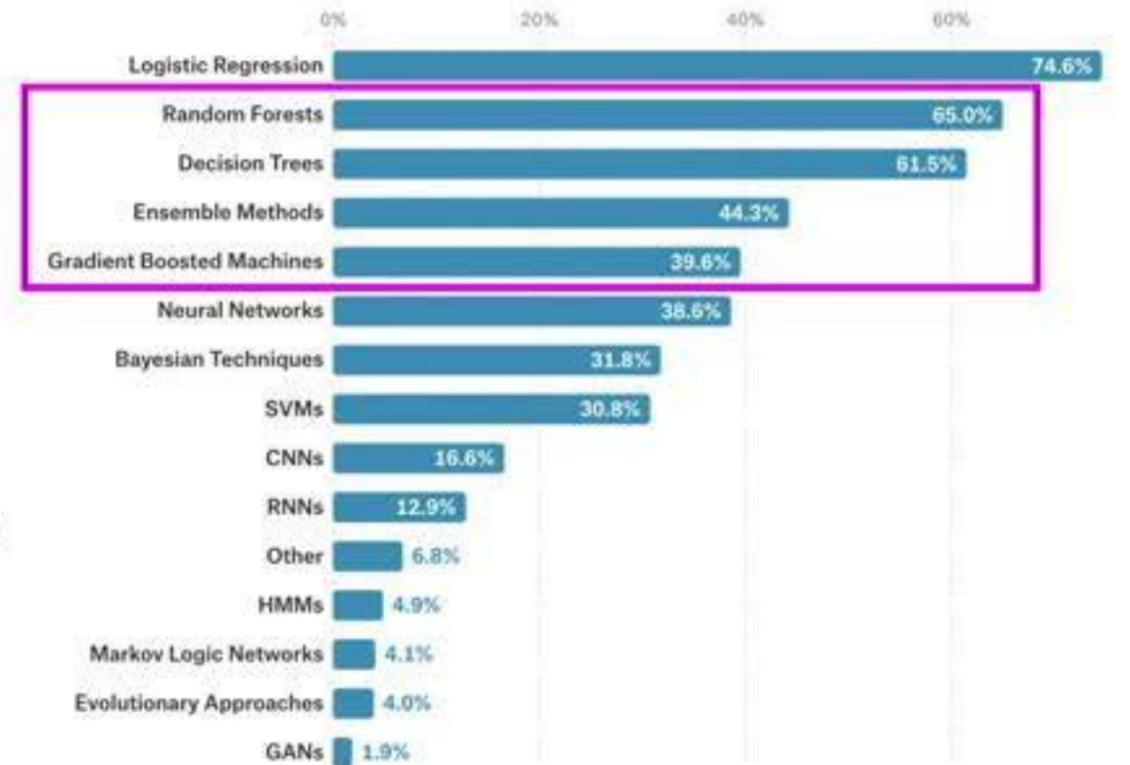
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Direct Solution

$$O(TL2^M) \text{ Exponential}$$

to

Tree SHAP

$$O(TLD^2) \text{ Polynomial}$$

Using SHAP values as building blocks for interpretable ML: SHAP summary plot



Scott

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Using SHAP values as building blocks for interpretable ML: SHAP summary plot



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- NHANES I 
National Health & Nutrition Examination Survey

Using SHAP values as building blocks for interpretable ML: SHAP summary plot



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- NHANES I 
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 - X: 14 common measurements

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9,932 individuals

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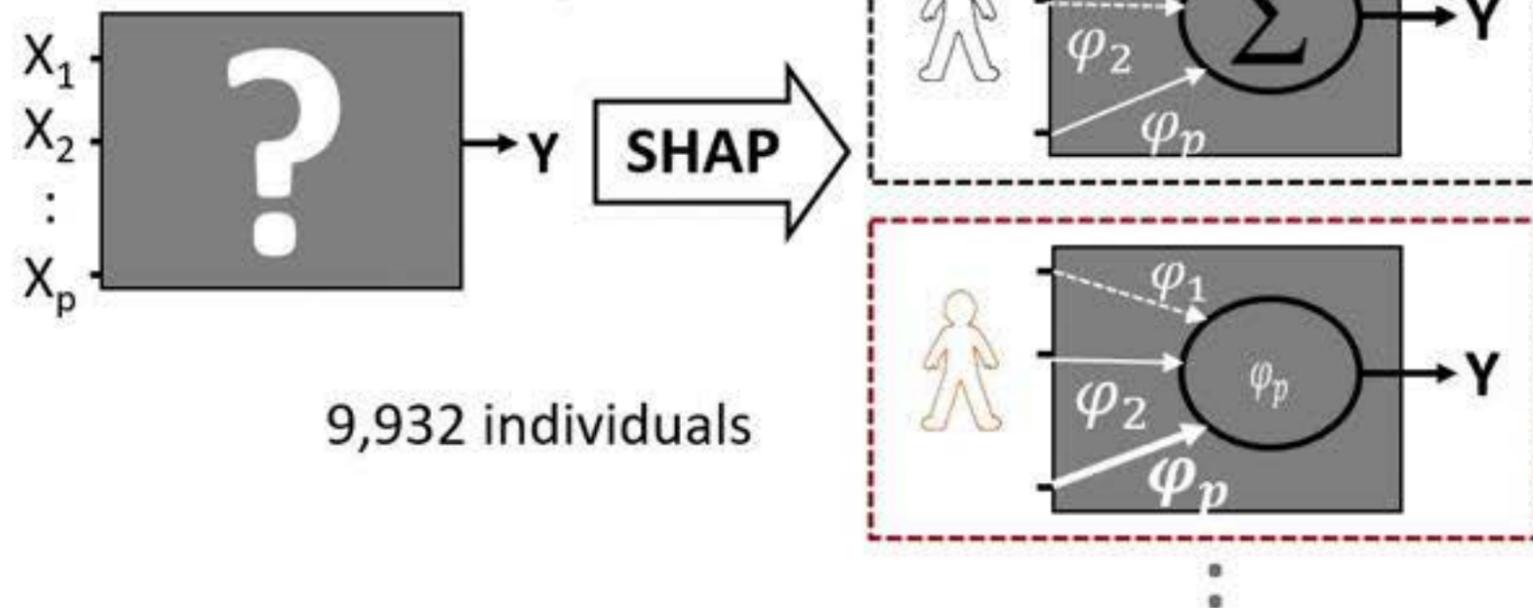
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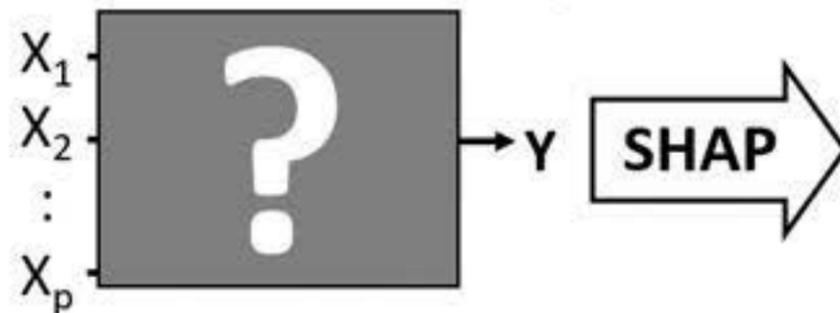
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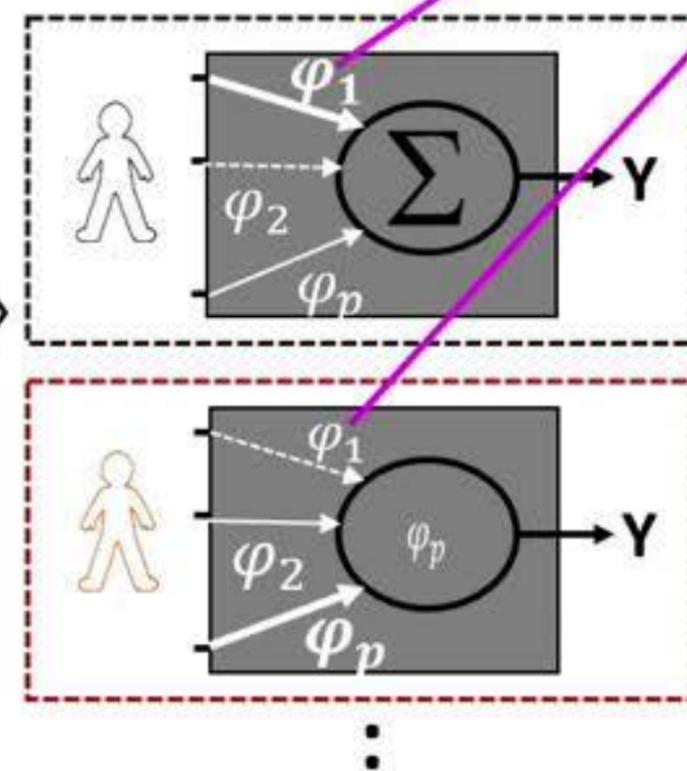


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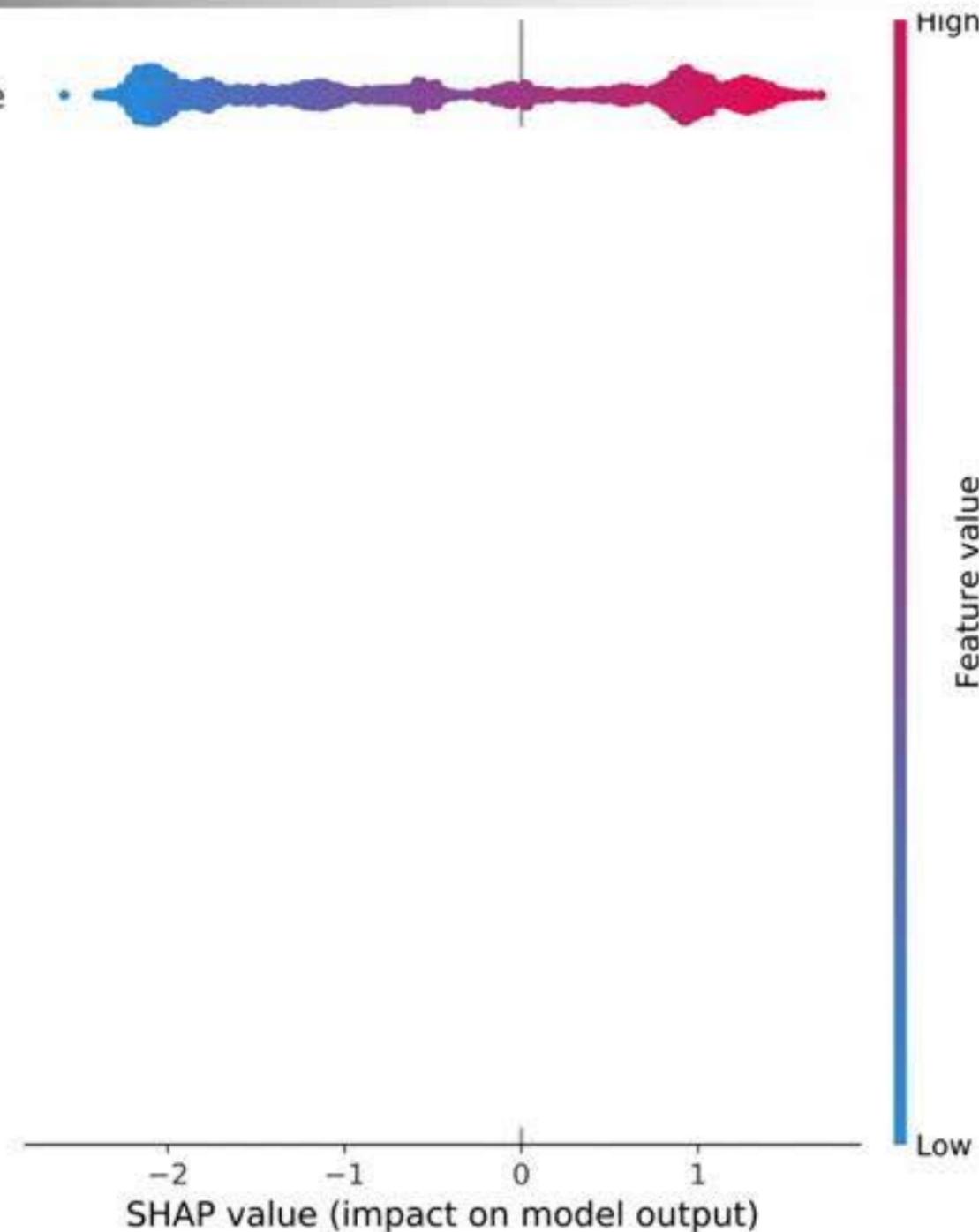
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9,932 individuals



Age



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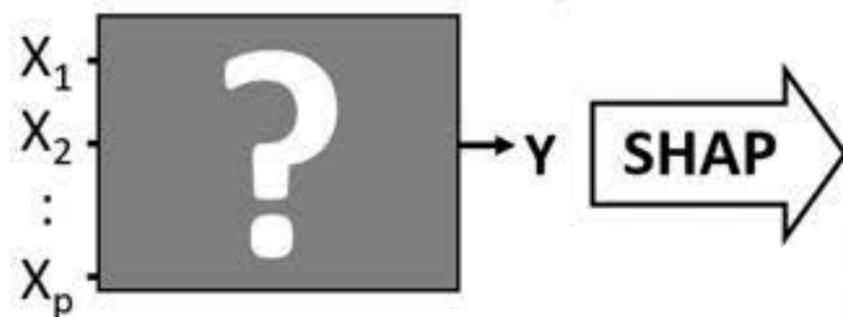
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National Health & Nutrition Examination Survey

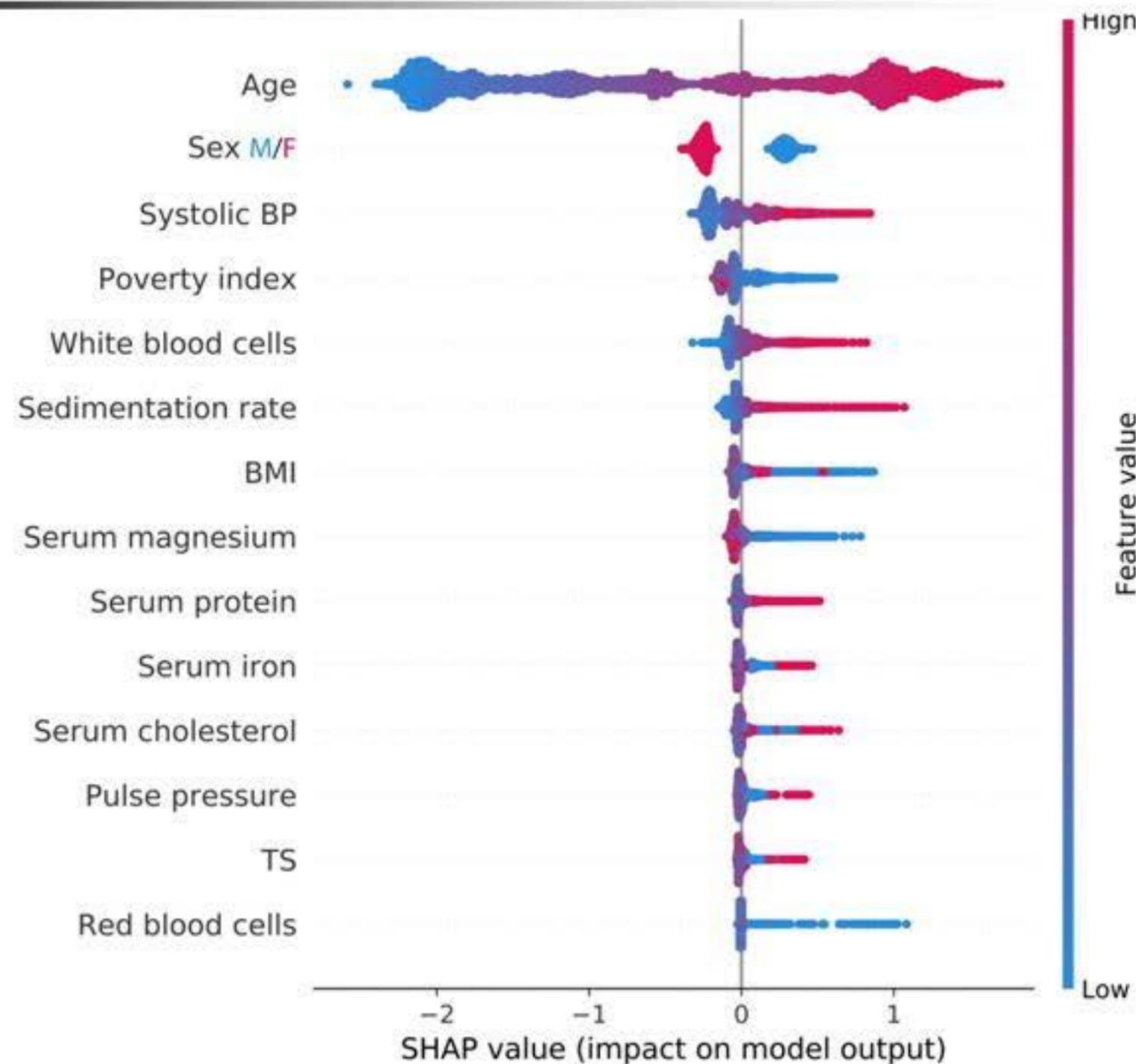
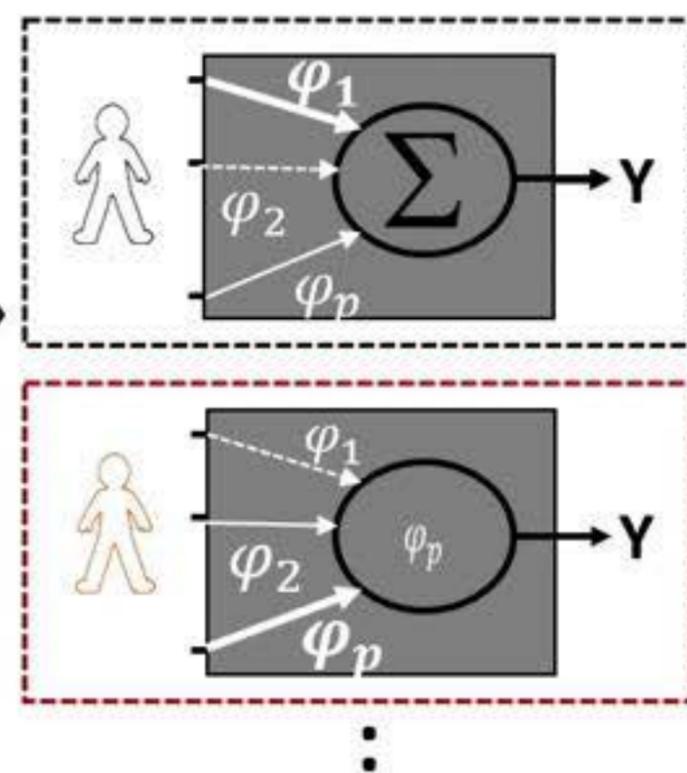
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SHAP



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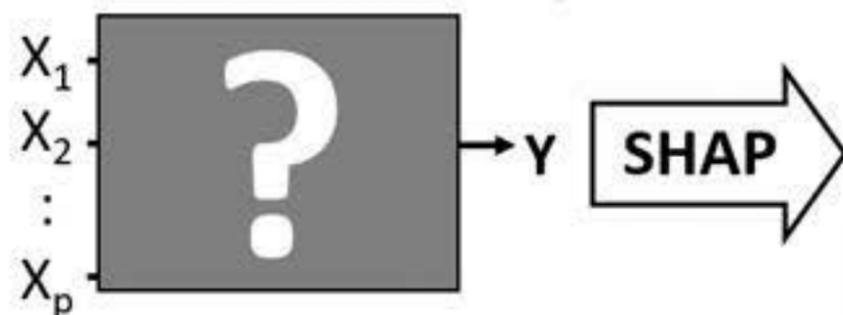
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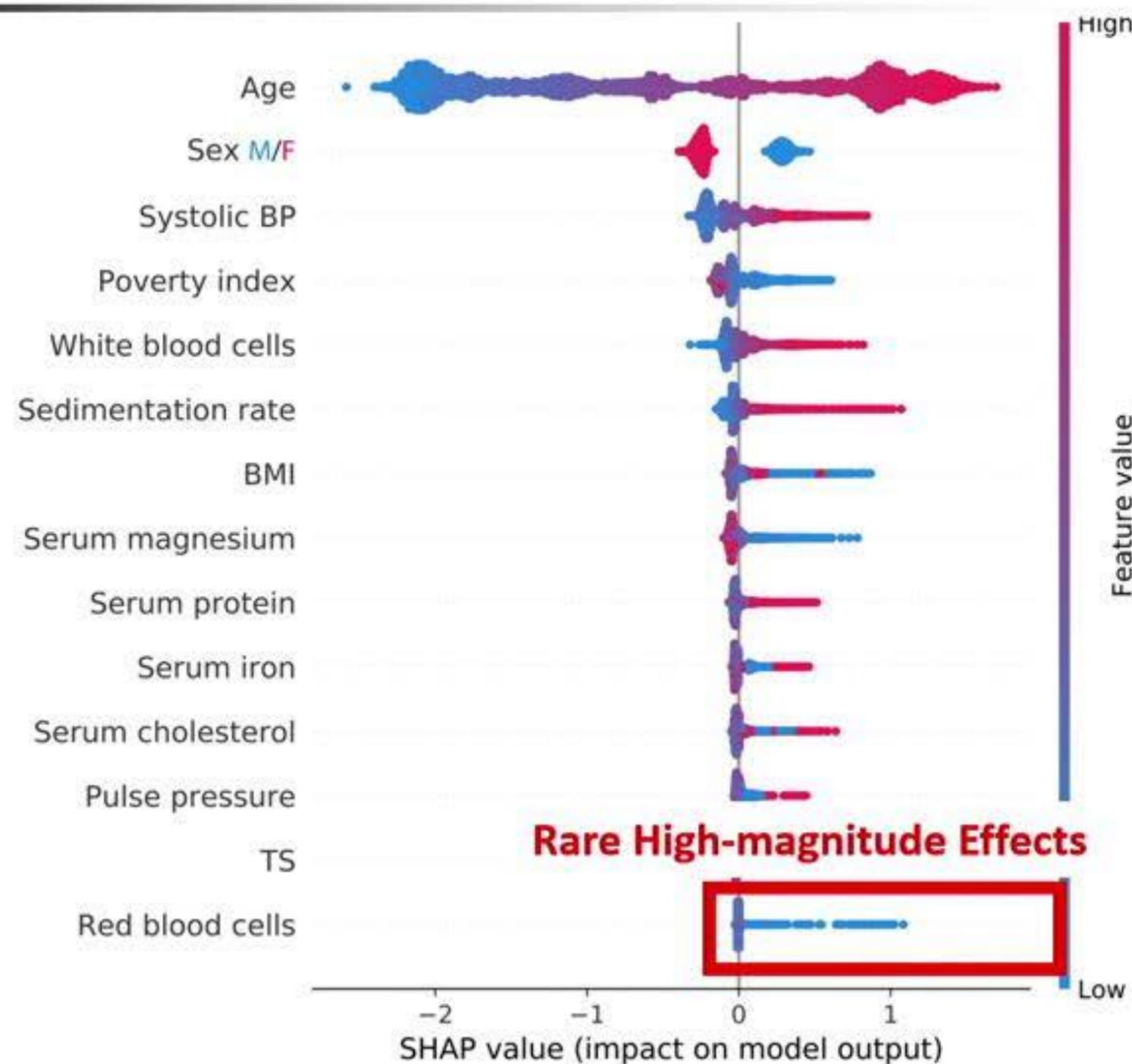
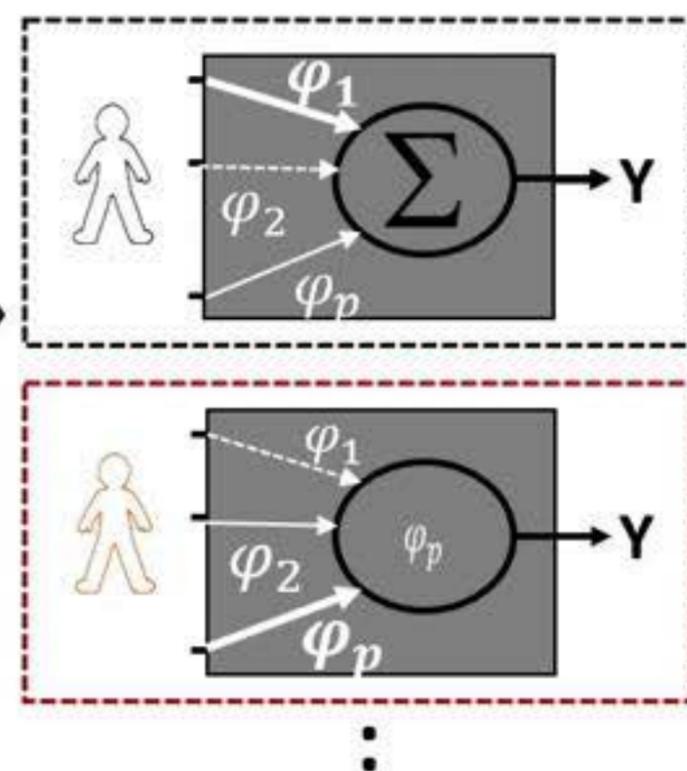
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- NHANES I 

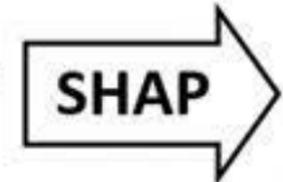
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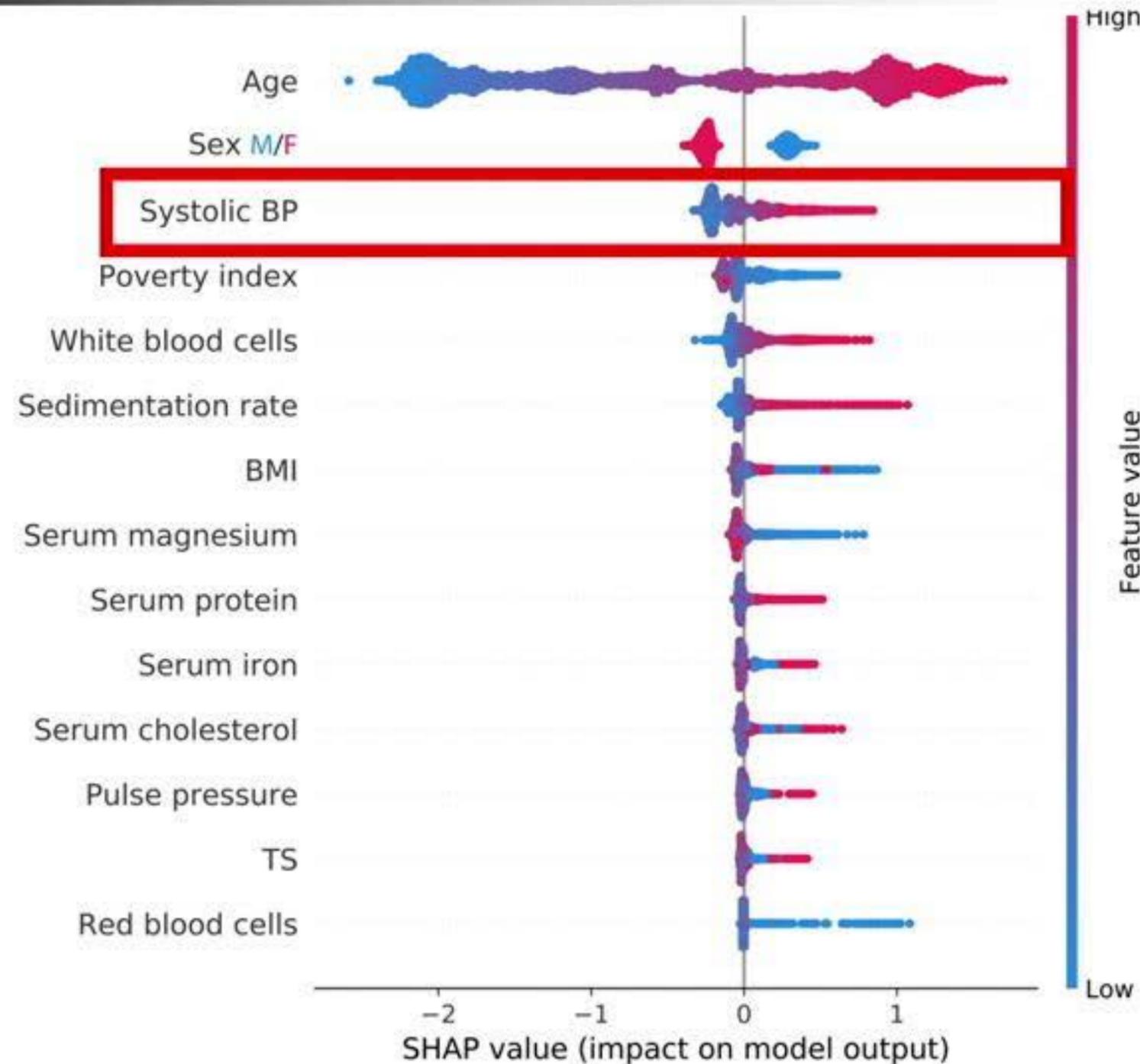
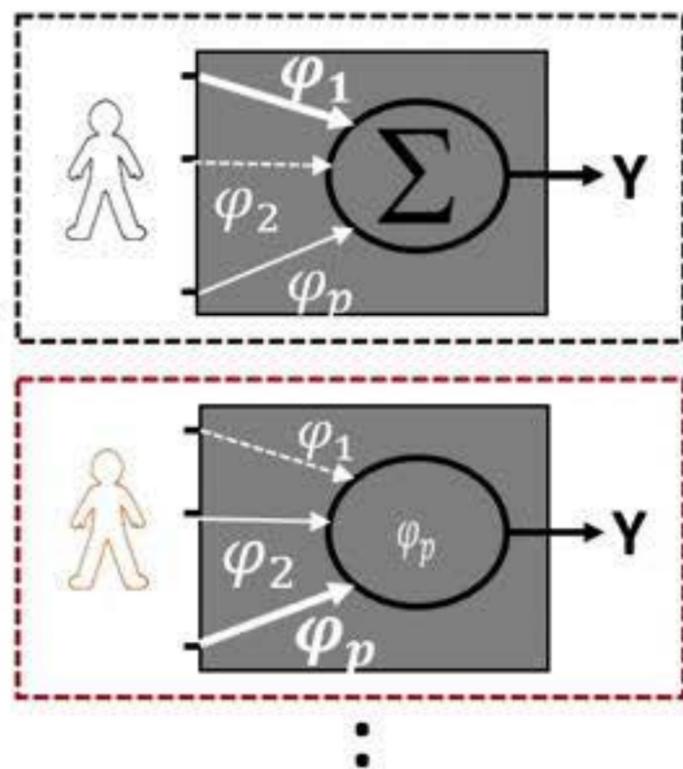
X_1
 X_2
⋮
 X_p



→ Y



9,932 individuals



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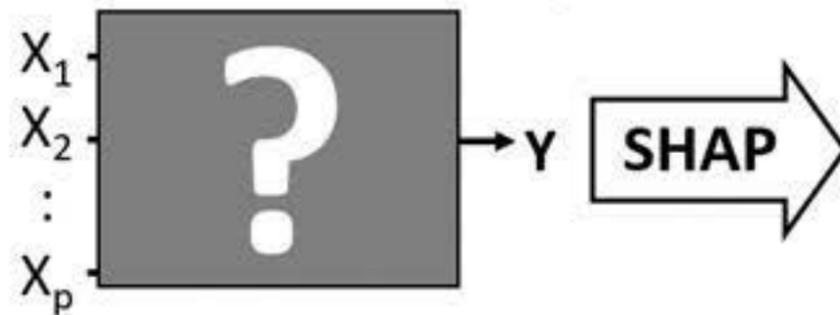
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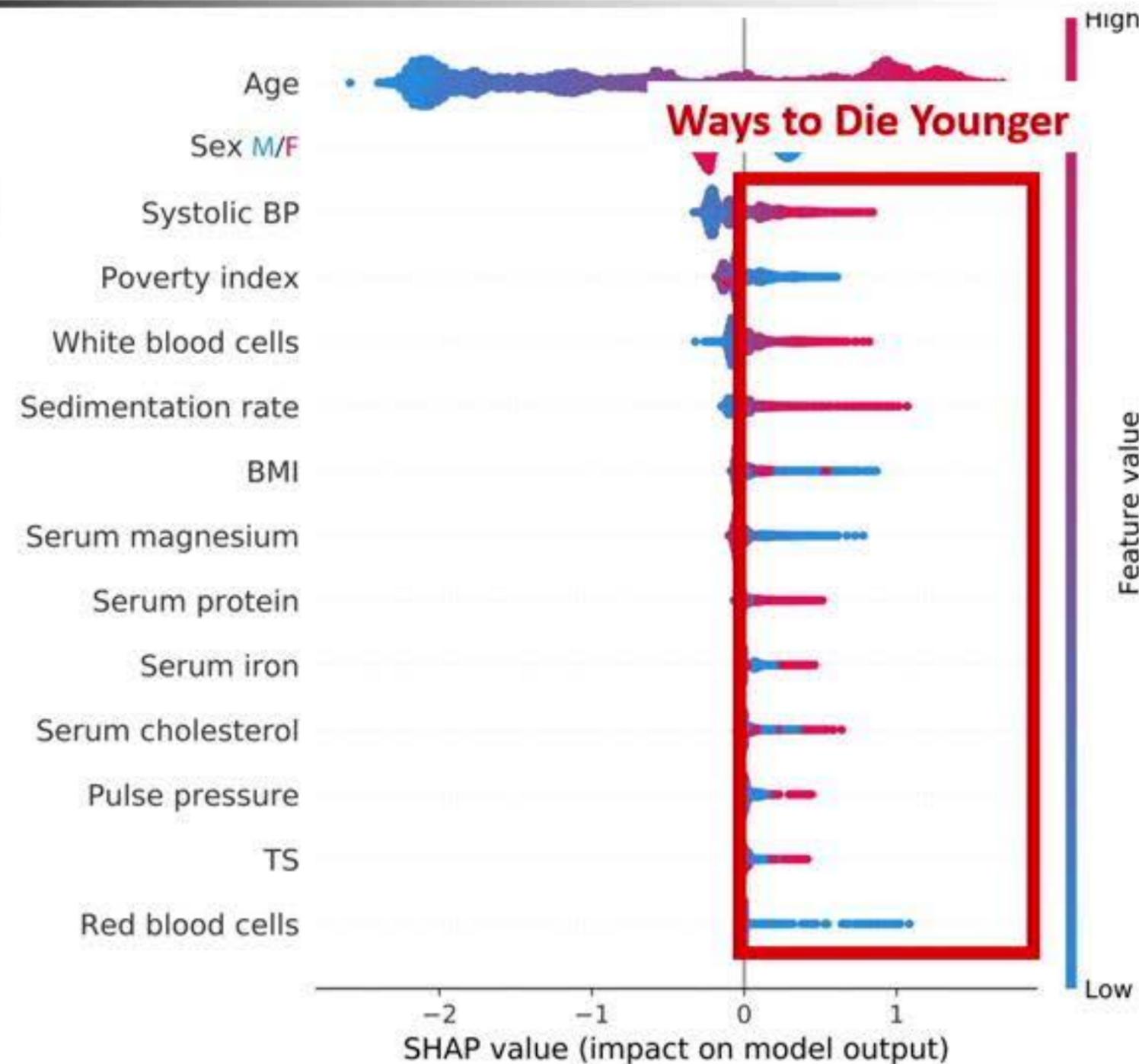
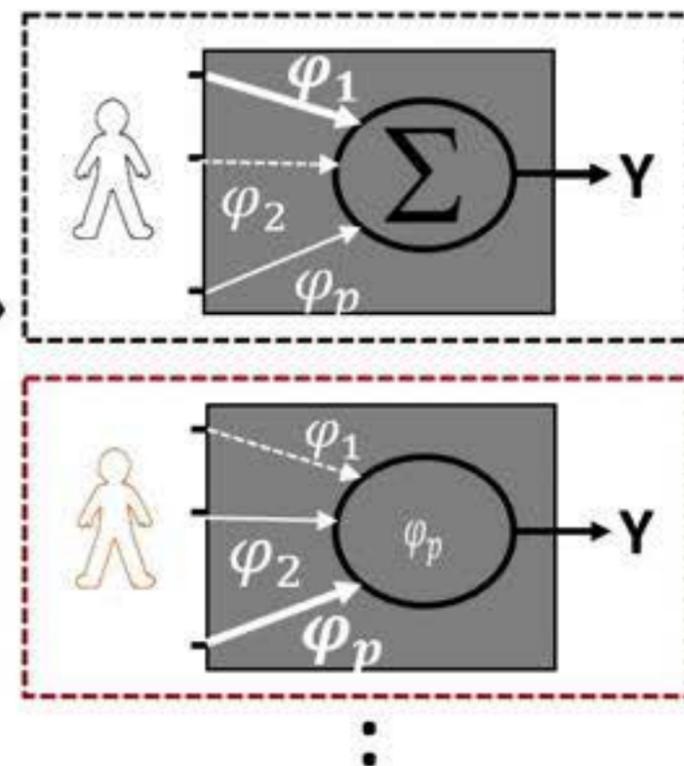
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SHAP



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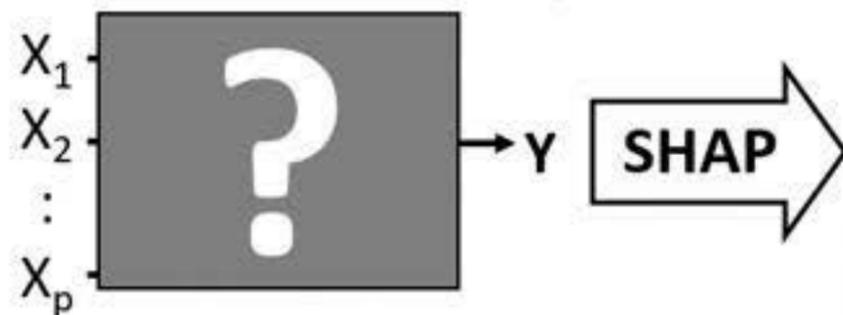
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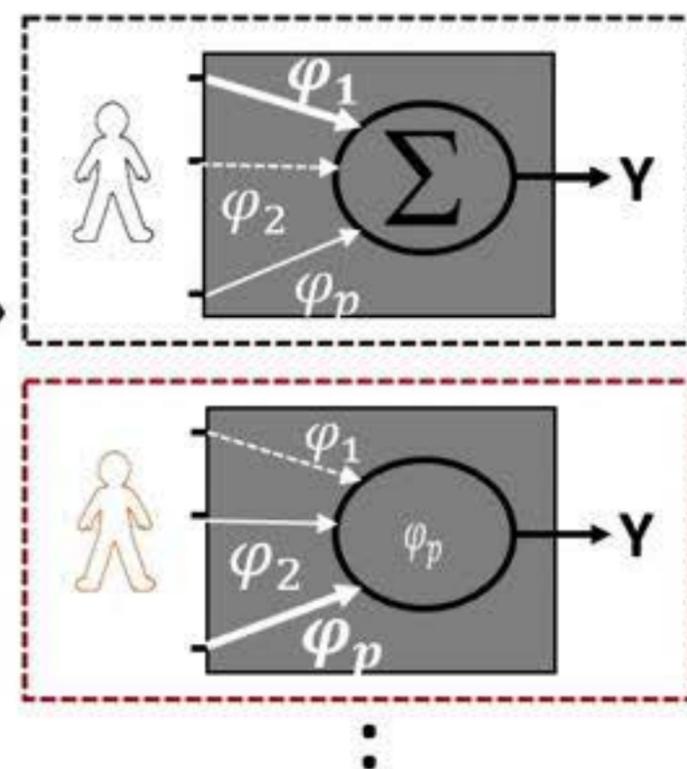
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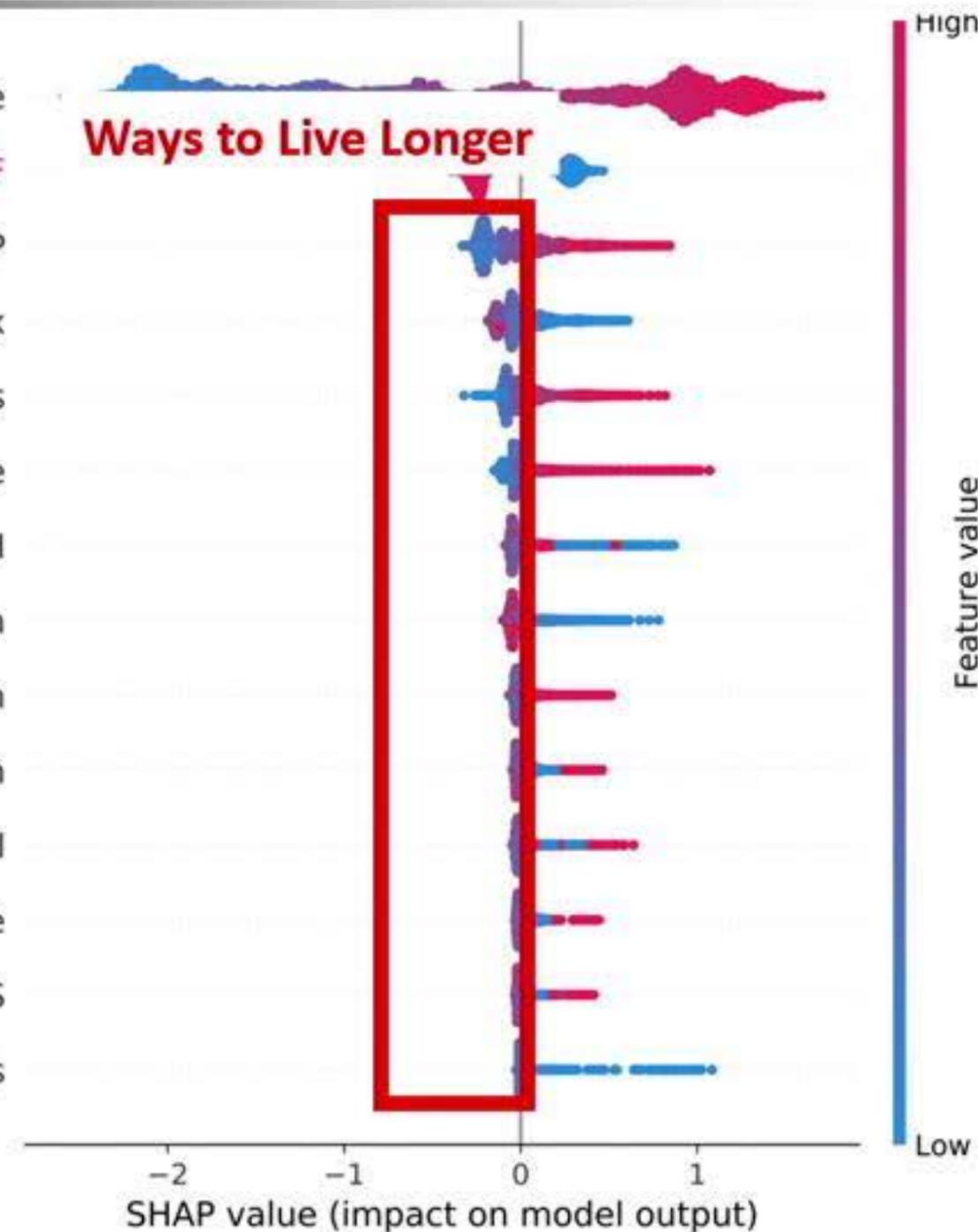
XGBoost (Cox Proportional Hazards model)



9,932 individuals



- Age
- Sex M/F
- Systolic BP
- Poverty index
- White blood cells
- Sedimentation rate
- BMI
- Serum magnesium
- Serum protein
- Serum iron
- Serum cholesterol
- Pulse pressure
- TS
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Using SHAP values as building blocks for interpretable ML: SHAP summary plot



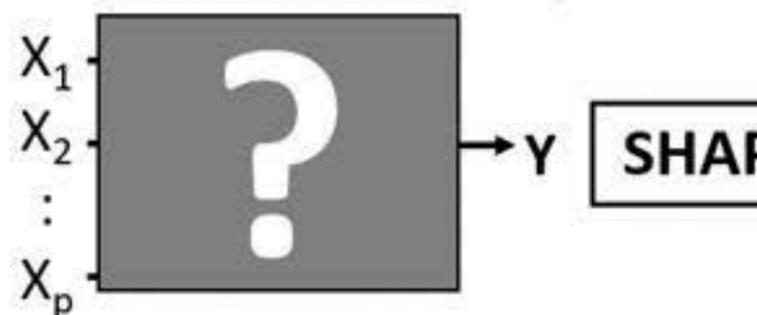
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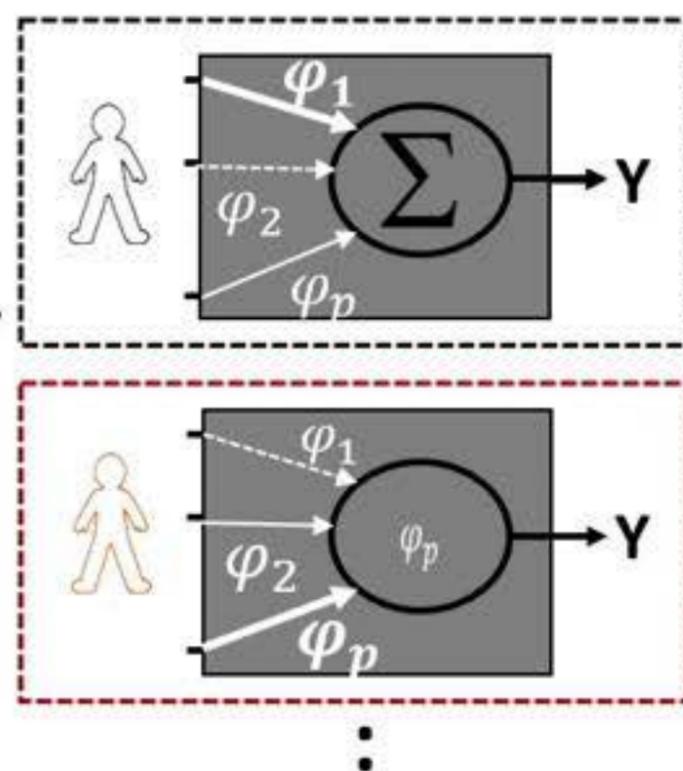
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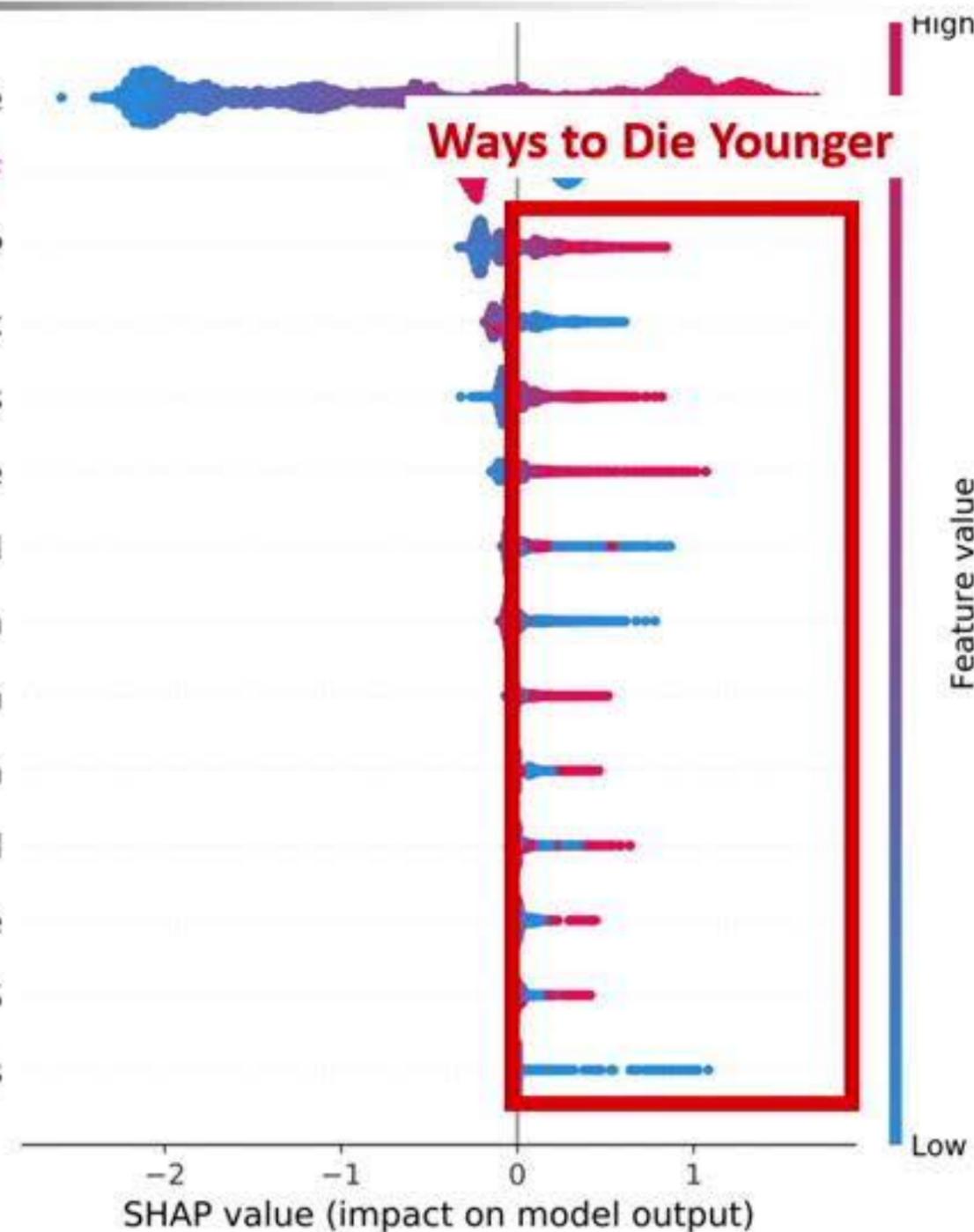


9,932 individuals

SHAP



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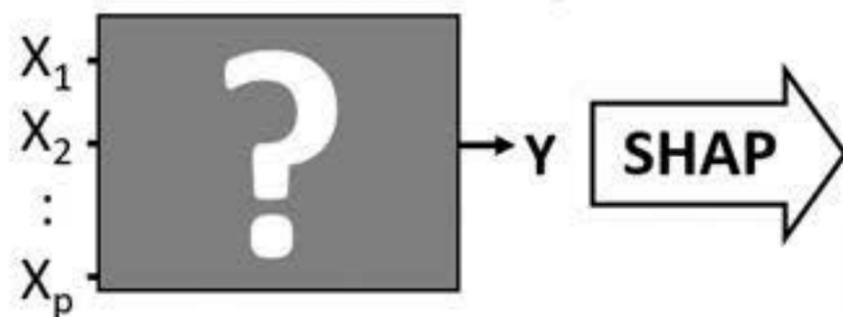
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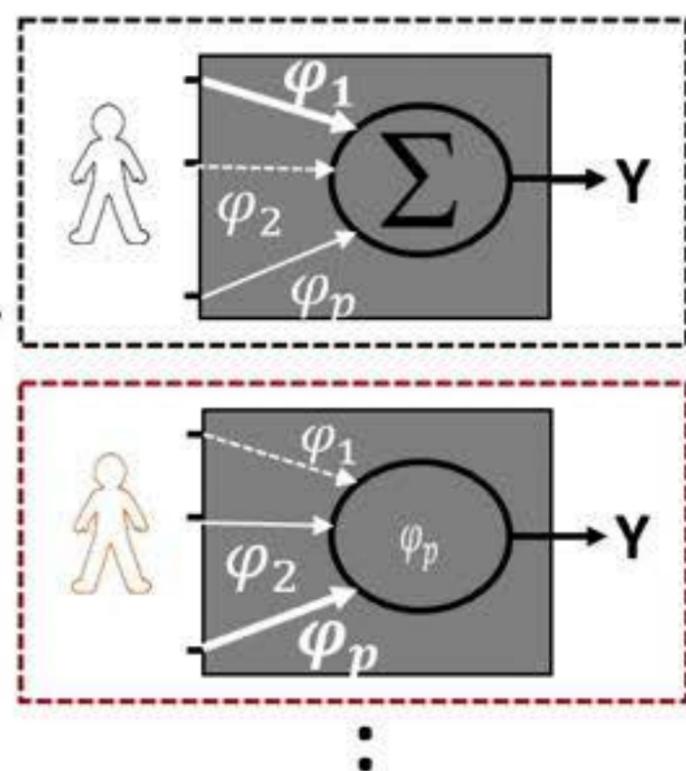
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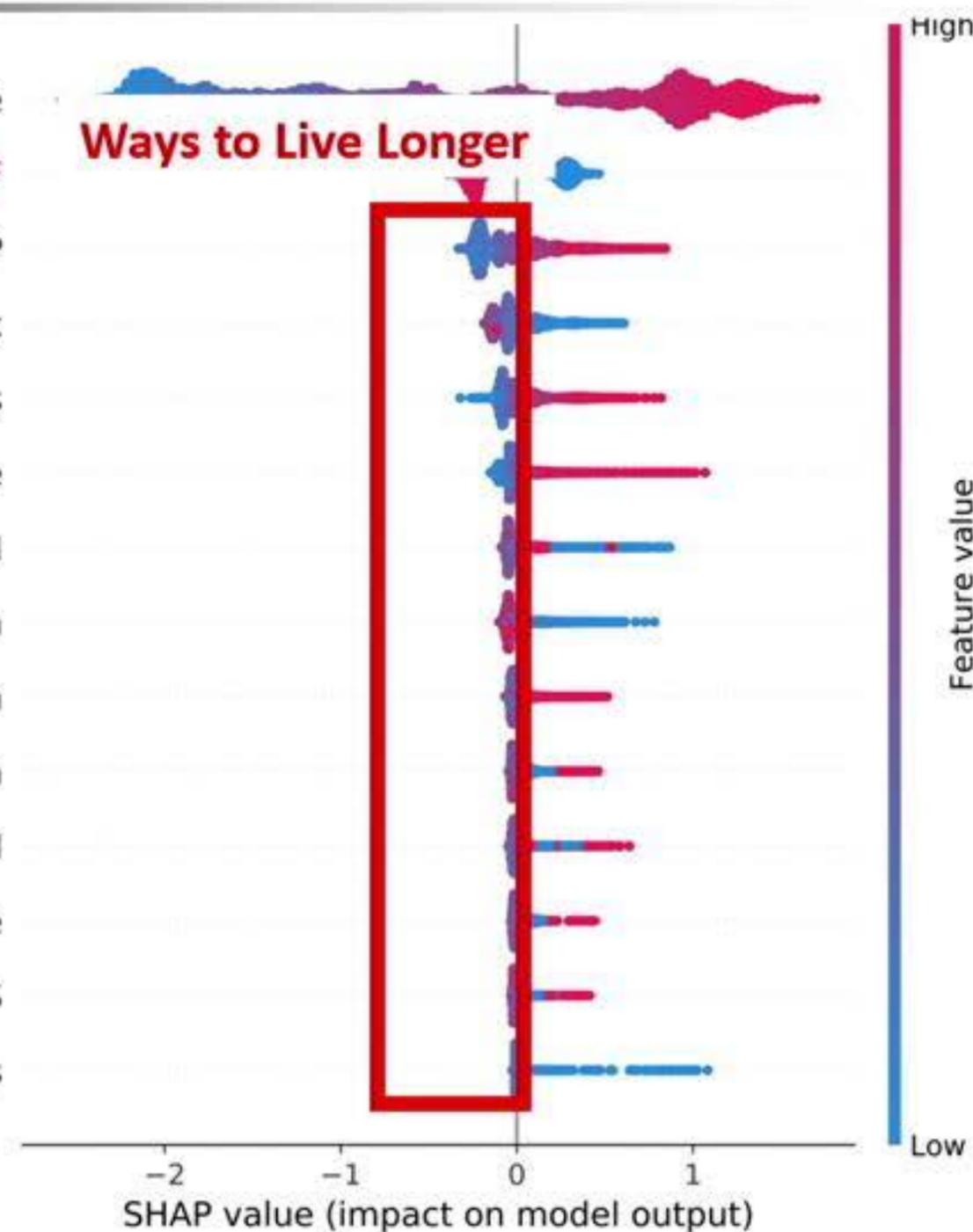
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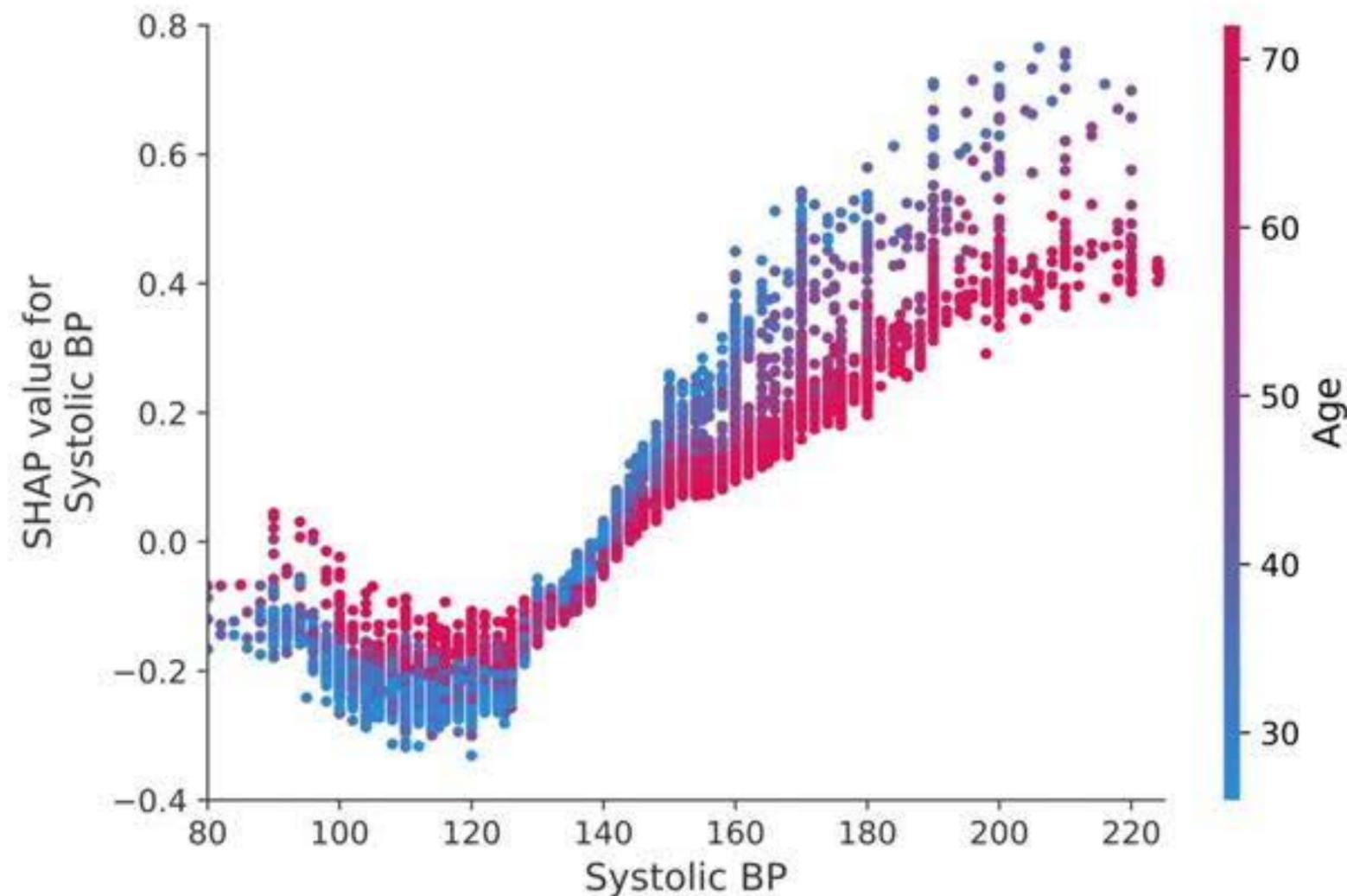


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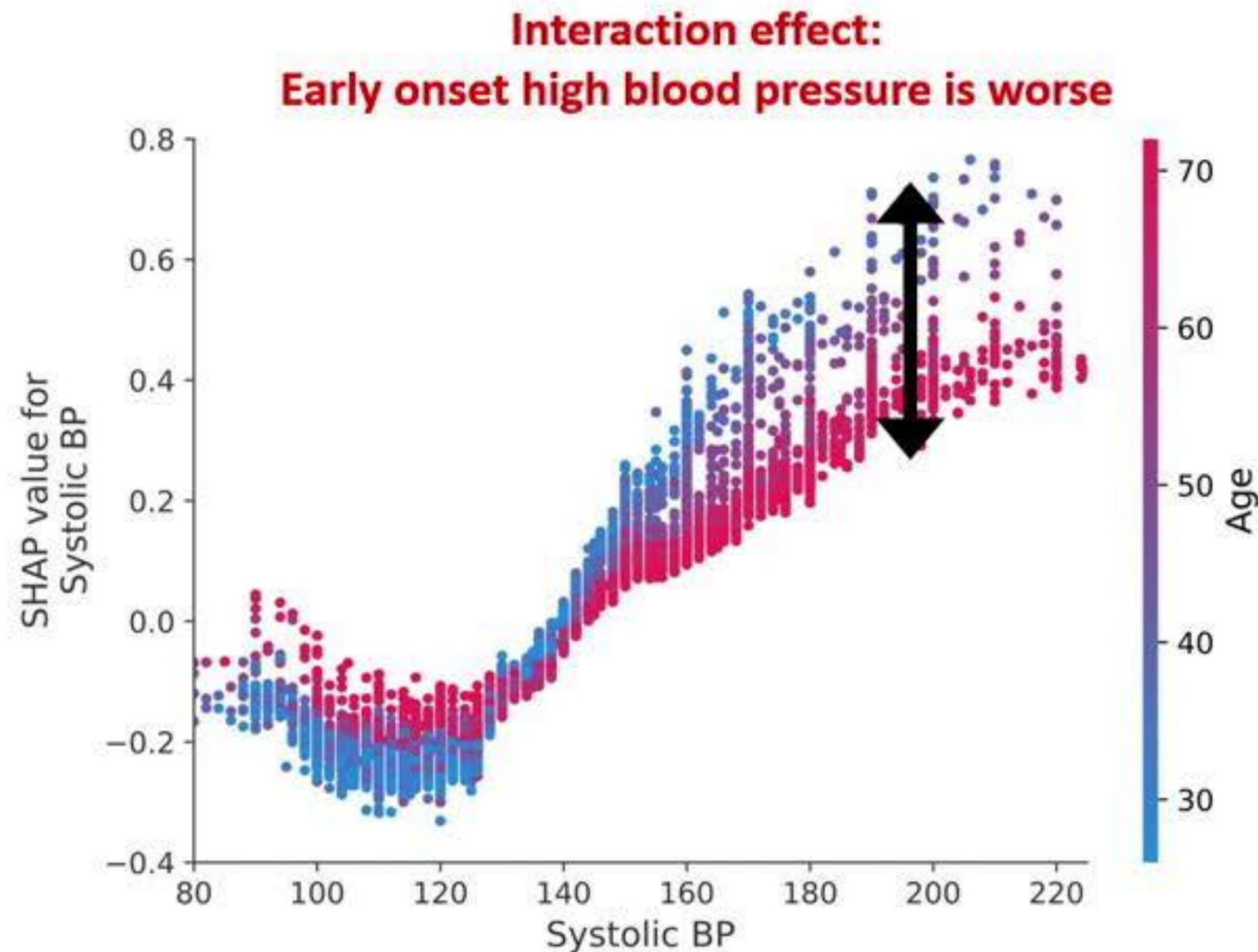
Ways to Live Longer



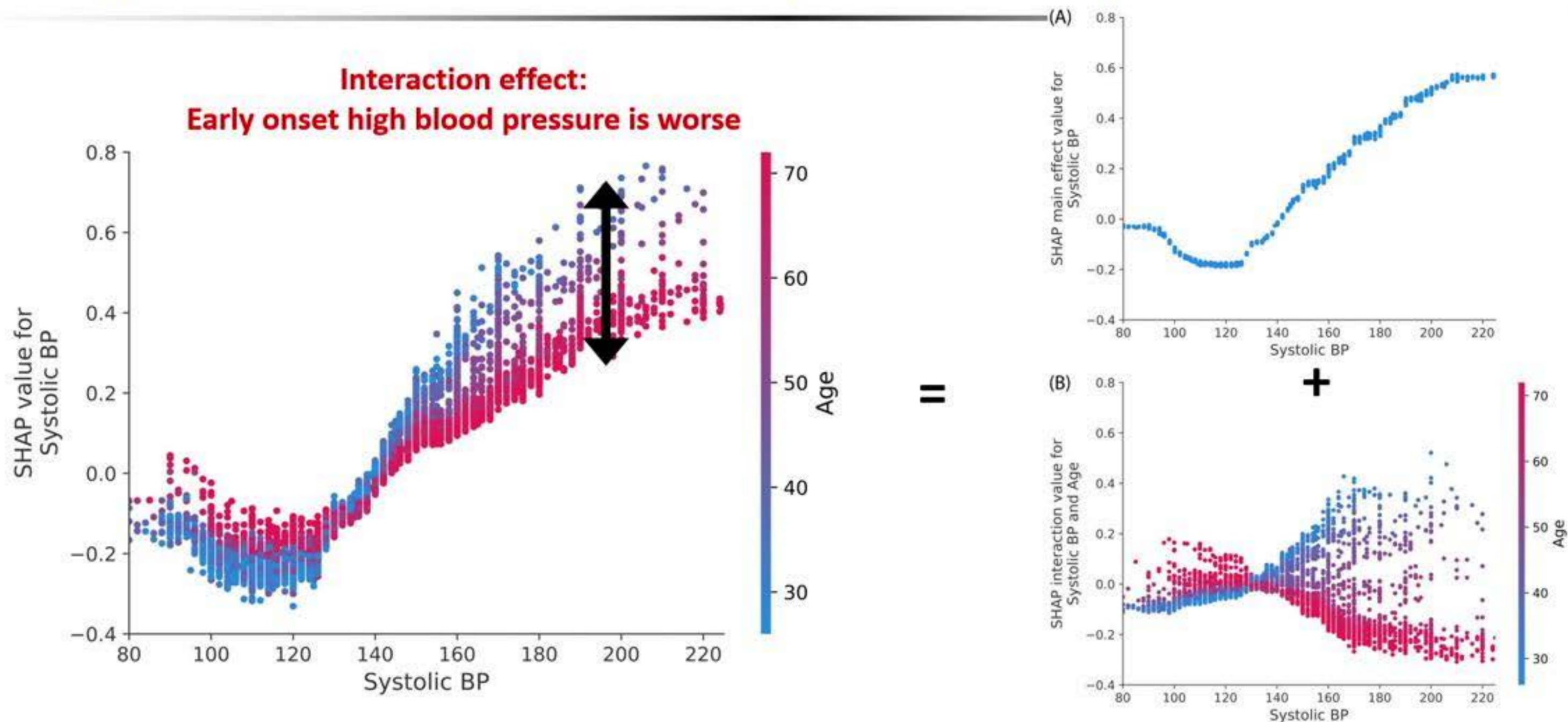
Using SHAP values as building blocks for interpretable ML: SHAP dependence plot



Using SHAP values as building blocks for interpretable ML: SHAP dependence plot



Using SHAP values as building blocks for interpretable ML: SHAP dependence plot



Using SHAP values as building blocks for interpretable ML: SHAP monitoring plot



Scott

Gabe

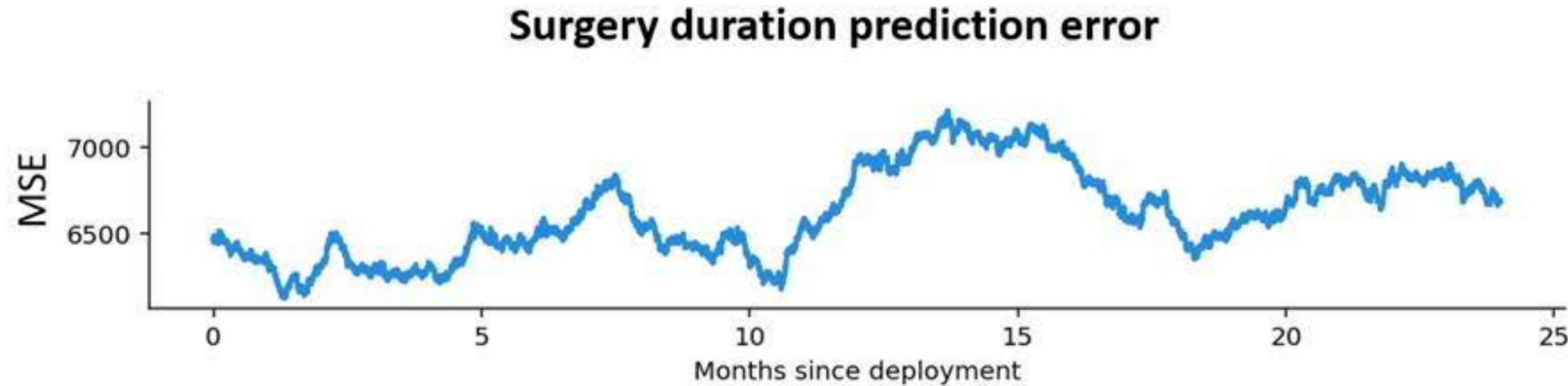
Hugh

- Monitoring a deployed model's performance is critical.

Using SHAP values as building blocks for interpretable ML: SHAP monitoring plot



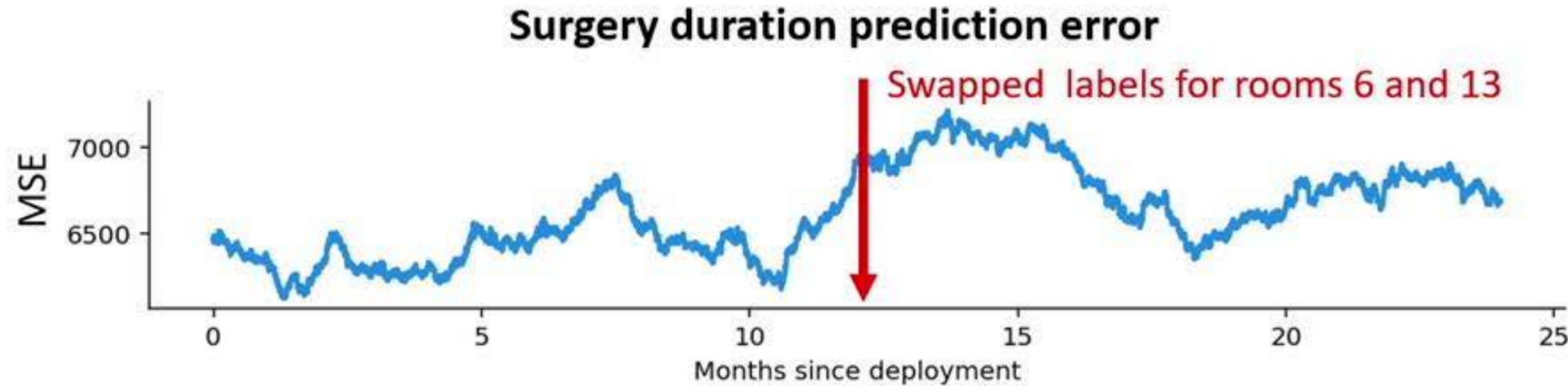
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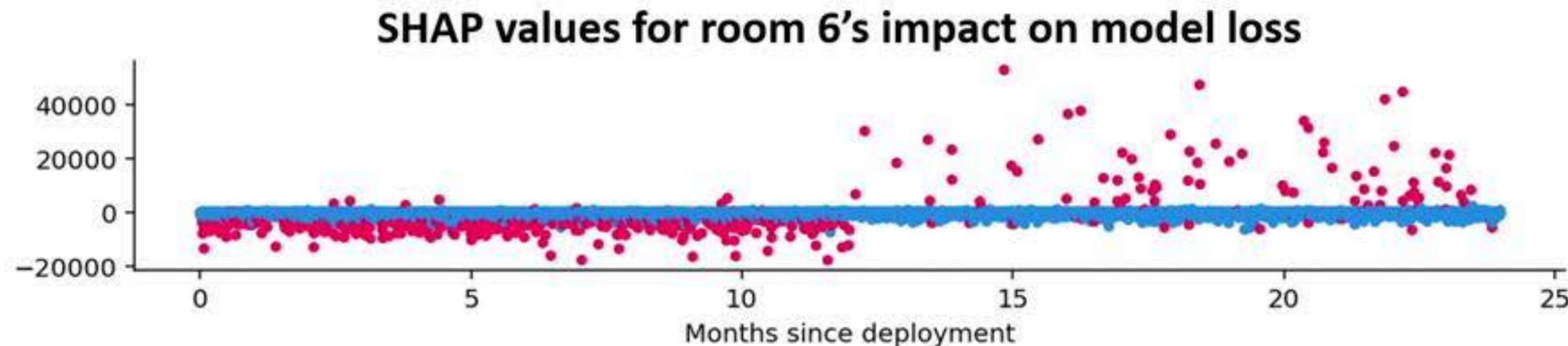
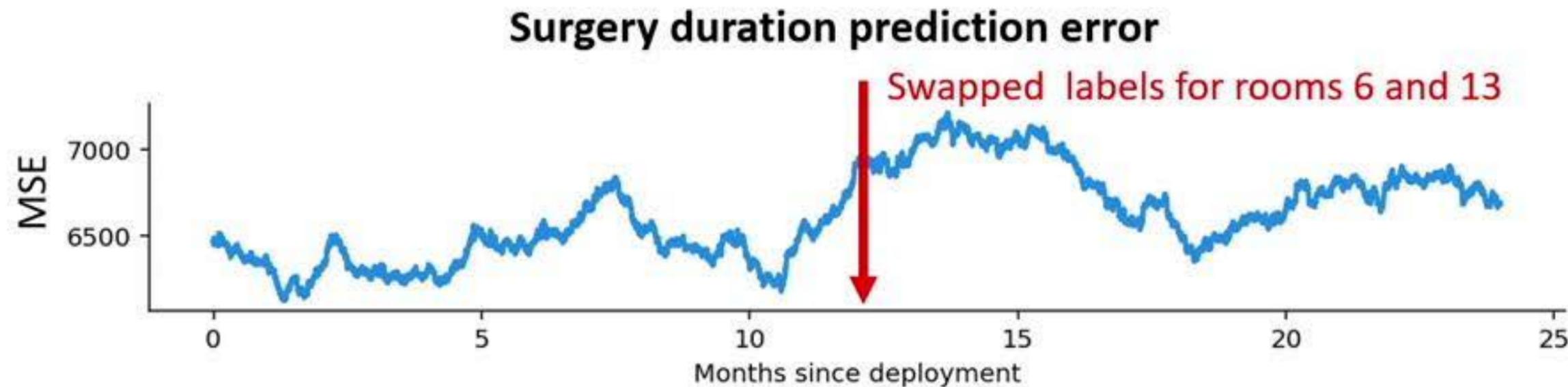
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- SHAP monitoring plots decompose the model's loss among each of the features.



Using SHAP values as building blocks for interpretable ML: SHAP monitoring plot



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Interpretable ML can transform important areas of medicine

Prediction & decision support systems in hospitals

- Make interpretable predictions from complex models.

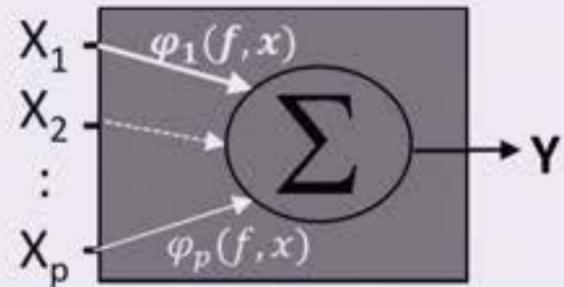
Cancer precision medicine

- Learn interpretable feature representations.

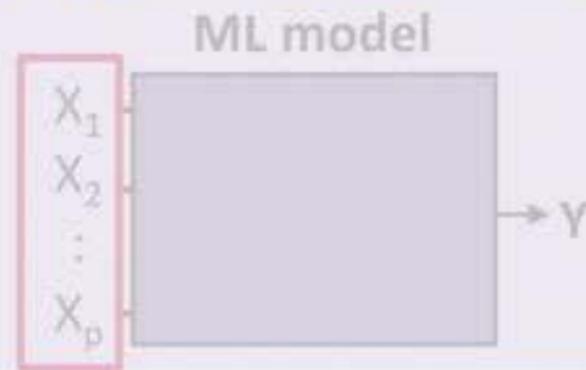
Alzheimer's disease therapeutic target discovery

- Integrate data sets for statistical power and interpretability.

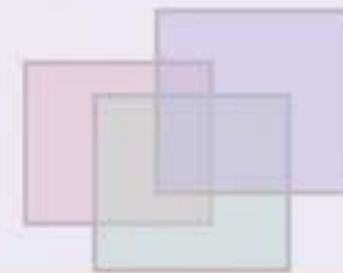
Black Box



General ML techniques



Data integration



Bedside applications



Basic science



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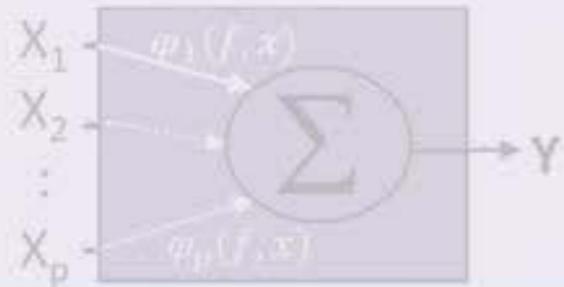
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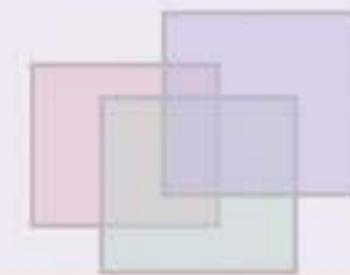


General ML techniques

ML model



Data integration



Bedside applications



Basic science



Precision medicine in cancer treatment

Patient X



Precision medicine in cancer treatment

- Acute myeloid leukemia (AML)
 - Cancer of the blood and bone marrow cells
 - 5 year survival rate: 26%

Patient X



Precision medicine in cancer treatment

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 - >100 anti-cancer drugs (62 FDA approved)

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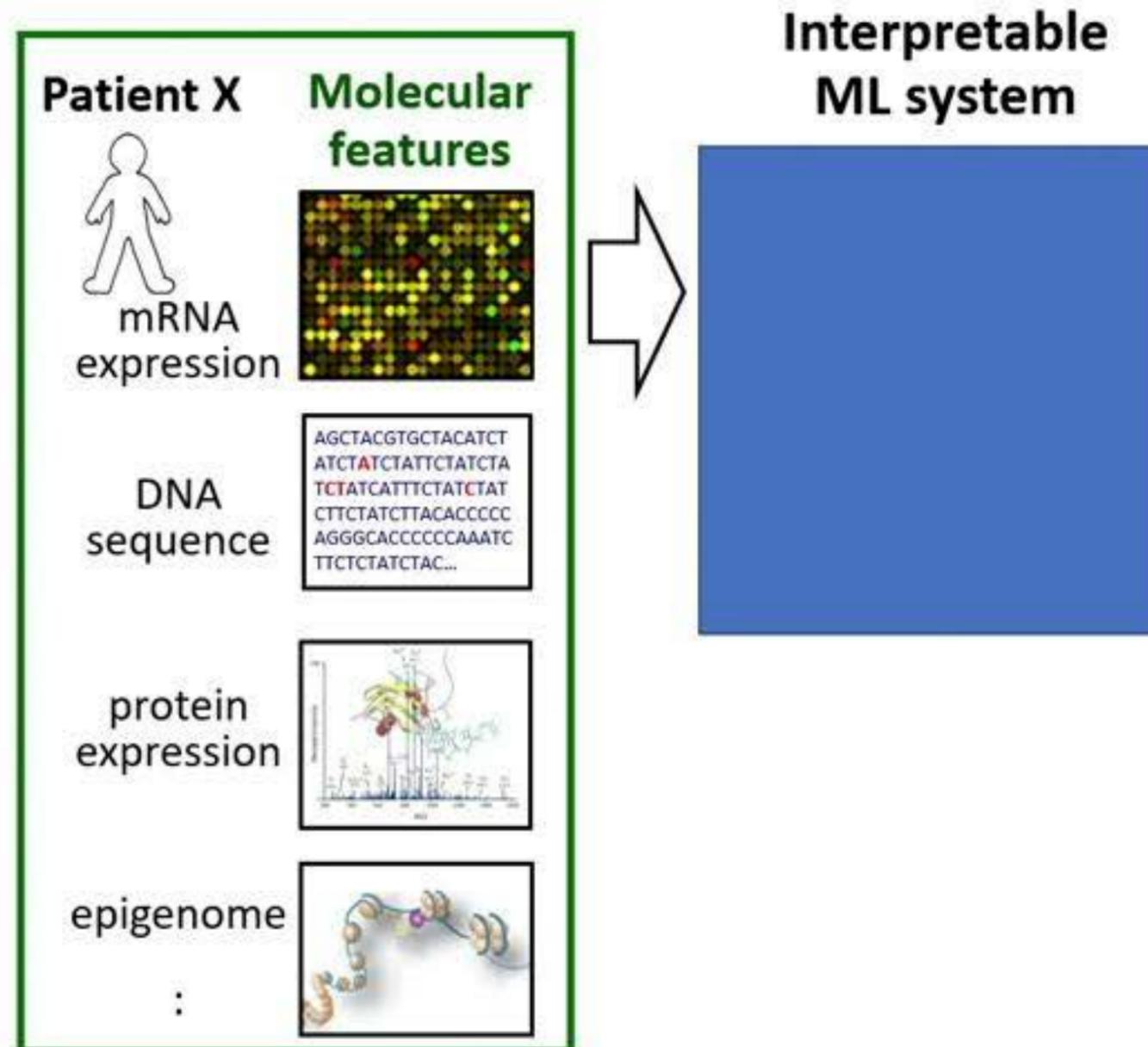


Interpretable
ML system



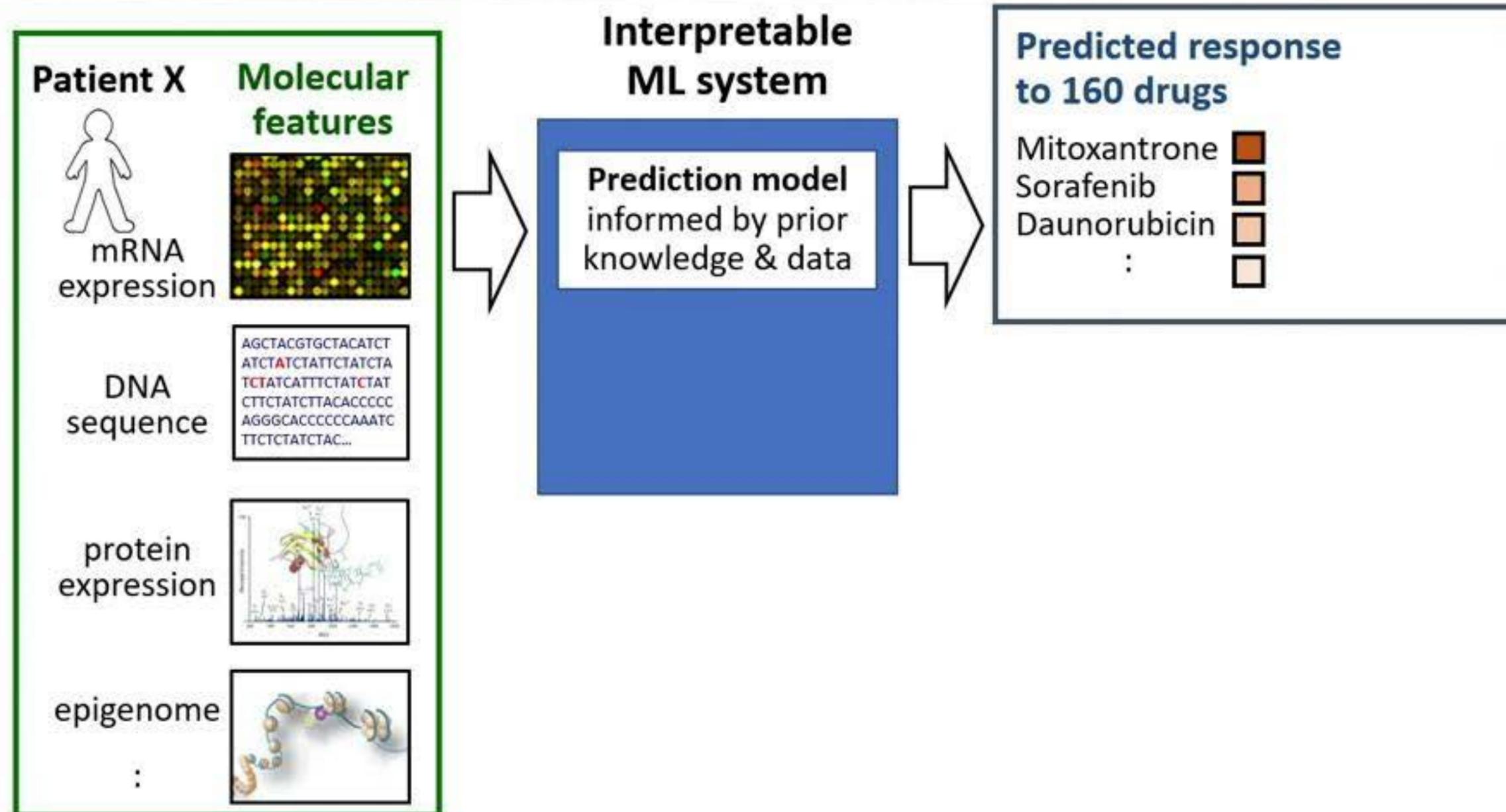
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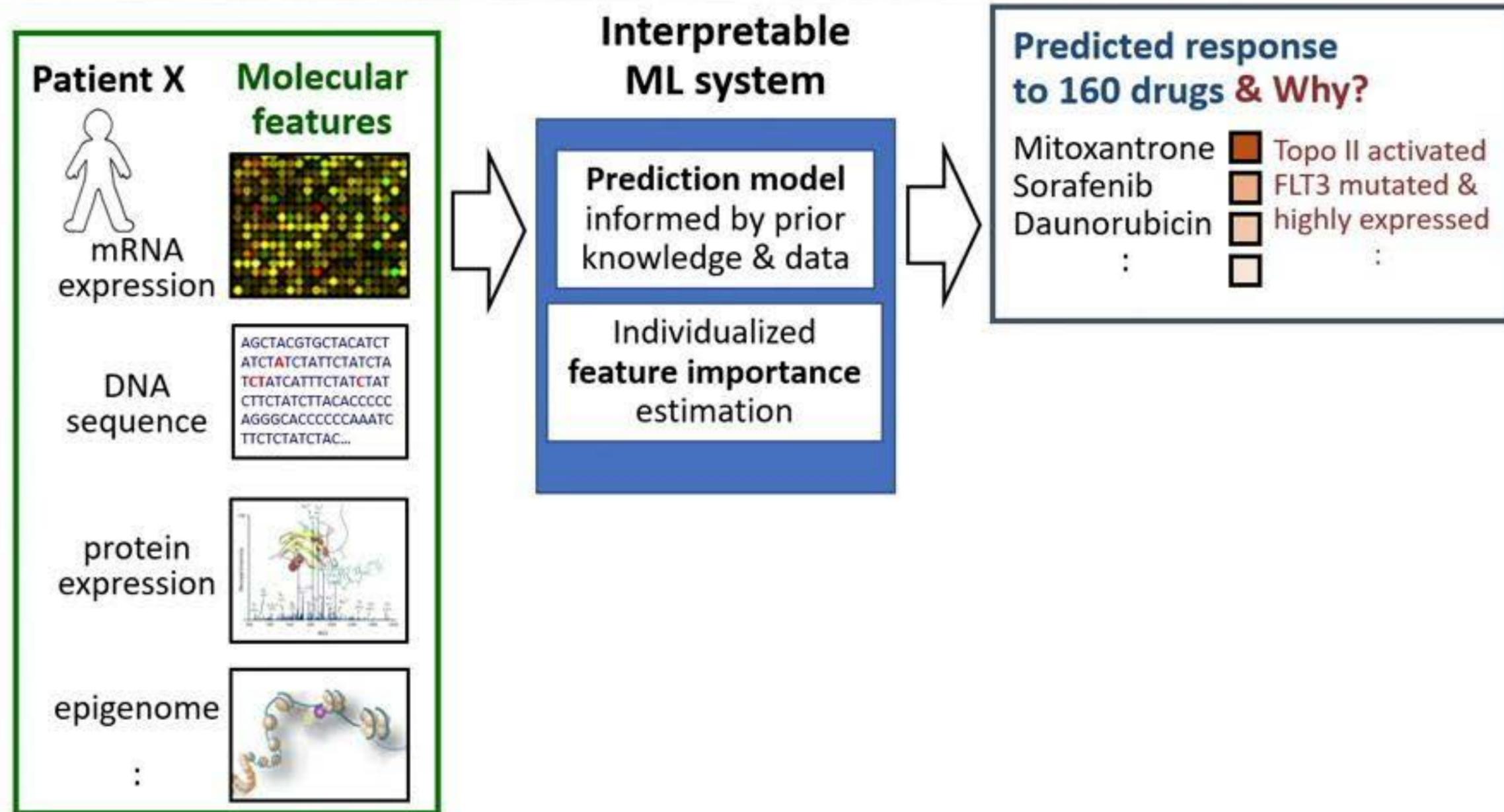
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 - Standard therapy is not personalized.



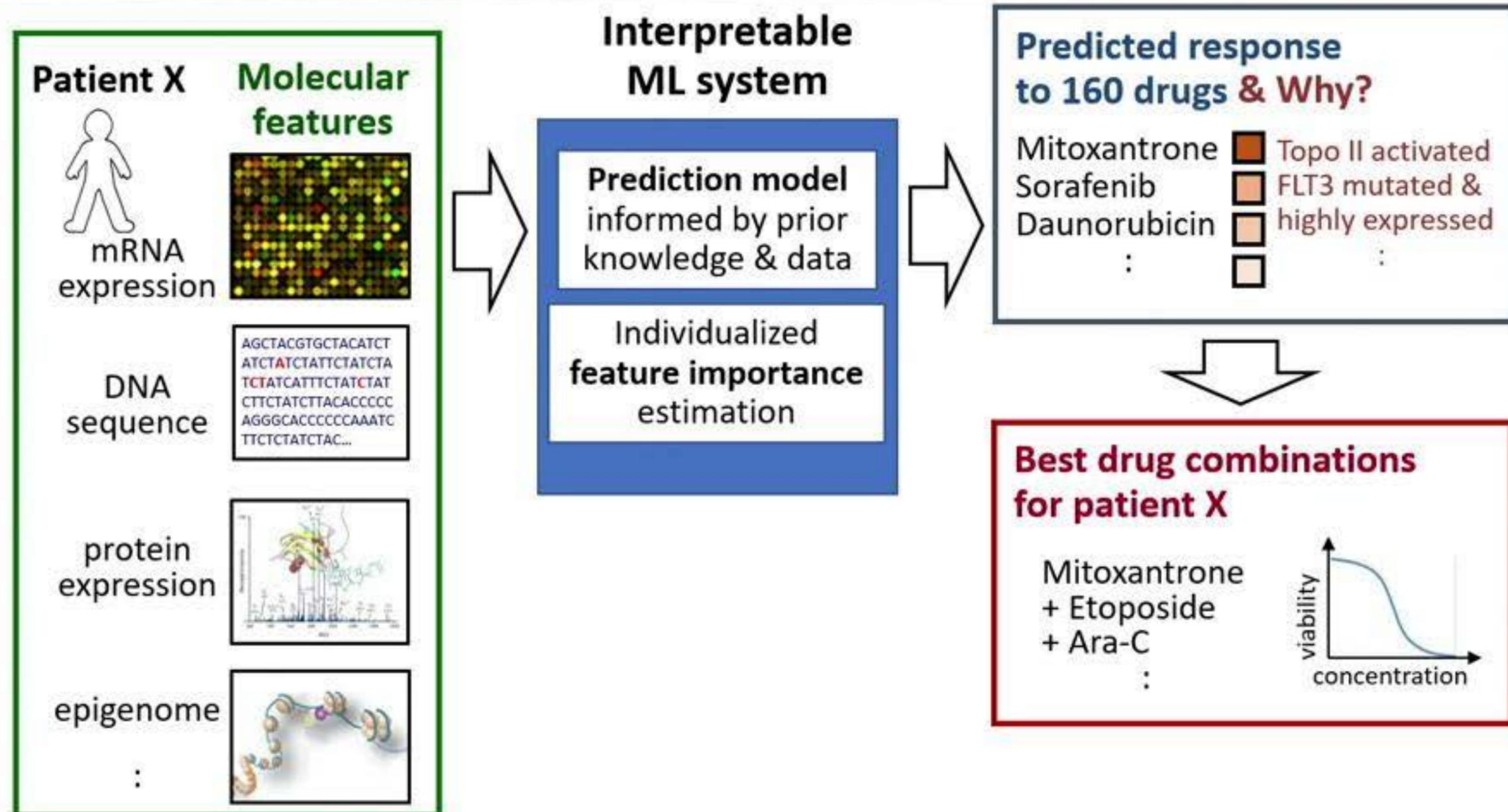
Precision medicine in cancer treatment

- Acute myeloid leukemia (AML)
 - Cancer of the blood and bone marrow cells
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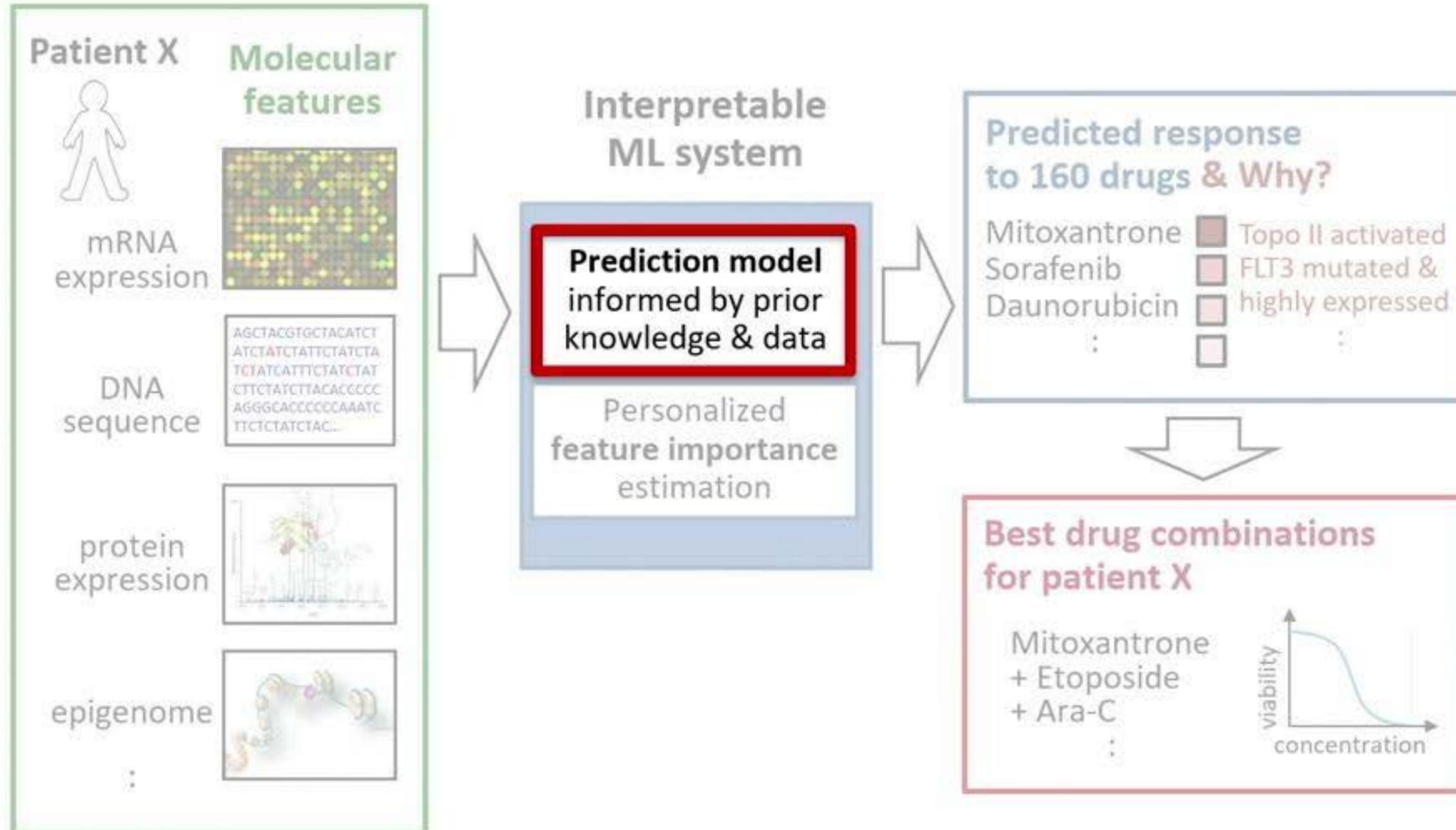


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Learn interpretable feature representation



A naïve solution: Supervised learning approach



Safiye

Training Data

Each patient



A naïve solution: Supervised learning approach



Safiye

Training Data

Each patient



Hematology

Drs. Pam Becker Tony Blau



A naïve solution: Supervised learning approach



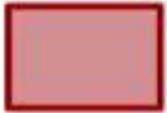
Safiye

Training Data

Each patient



Molecular profiling

- mRNA expression 
- DNA sequence 
- protein expression 

Hematology

Drs. Pam Becker Tony Blau

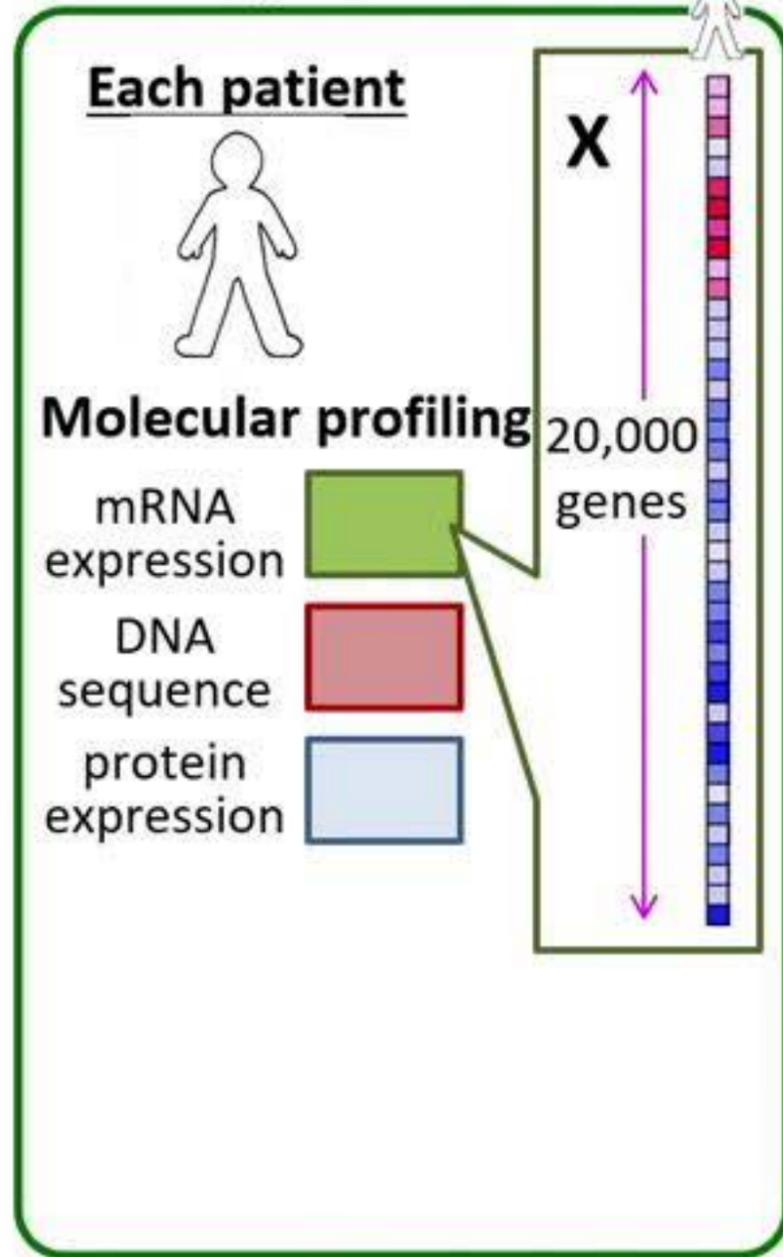


A naïve solution: Supervised learning approach



Safiye

Training Data



Hematology

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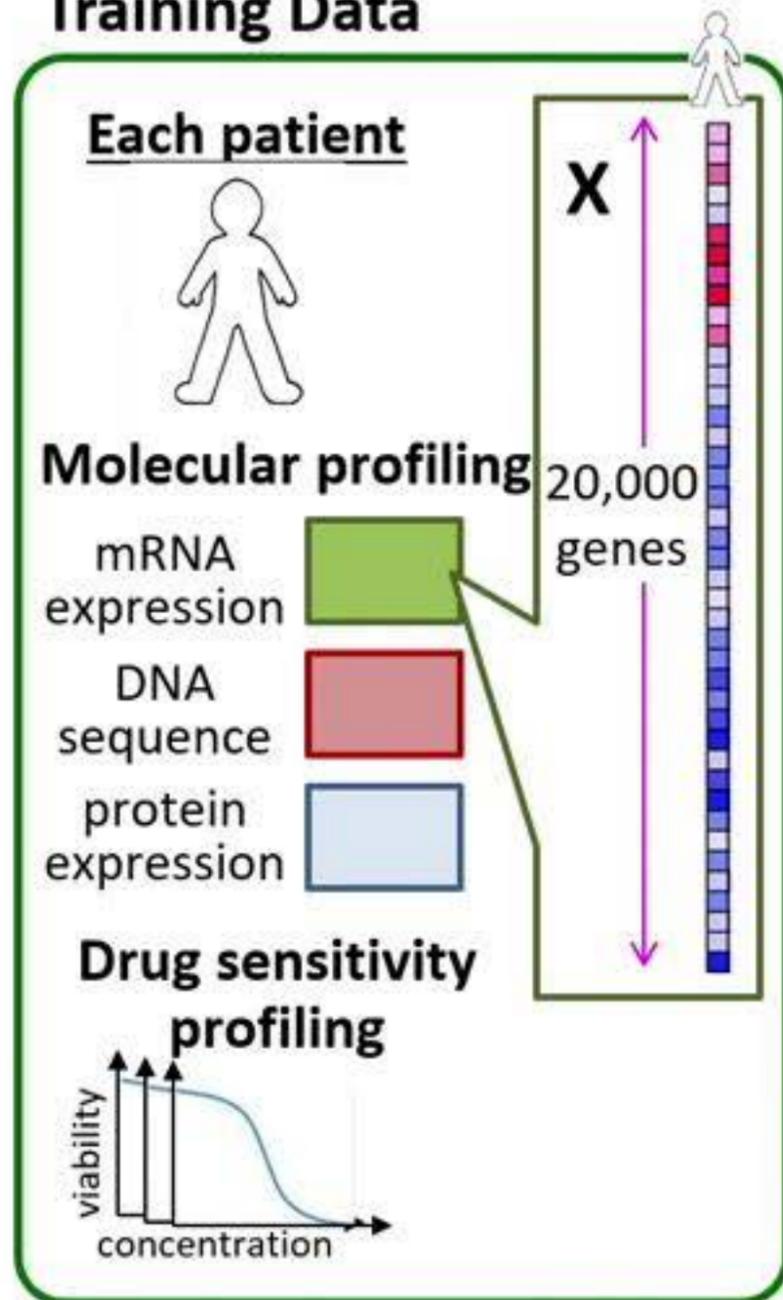


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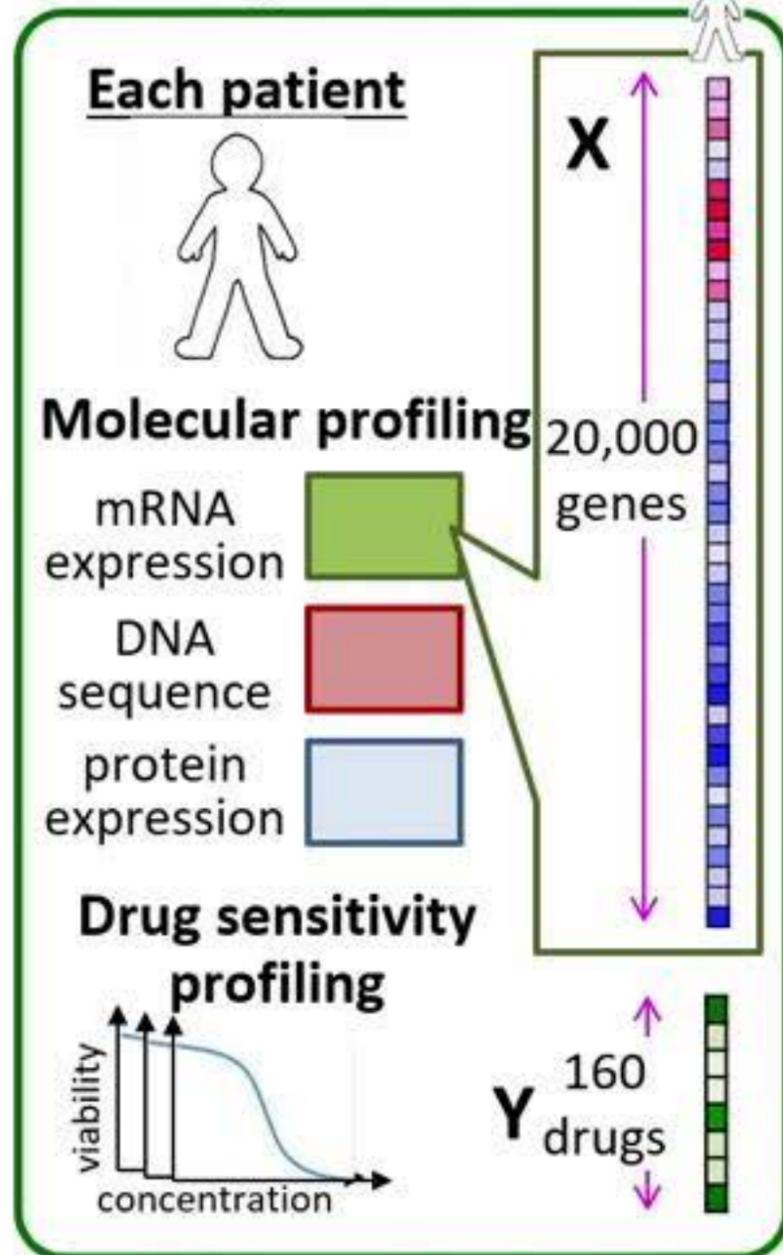


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Safiye

Training Data



Hematology

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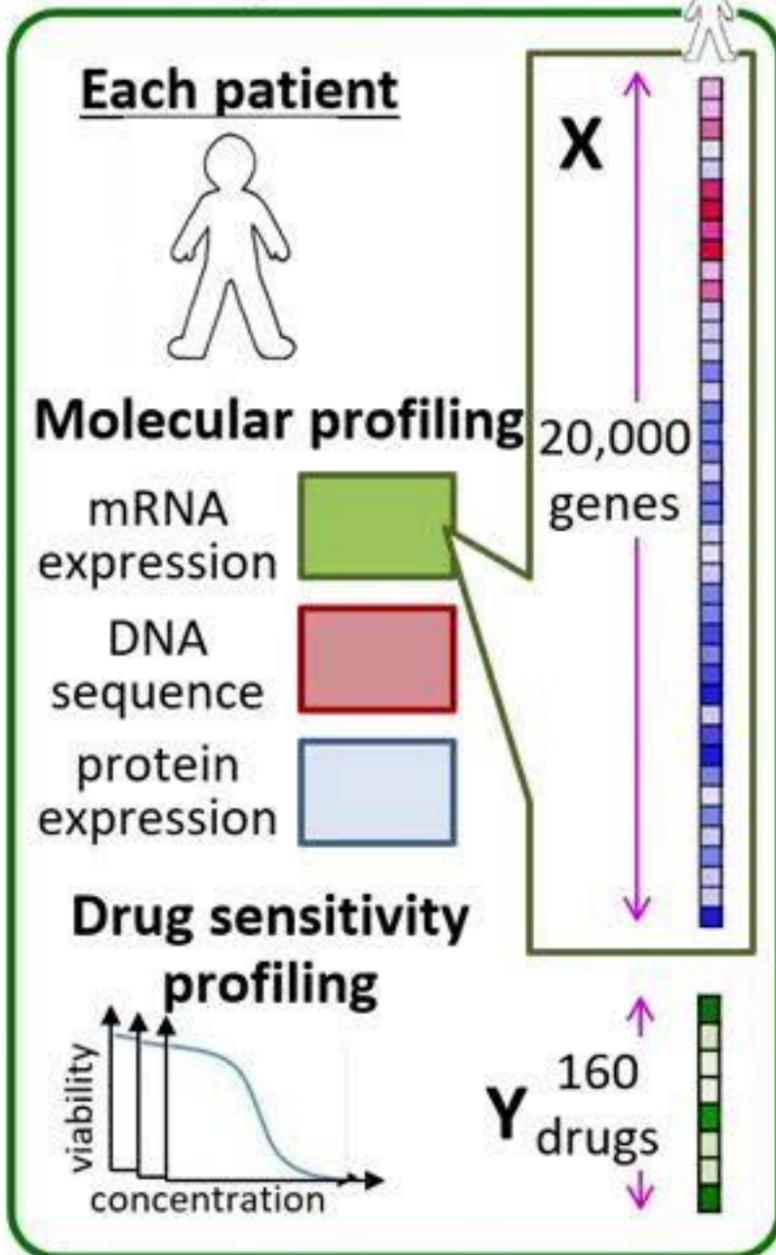


A naïve solution: Supervised learning approach

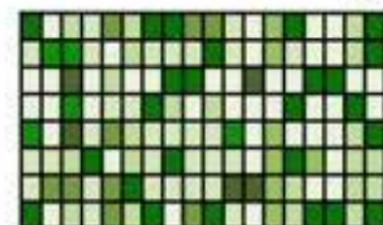
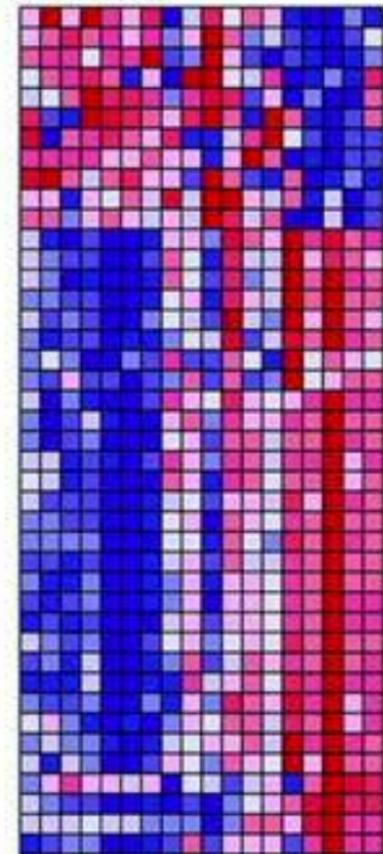


Safiye

Training Data



Samples: 200 AML patients



Hematology

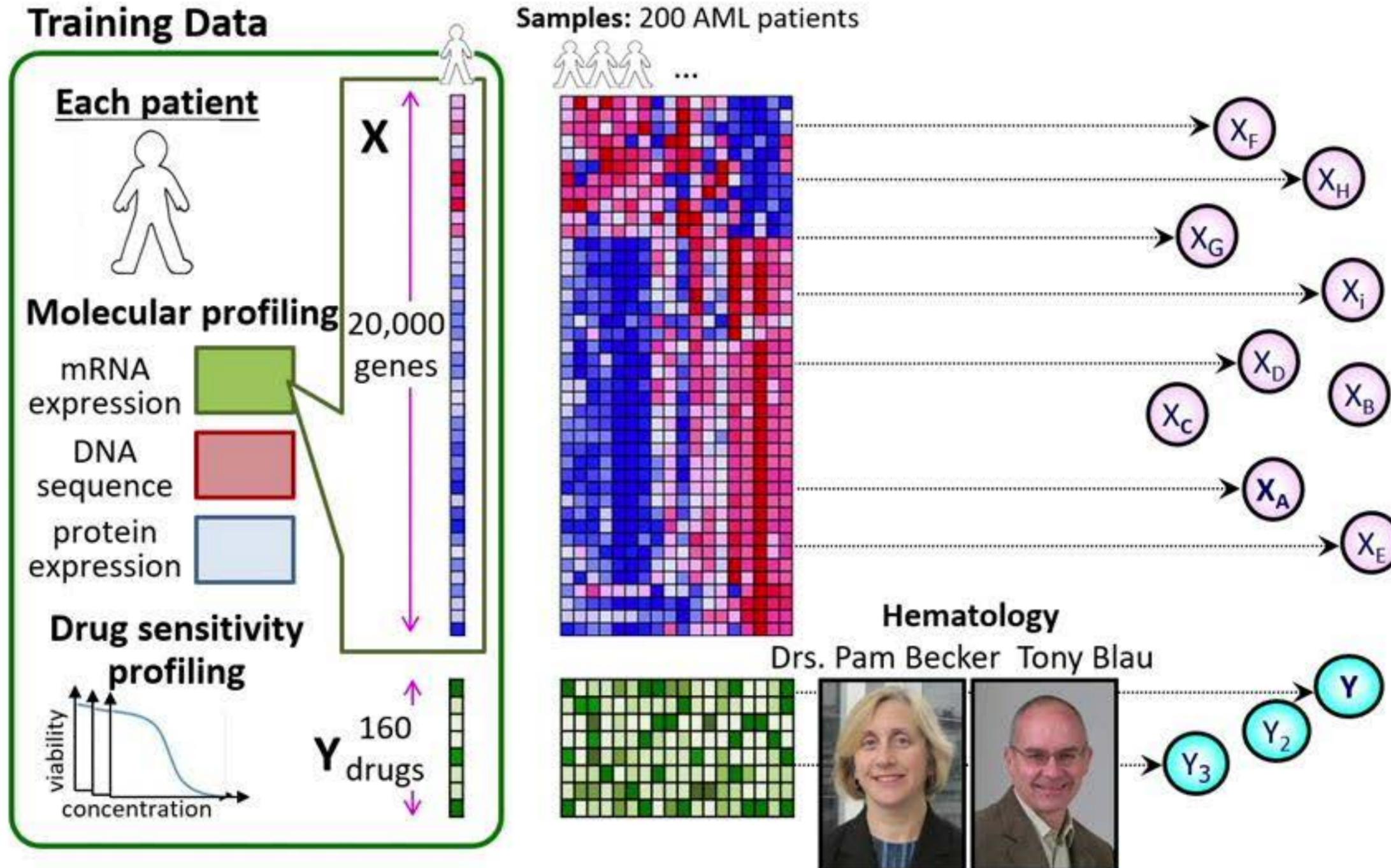
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A naïve solution: Supervised learning approach



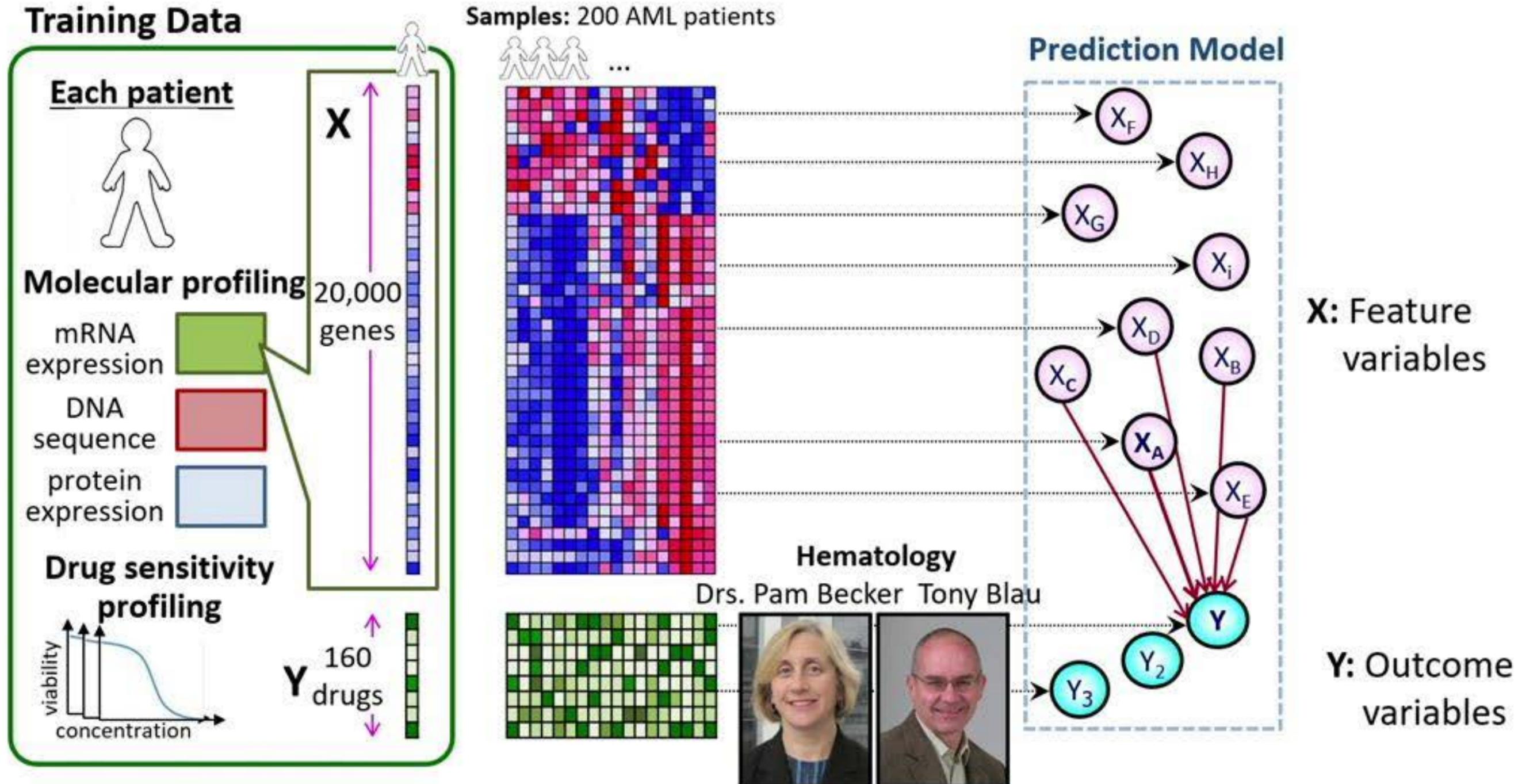
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A naïve solution: Supervised learning approach



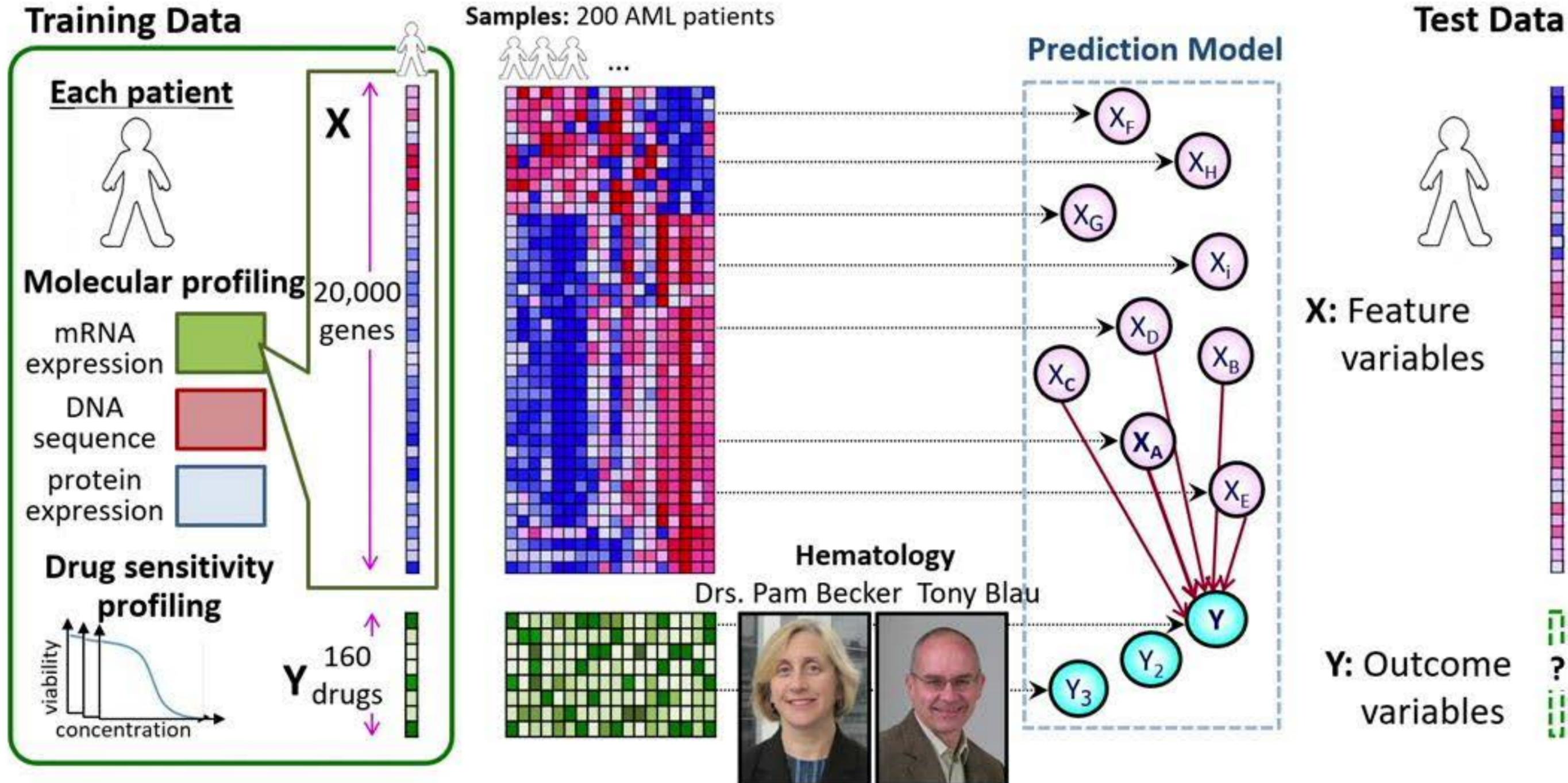
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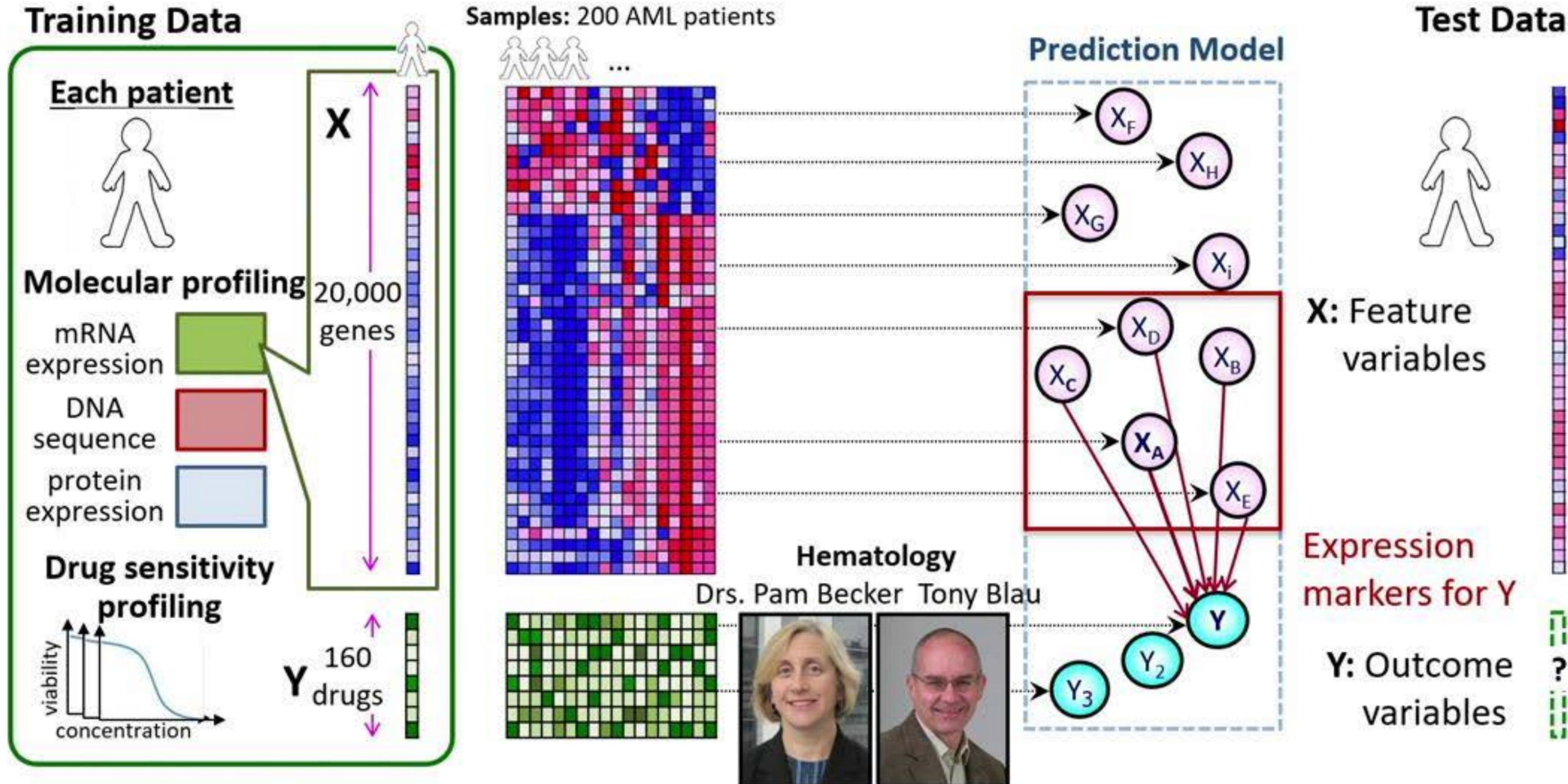
Safiye



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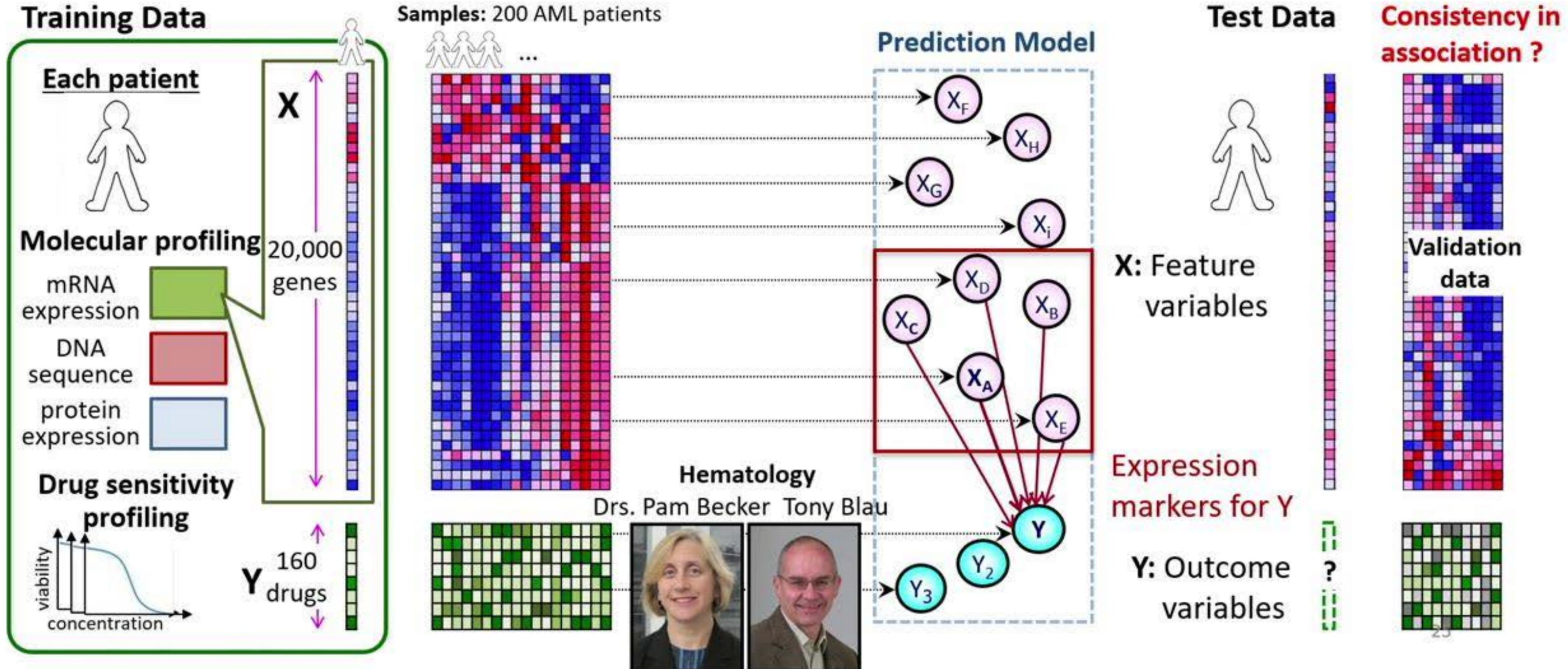
Safiye



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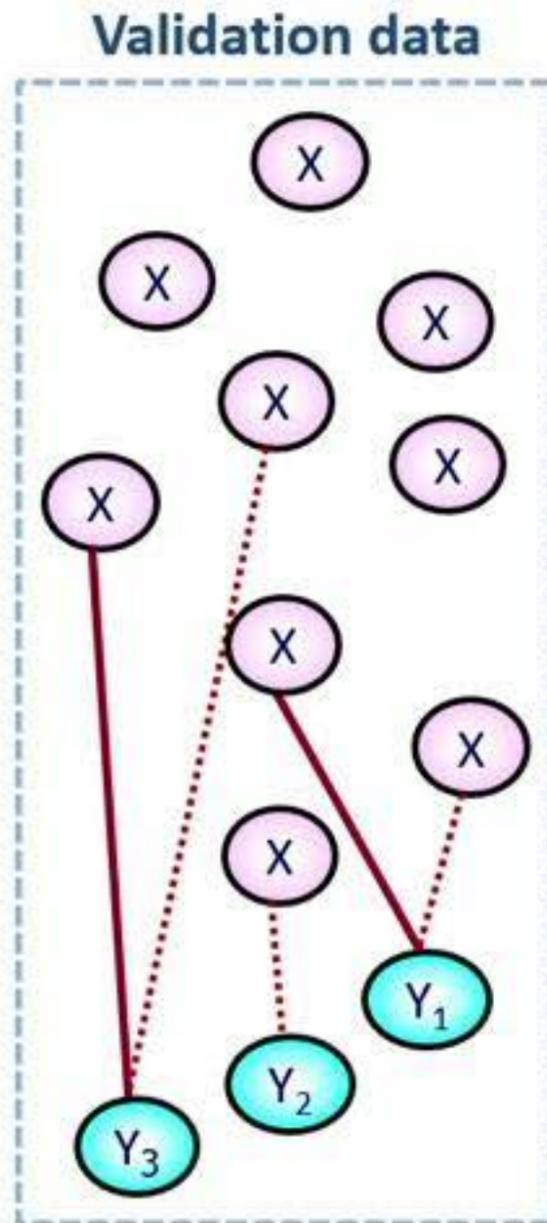
Safiye



Only a small fraction of significant gene-drug associations are replicated in validation data



Safiye

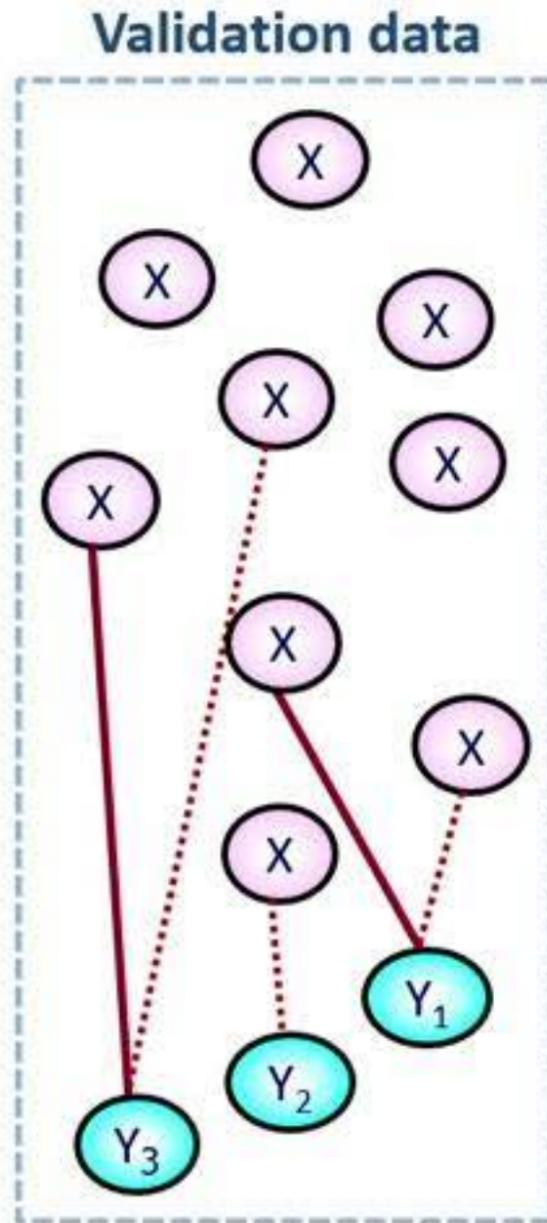


$$\text{Consistency rate (True Discovery Rate)} = \frac{\text{Number of replicated associations (—)}}{\text{Number of significant associations (— or \cdots)}}$$

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Safiye



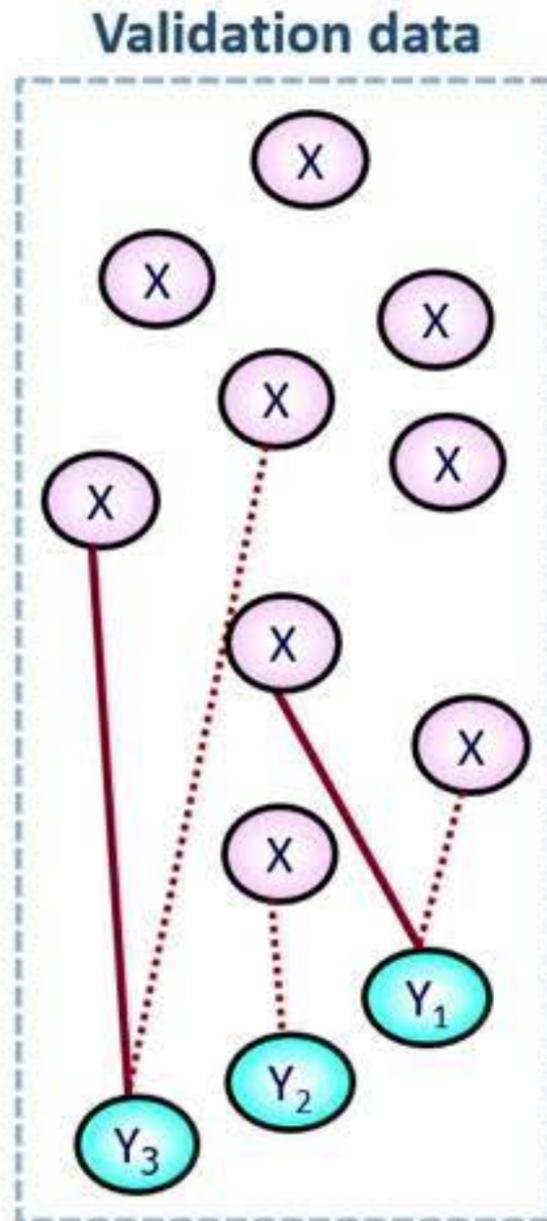
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ordered list of gene-drug pairs based on degrees of associations

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Safiye



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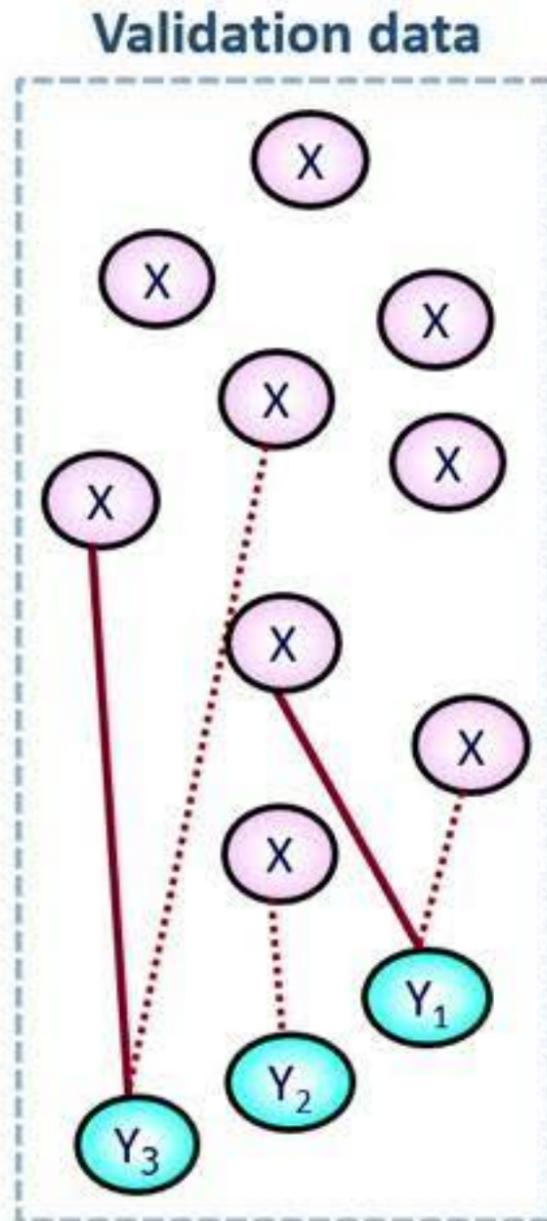
200 400 600 800 1000 1200 1400 1600 1800 2000 2200

average # associations per drug to follow up on

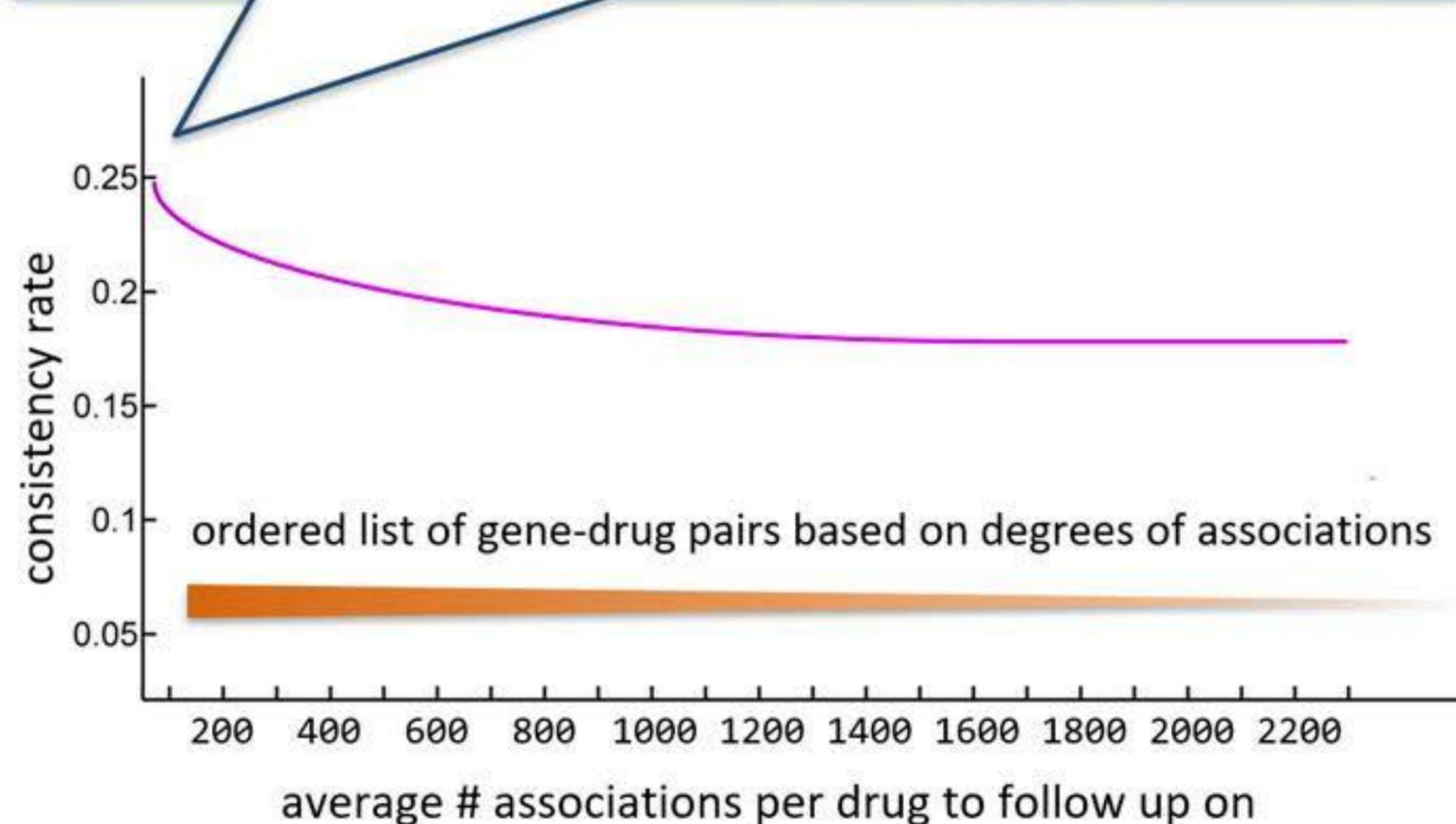
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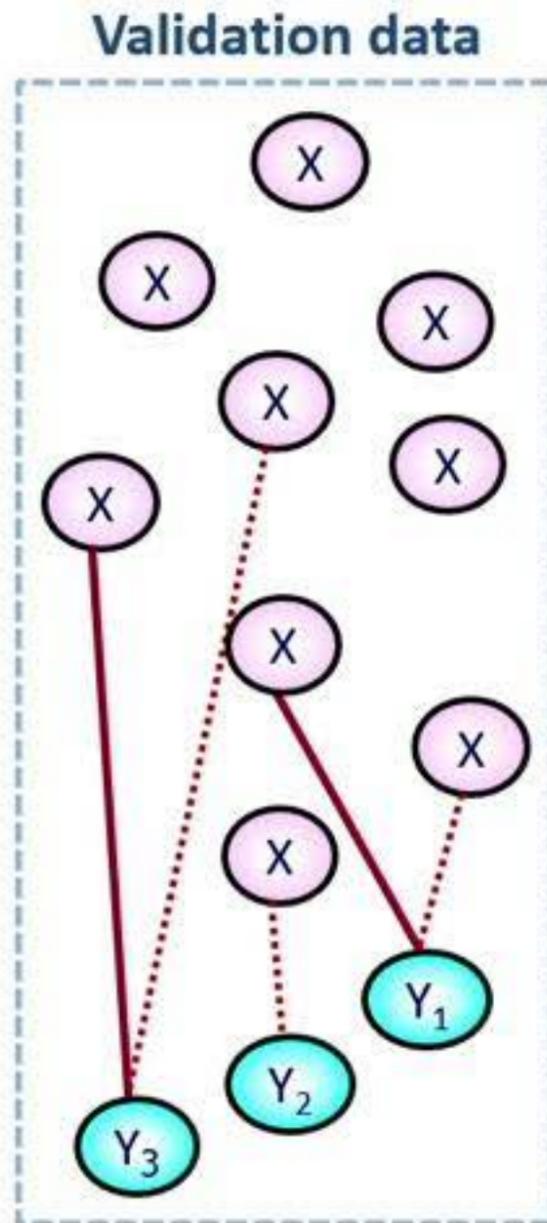


Lee*, Celik*, et al. (2018)
Nature Communications

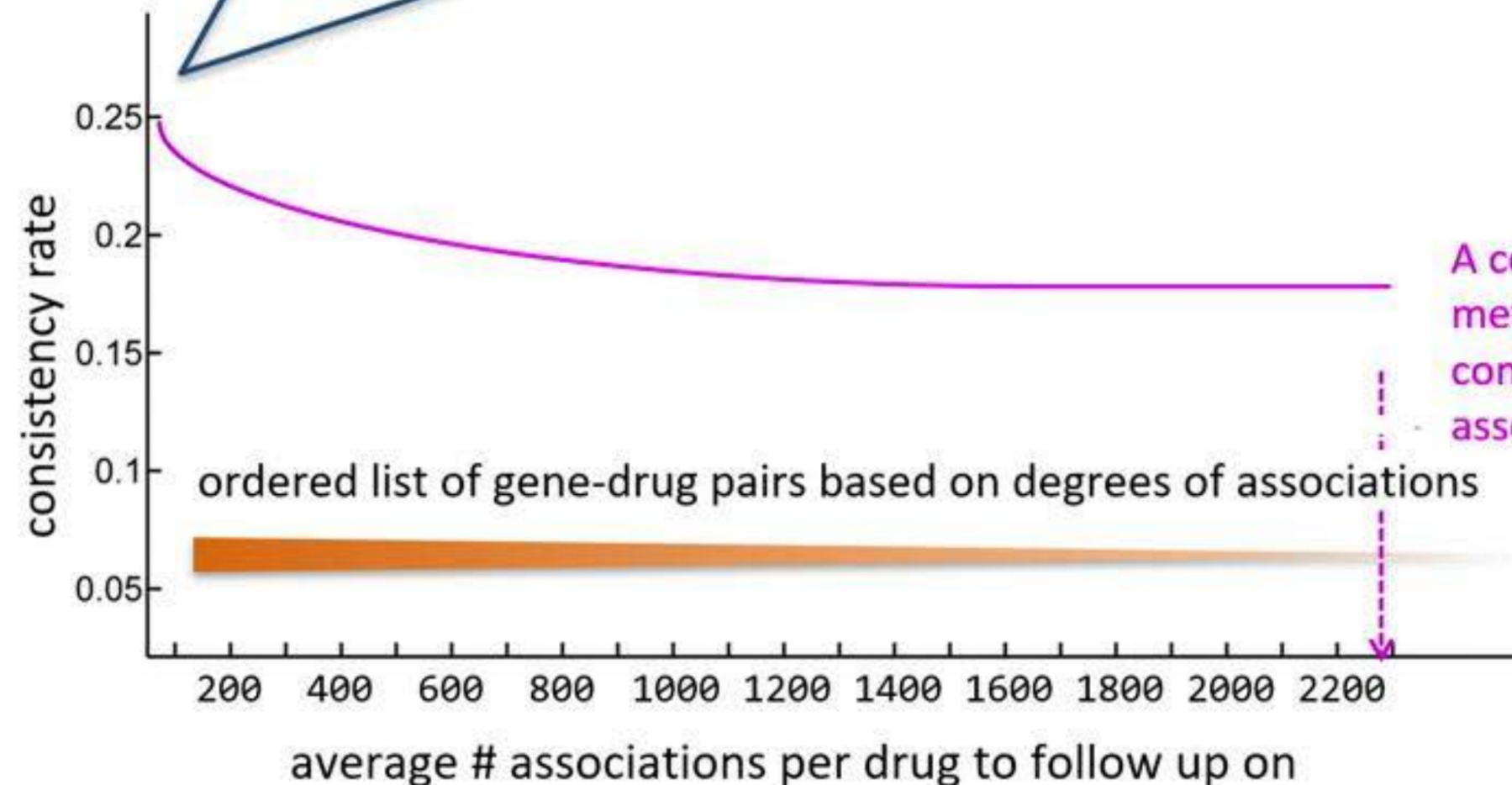
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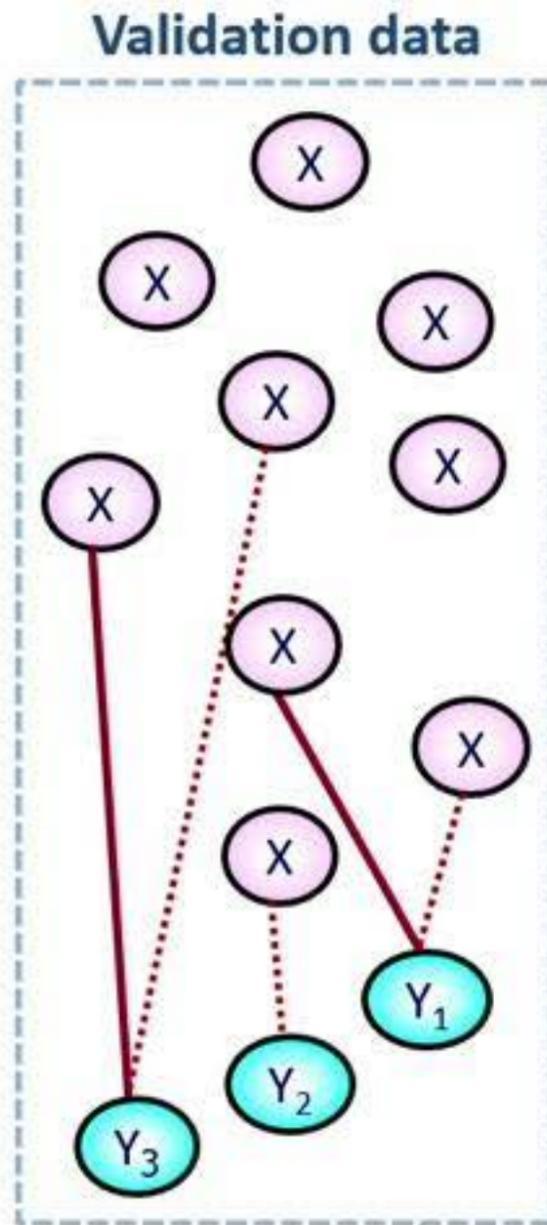


A conventional statistical method suggests to consider the gene-drug associations up to here.

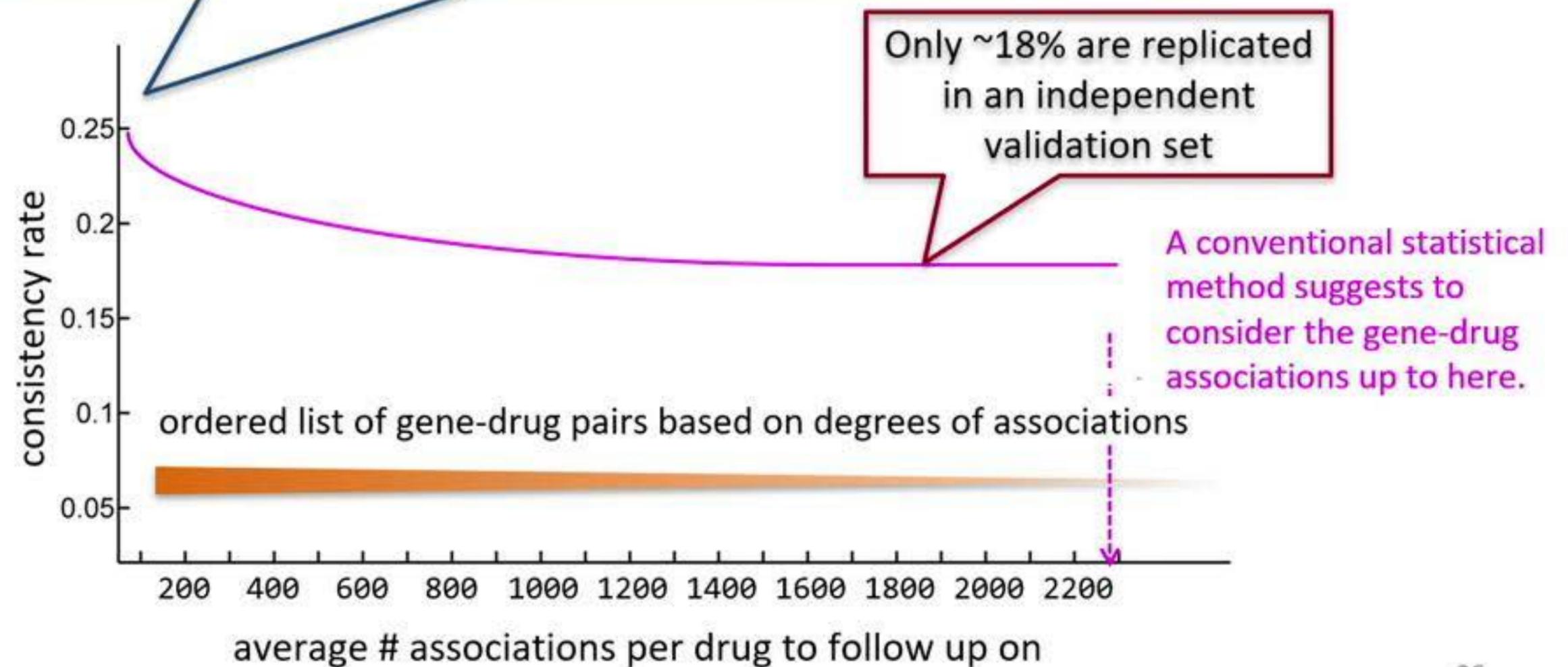
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Safiye



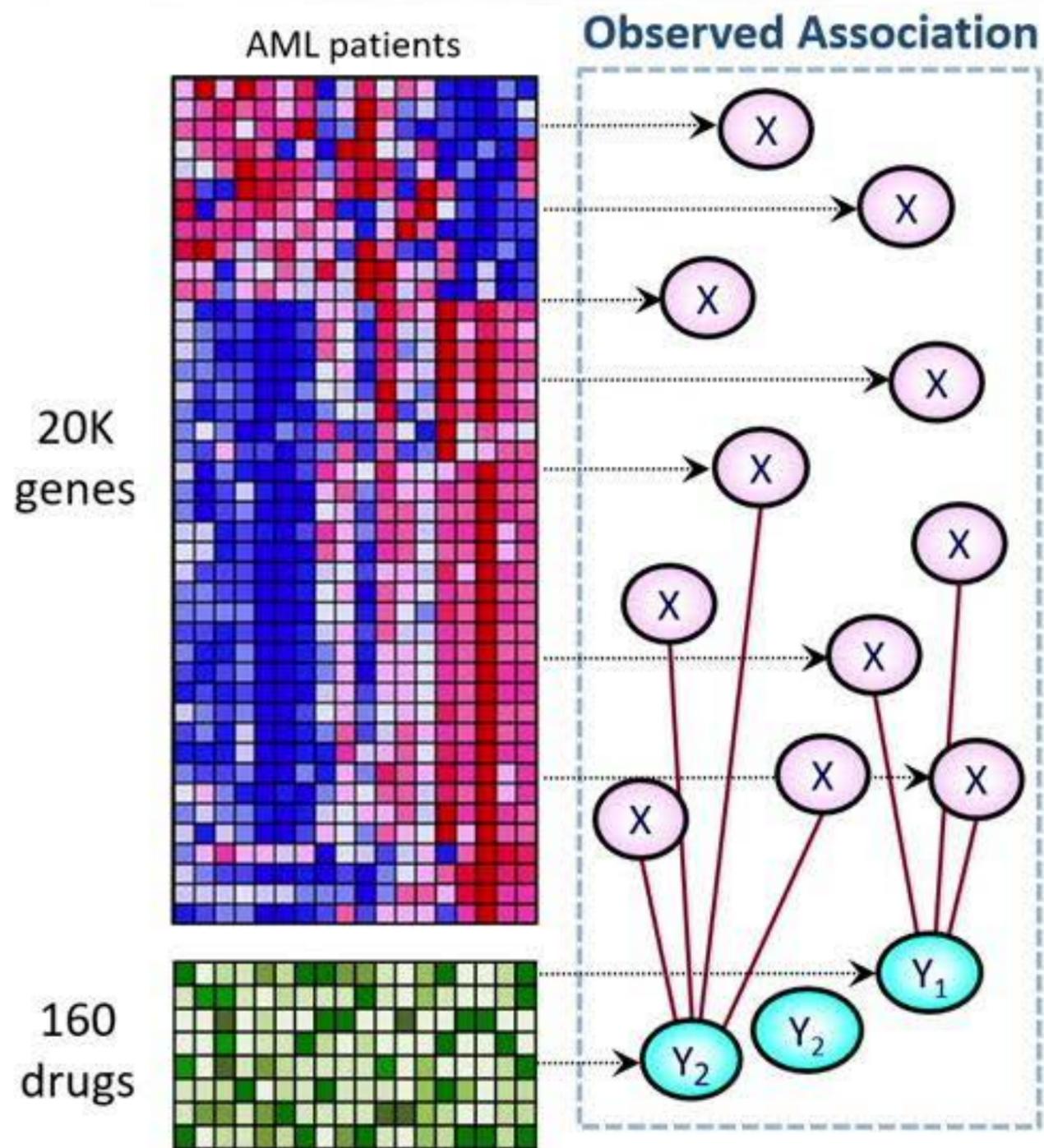
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Supervised learning approach has serious drawbacks



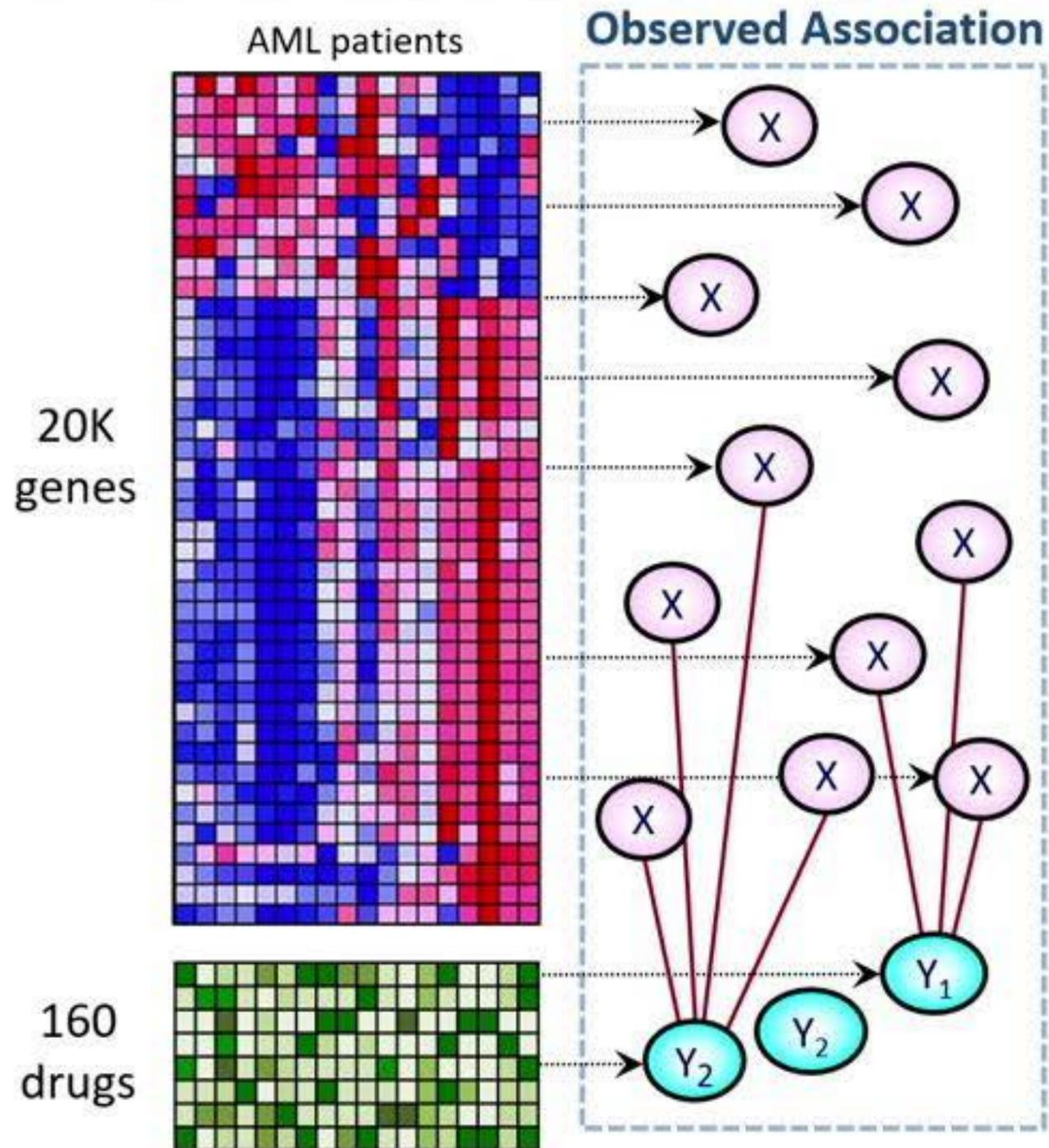
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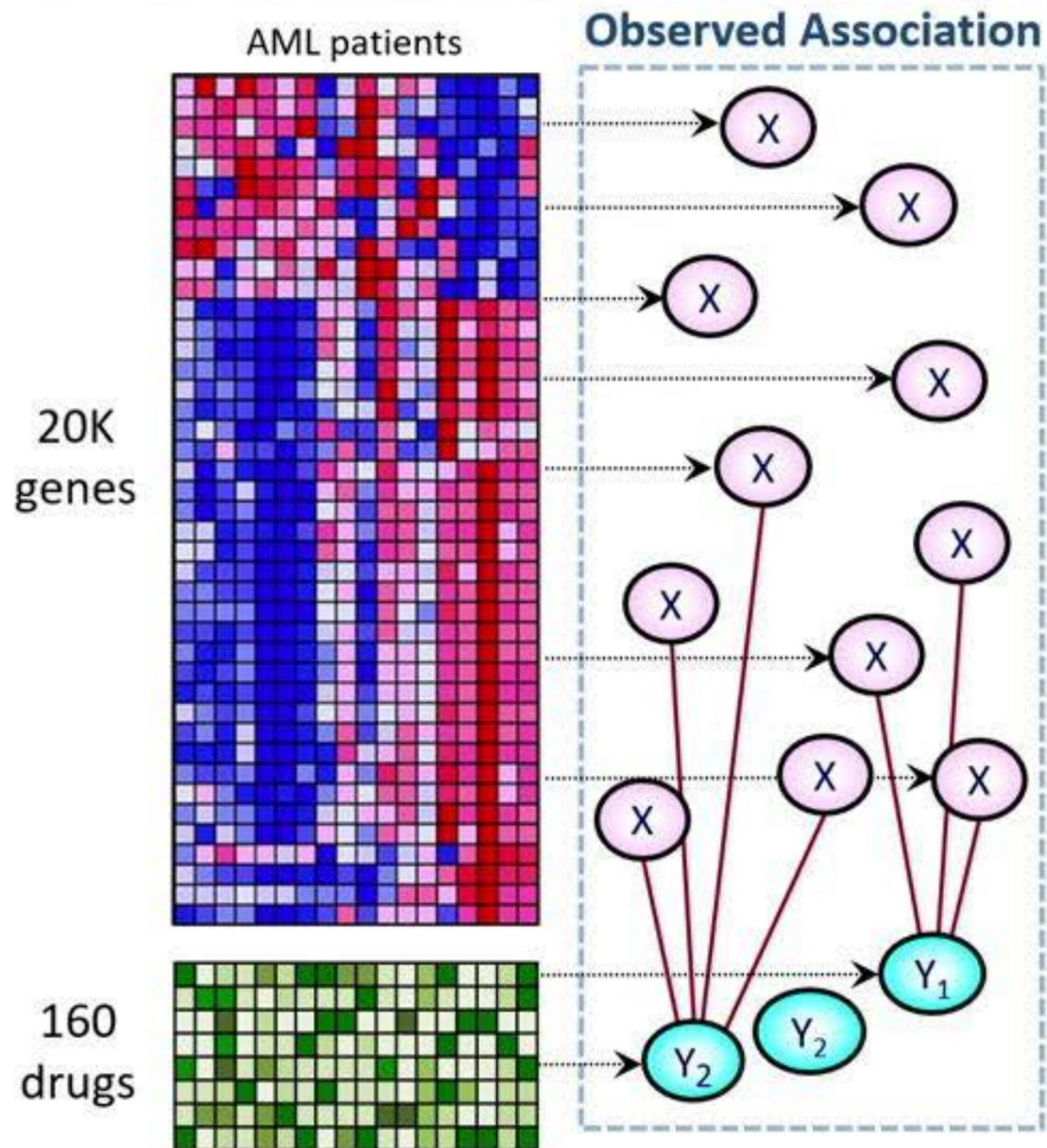


- **High-dimensionality**
 - # of (genes x drugs) \gg # of patients

Supervised learning approach has serious drawbacks



Safiye



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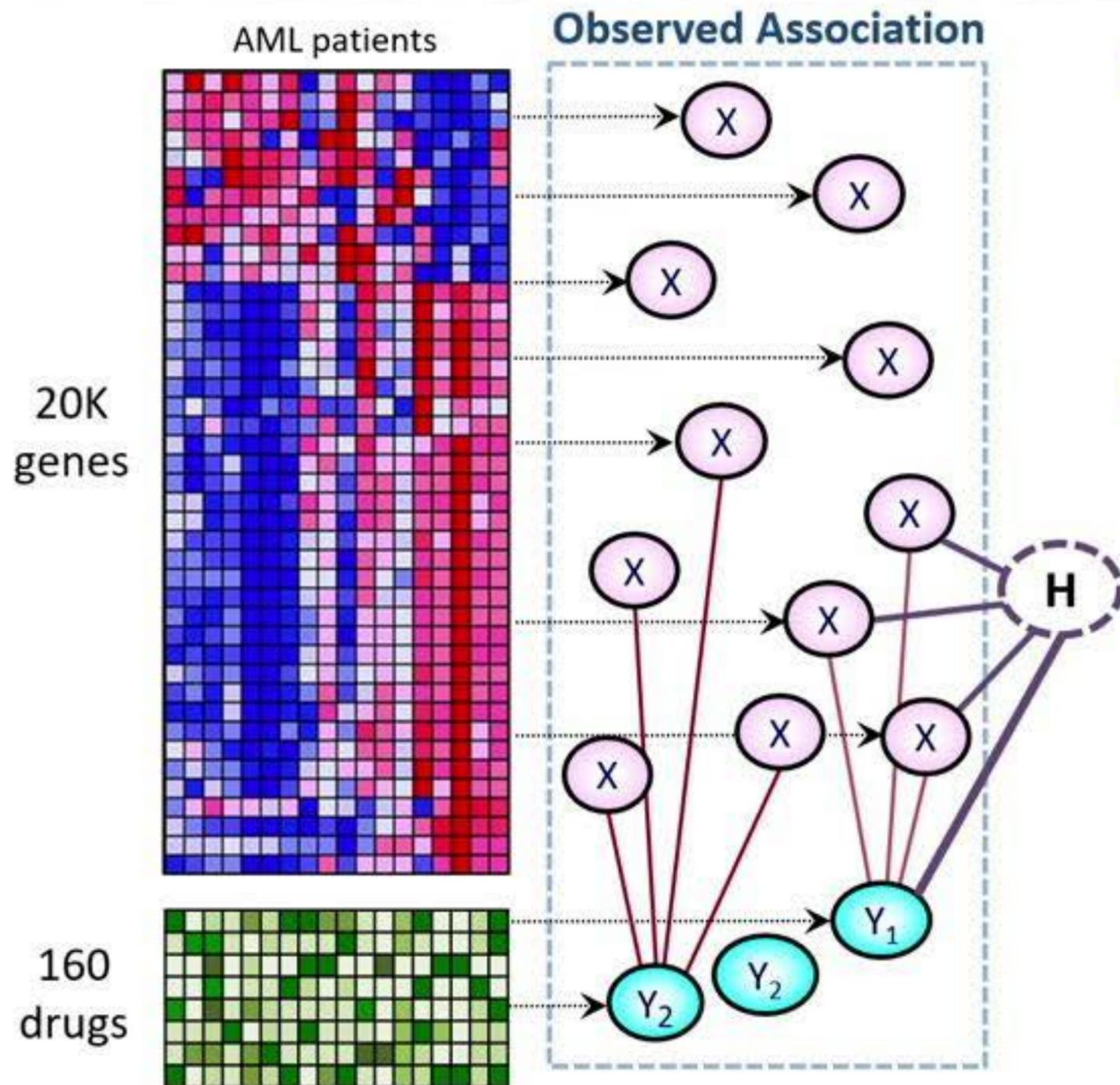
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Supervised learning approach has serious drawbacks



Safiye



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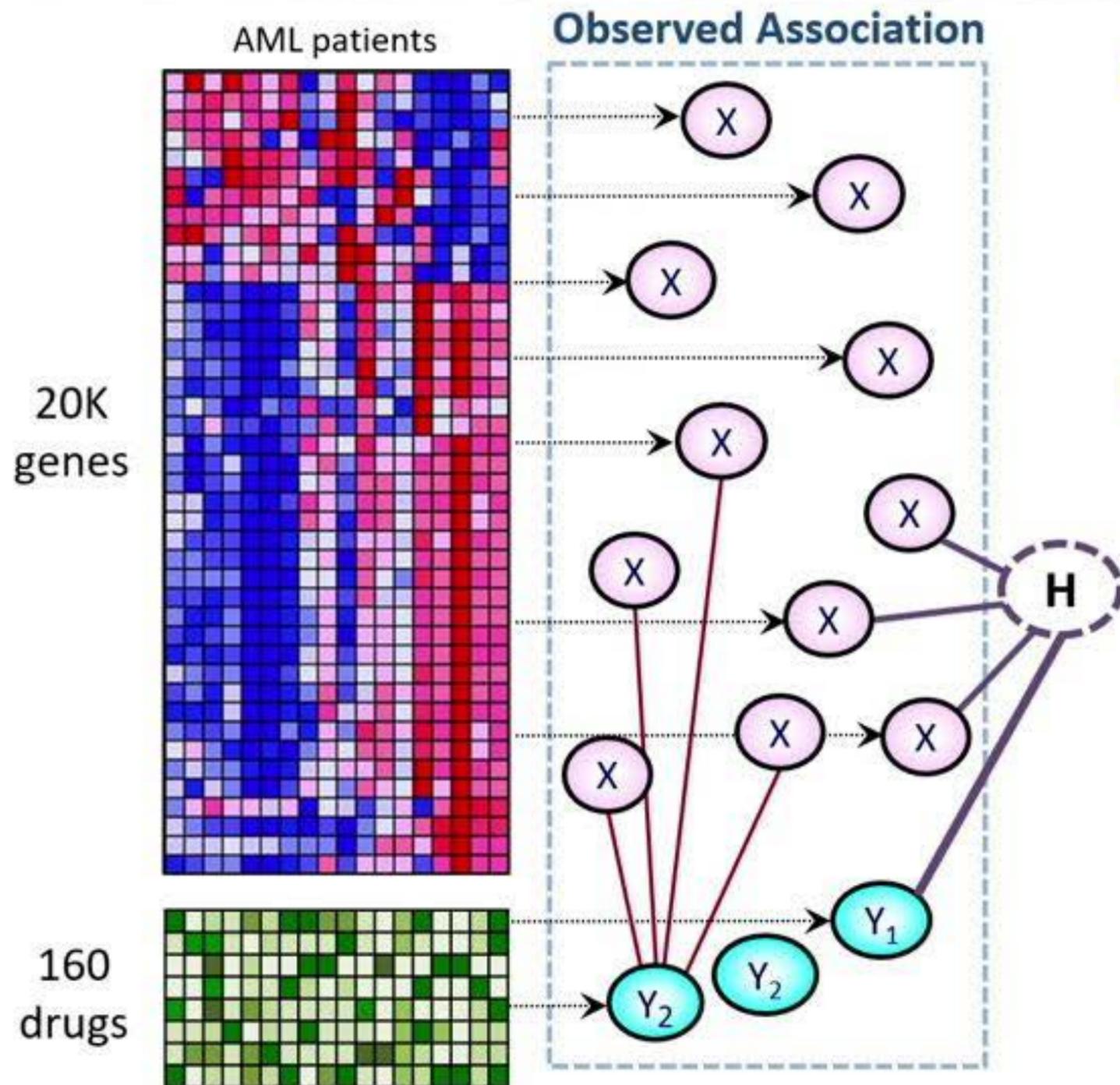
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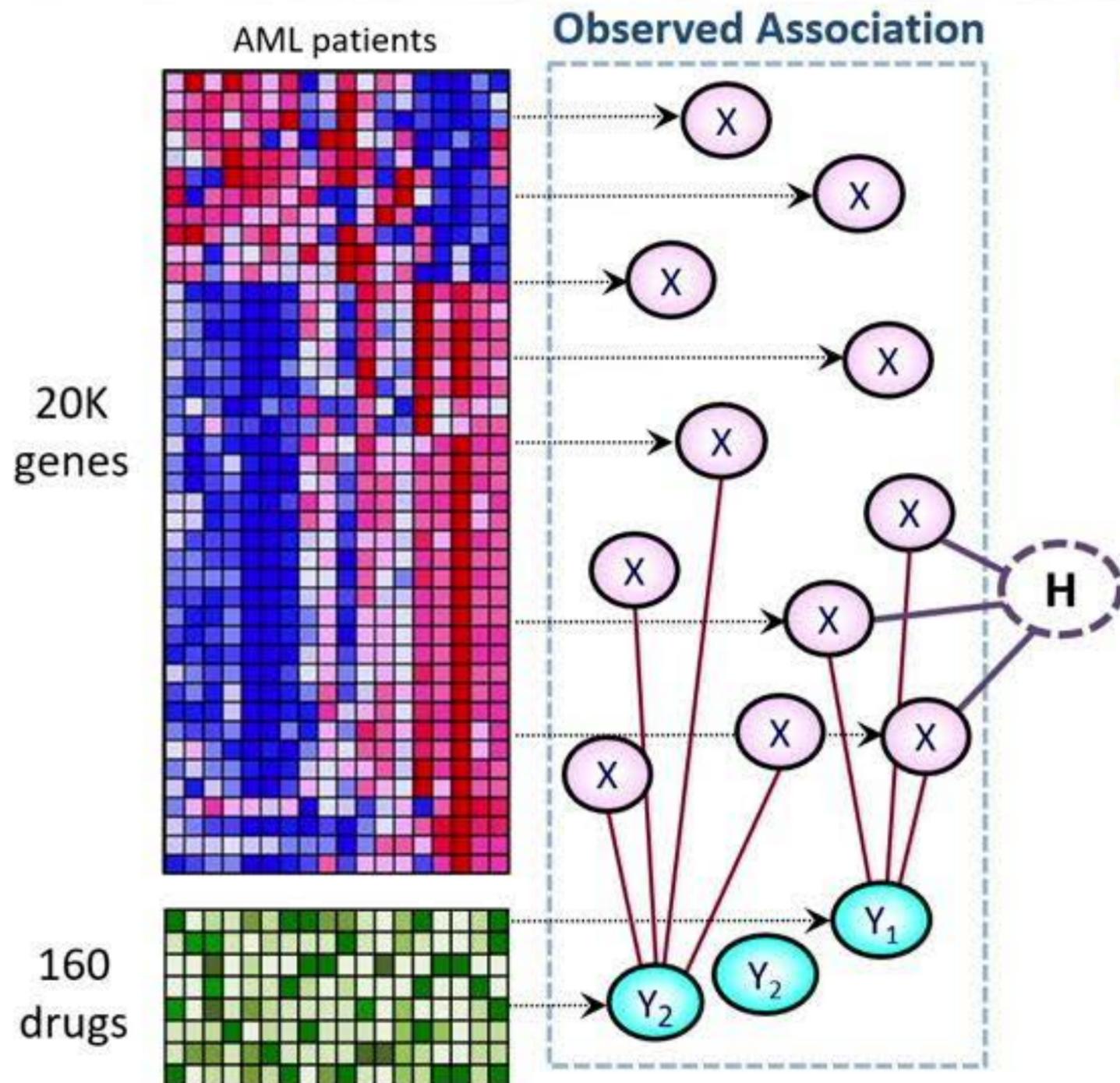
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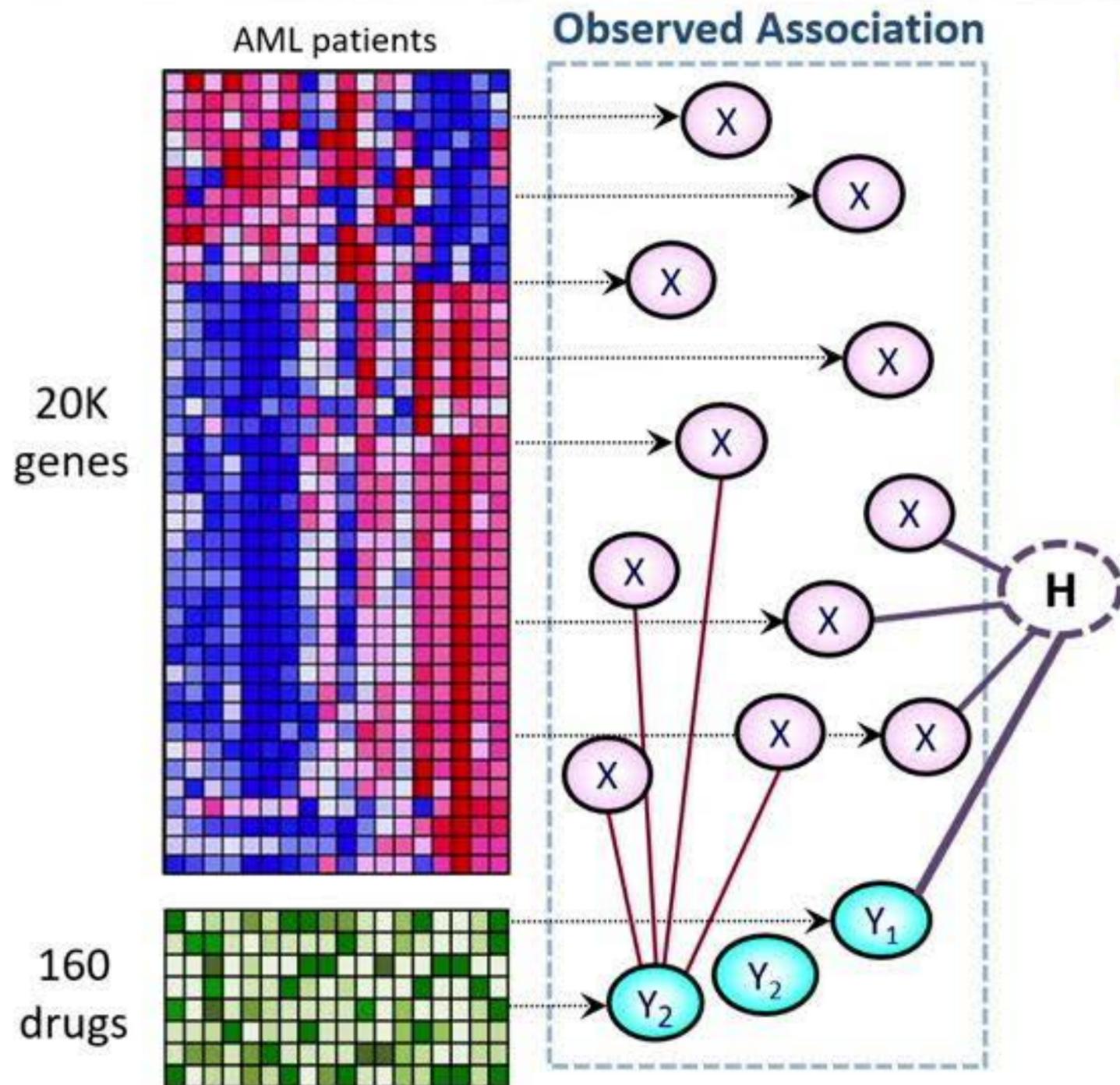
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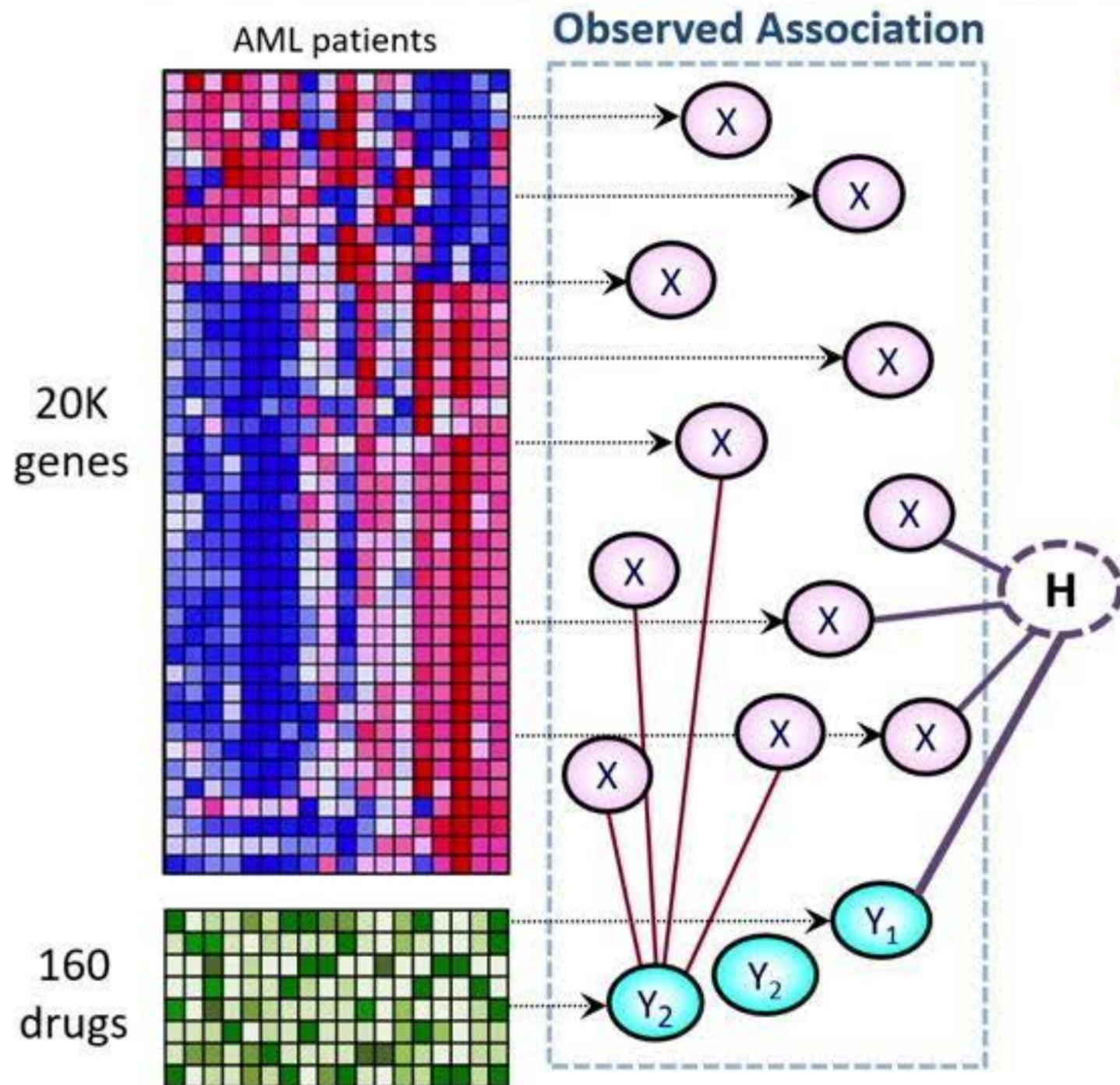
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Safiye



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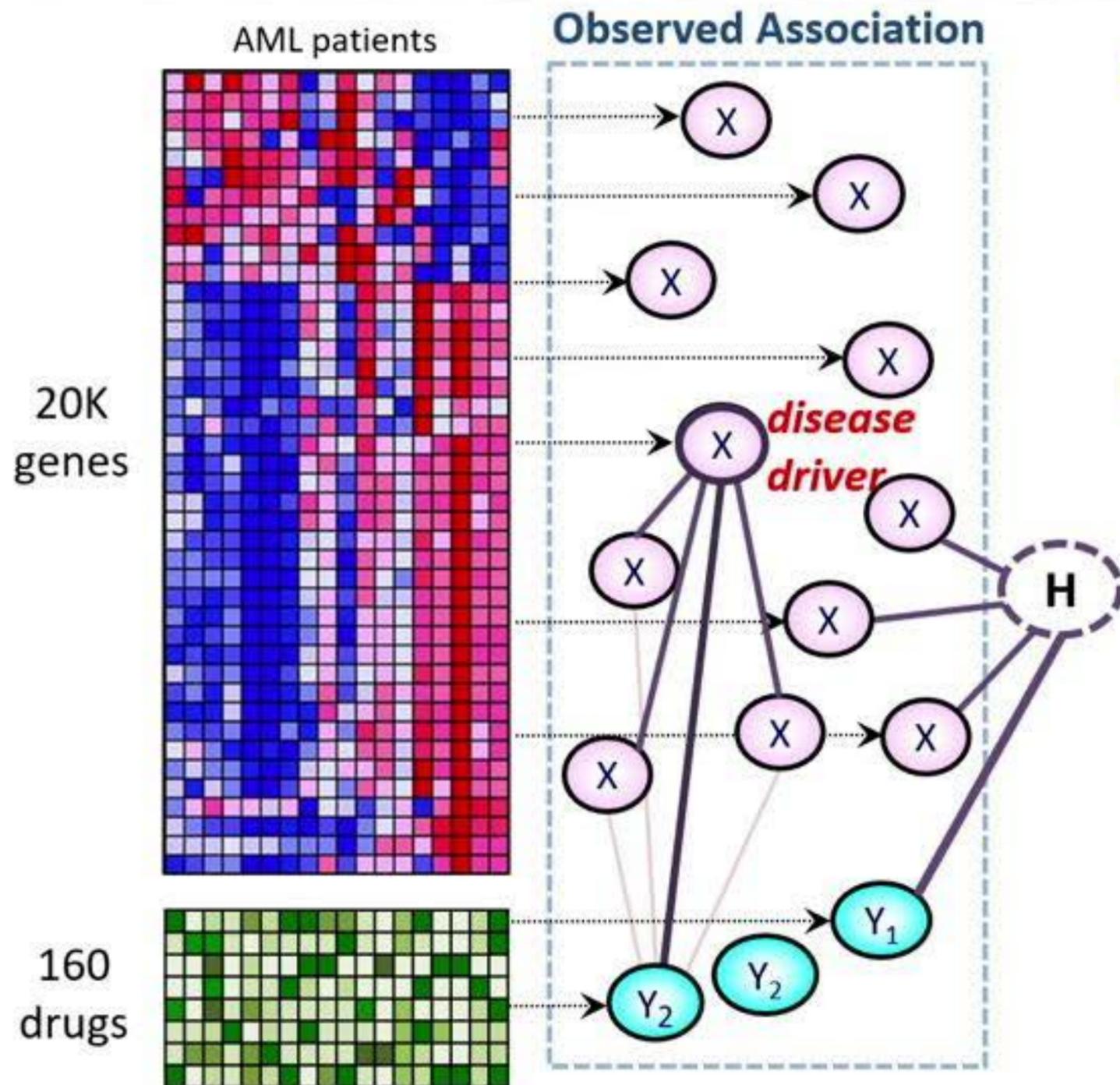
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Safiye



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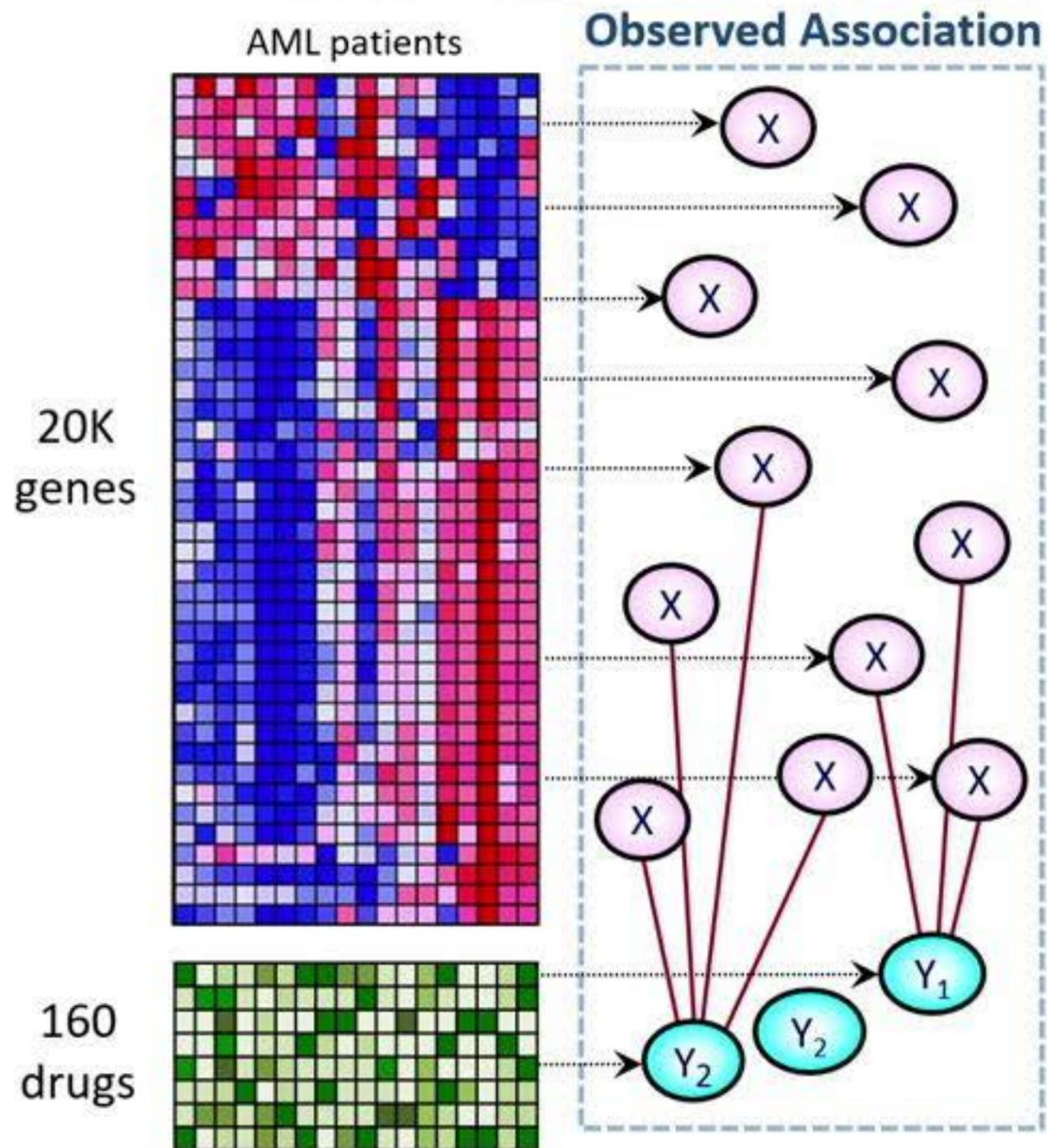
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Safiye



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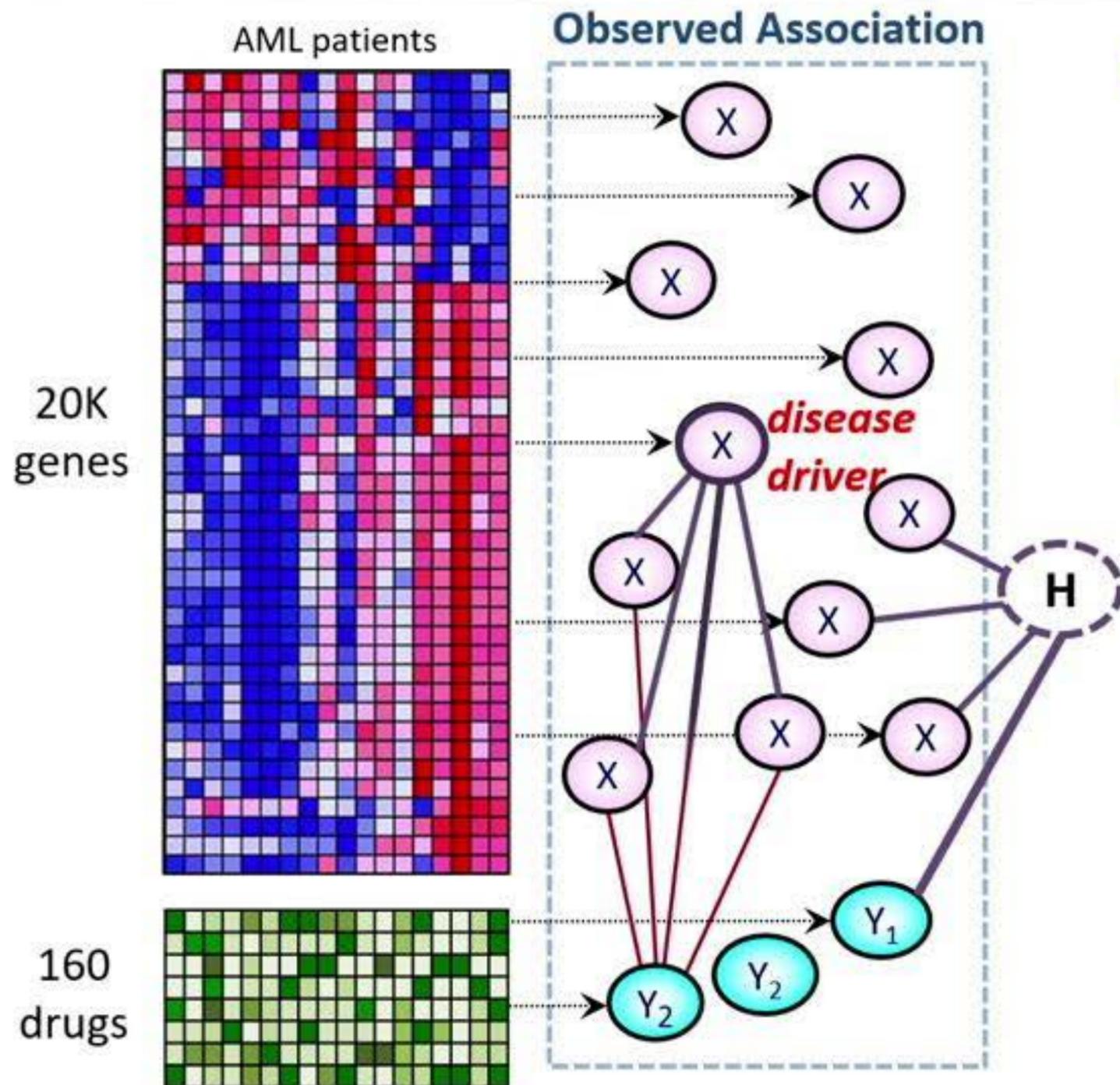
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Safiye



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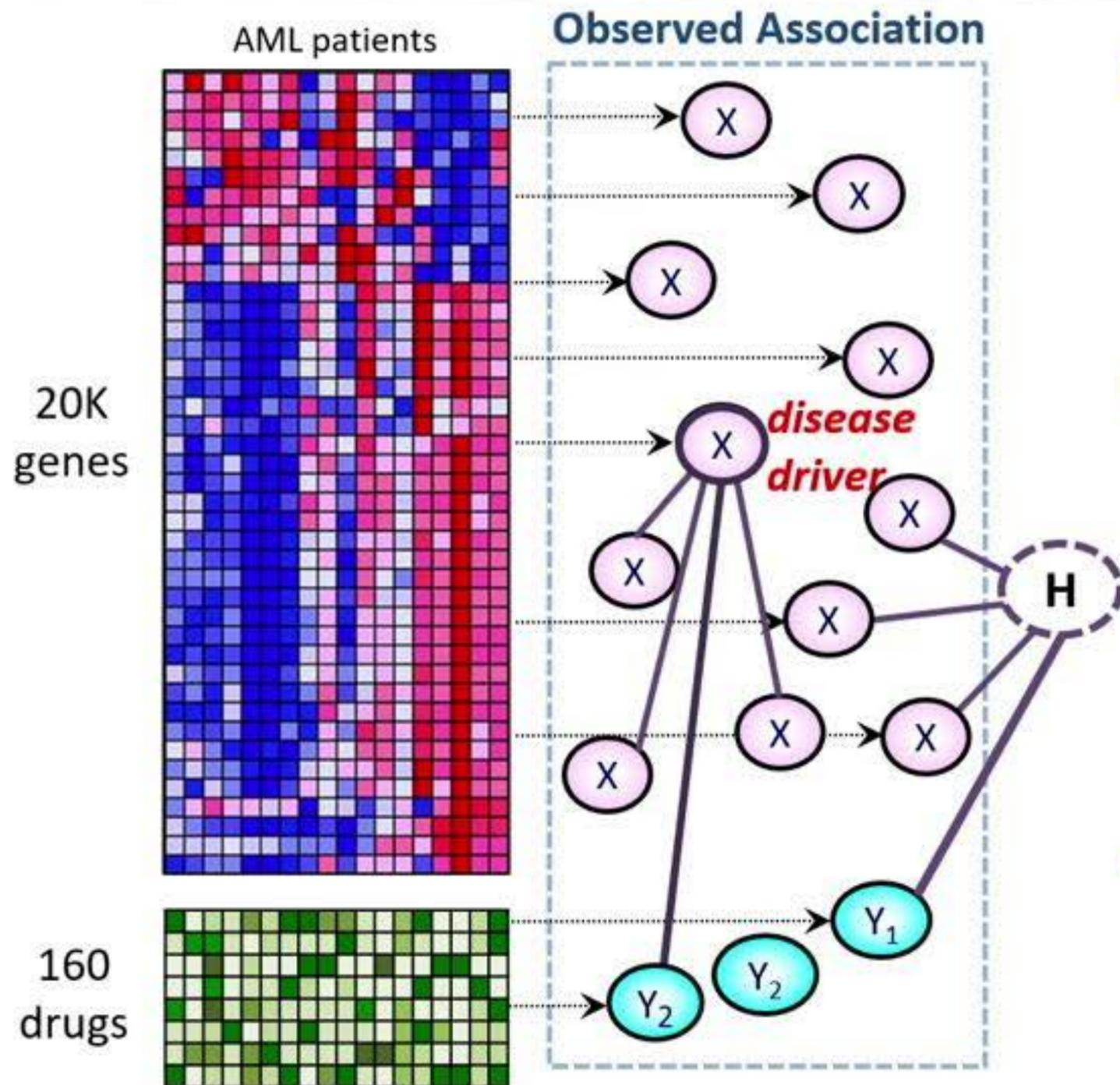
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Safiye

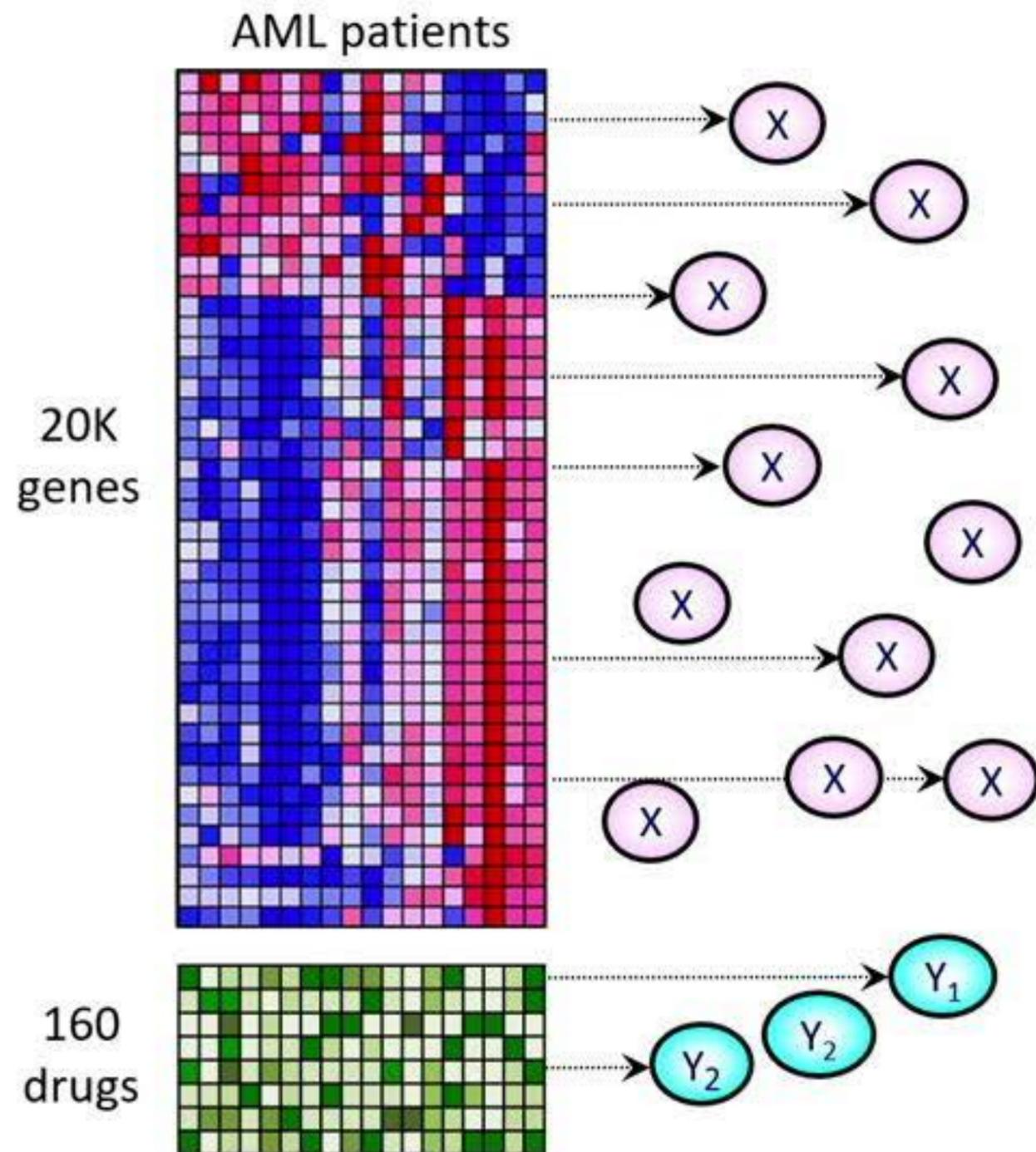


- **High-dimensionality**
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- **Confusion caused by**
 - Hidden variables (e.g., batch effect, unknown disease subtype)
 - Correlation with a true marker
- **Our solution** – Unsupervised feature learning to select genes likely to **explain associations**.

MERGE: Machine learning approach to integrate big data to select robust expression markers



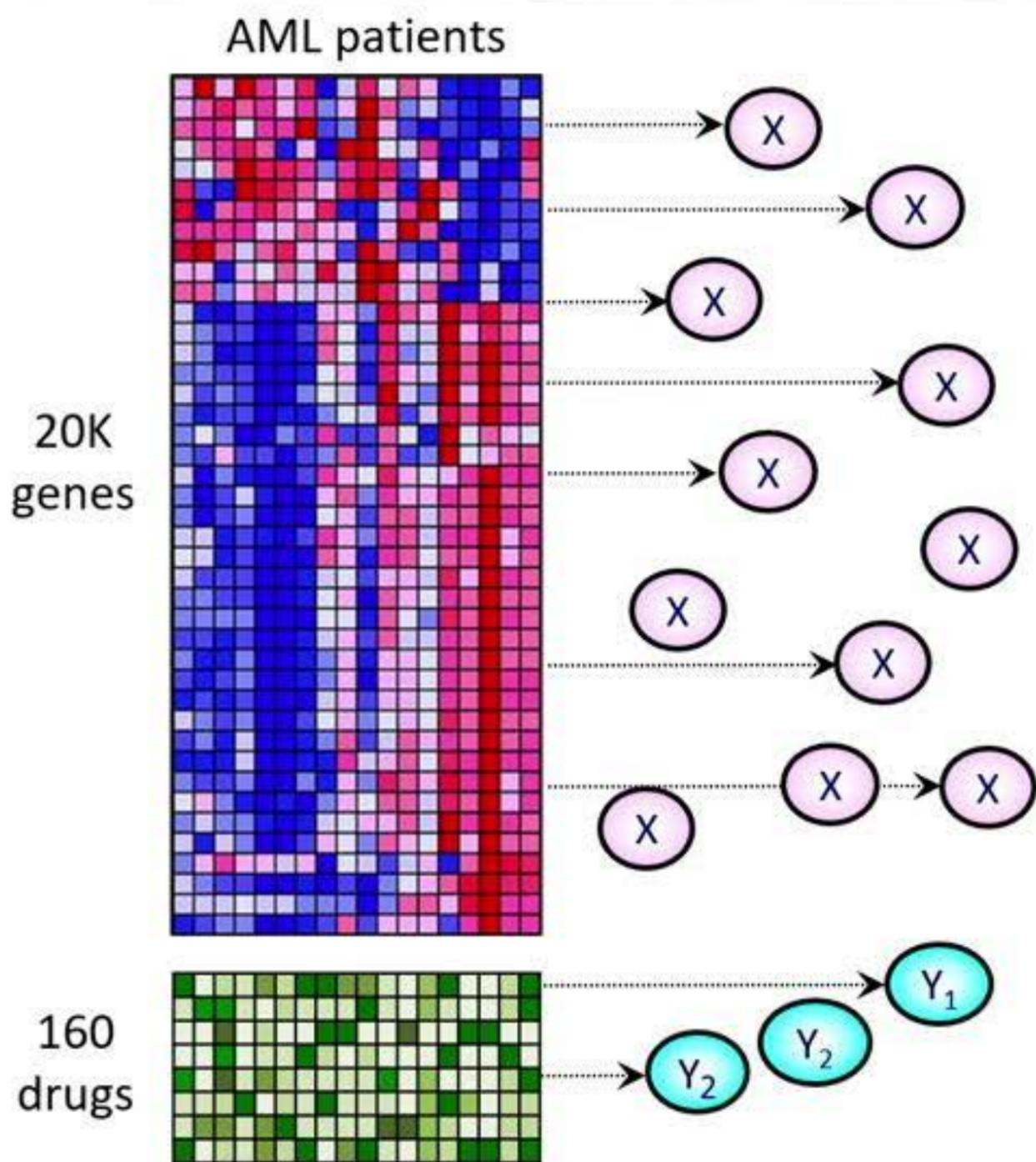
Safiye



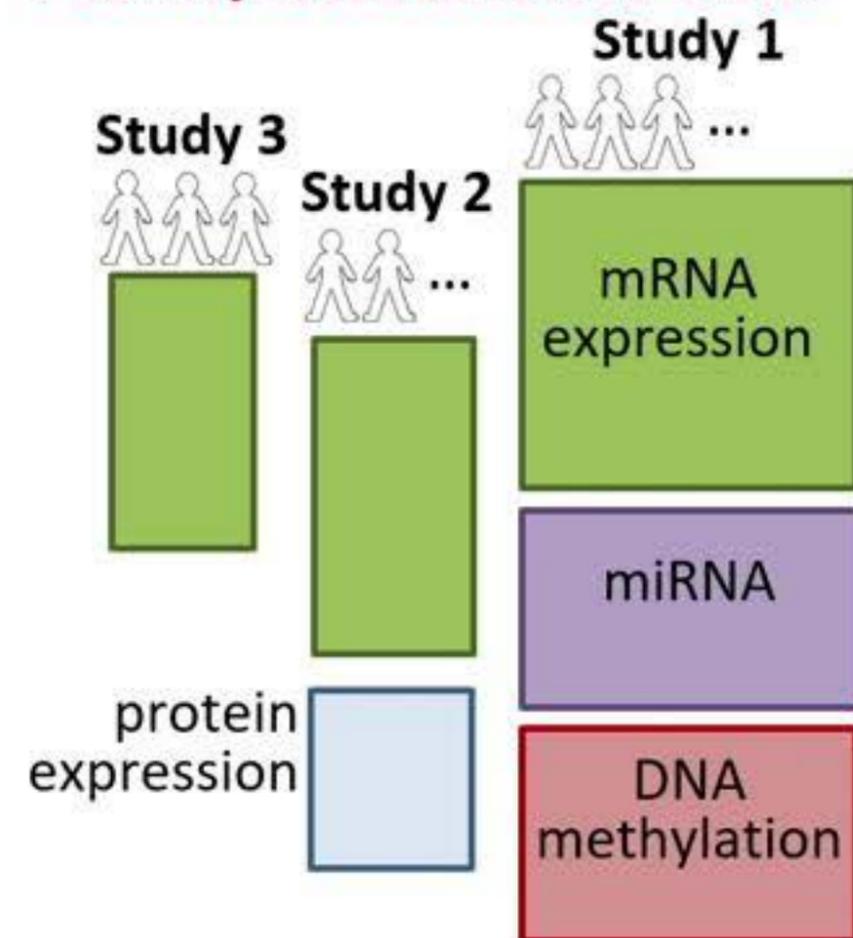
MERGE: Machine learning approach to integrate big data to select robust expression markers



Safiye



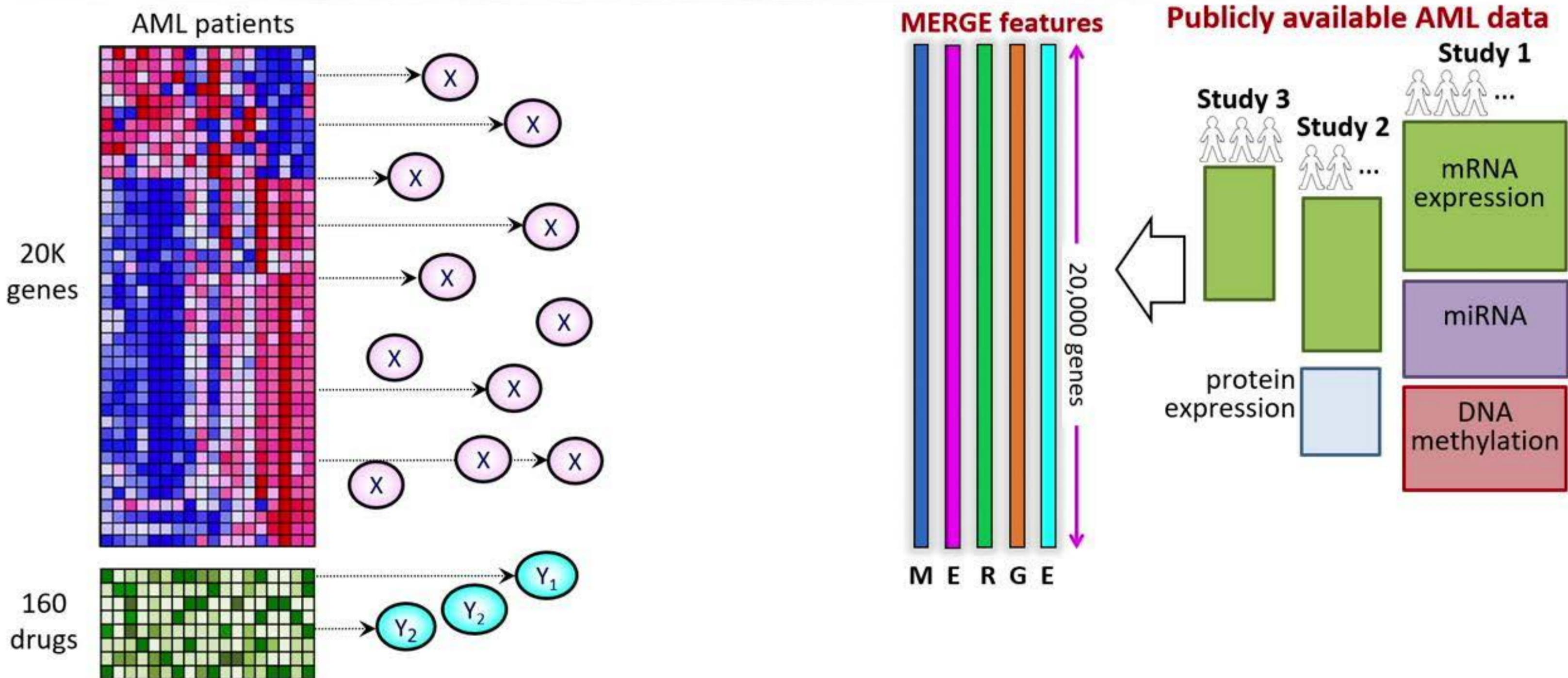
Publicly available AML data



MERGE: Machine learning approach to integrate big data to select robust expression markers



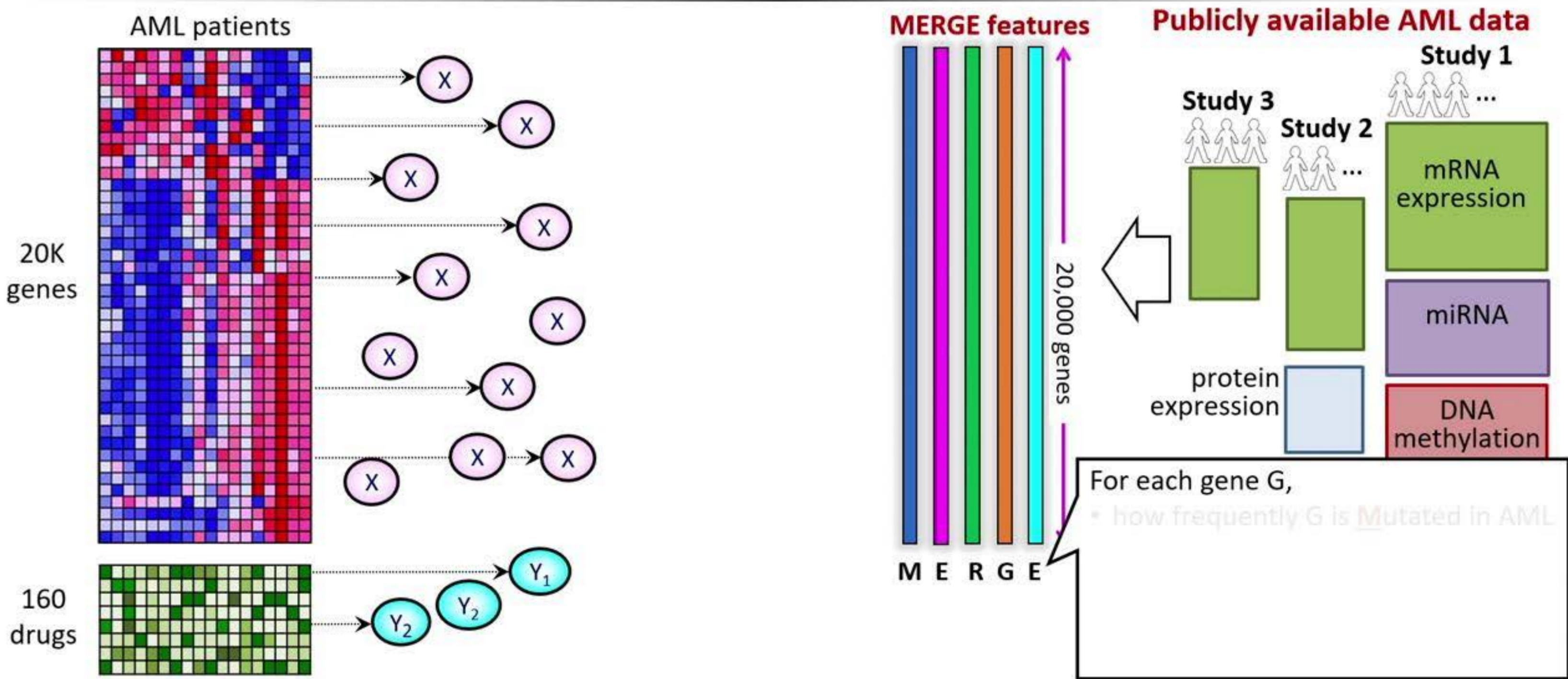
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MERGE: Machine learning approach to integrate big data to select robust expression markers



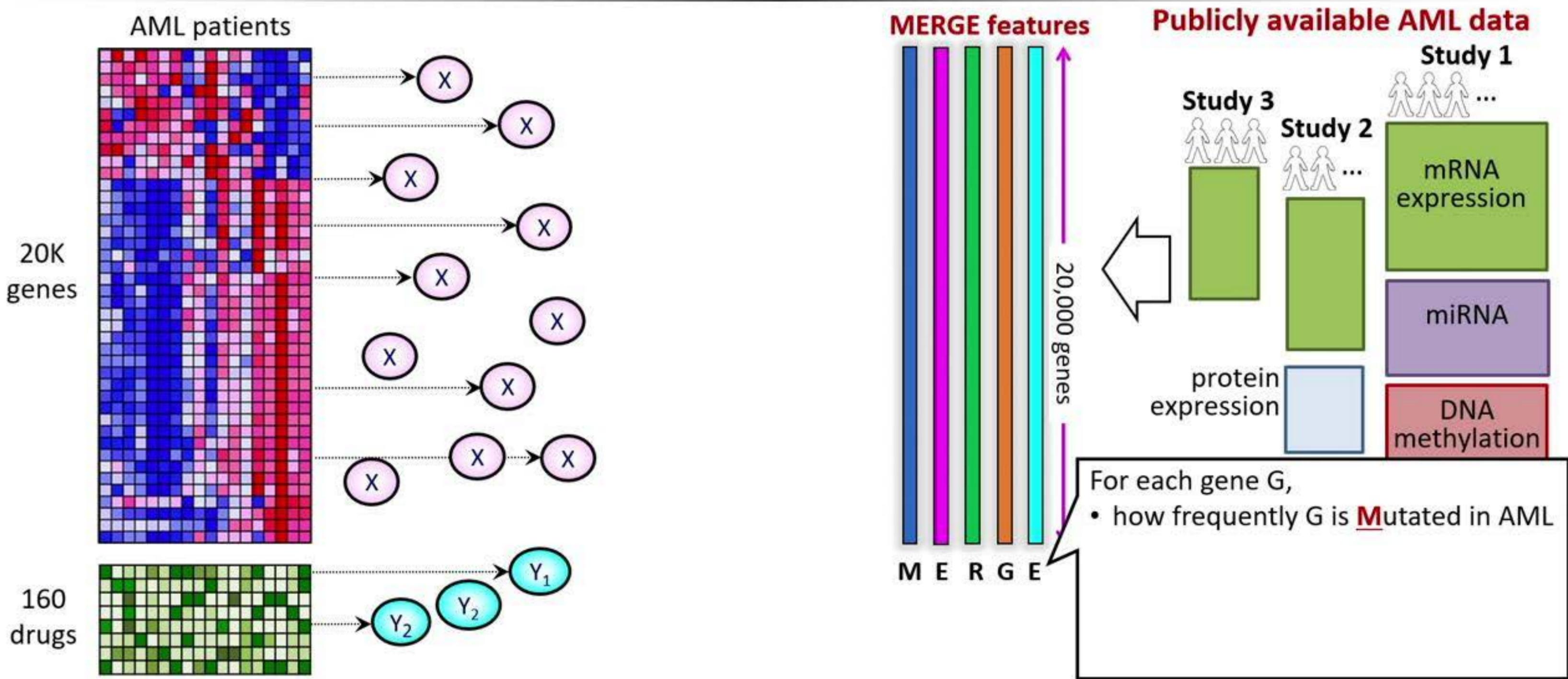
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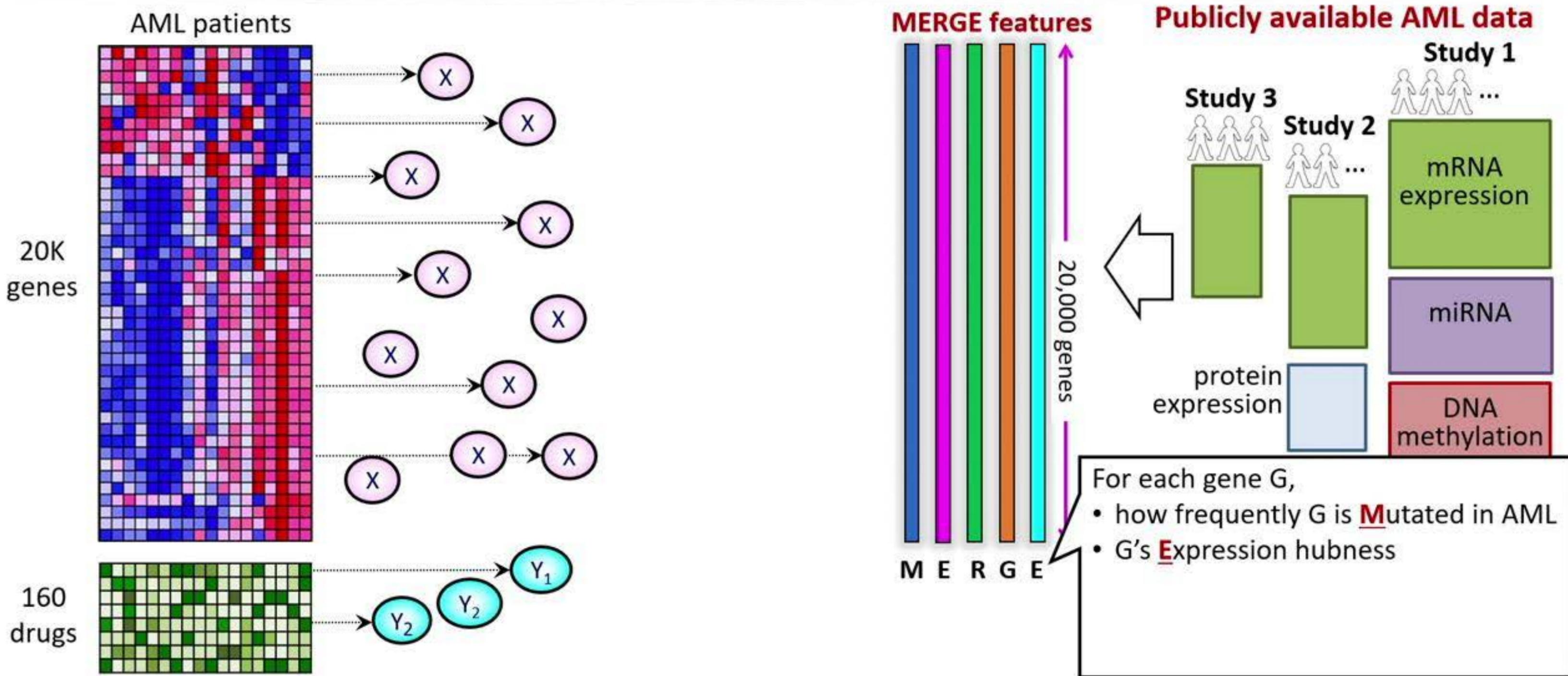
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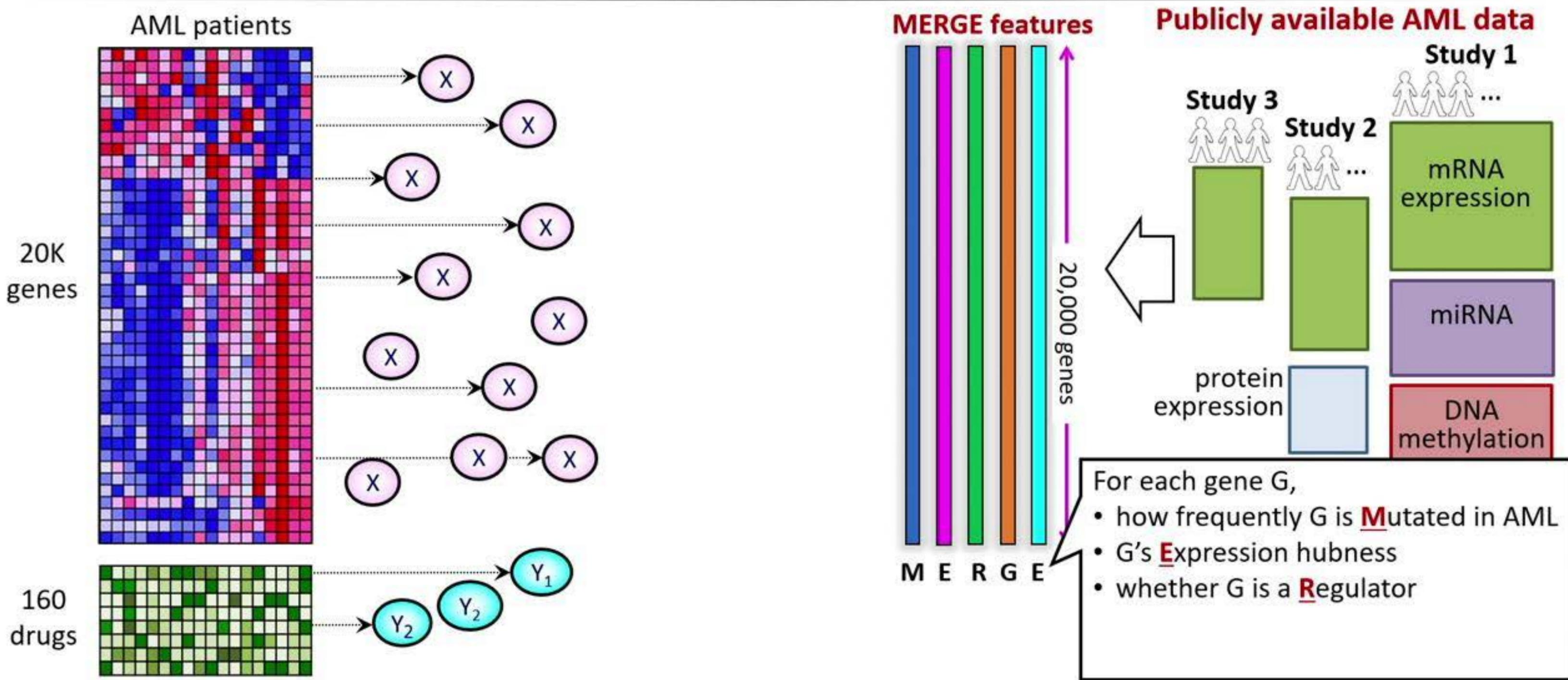
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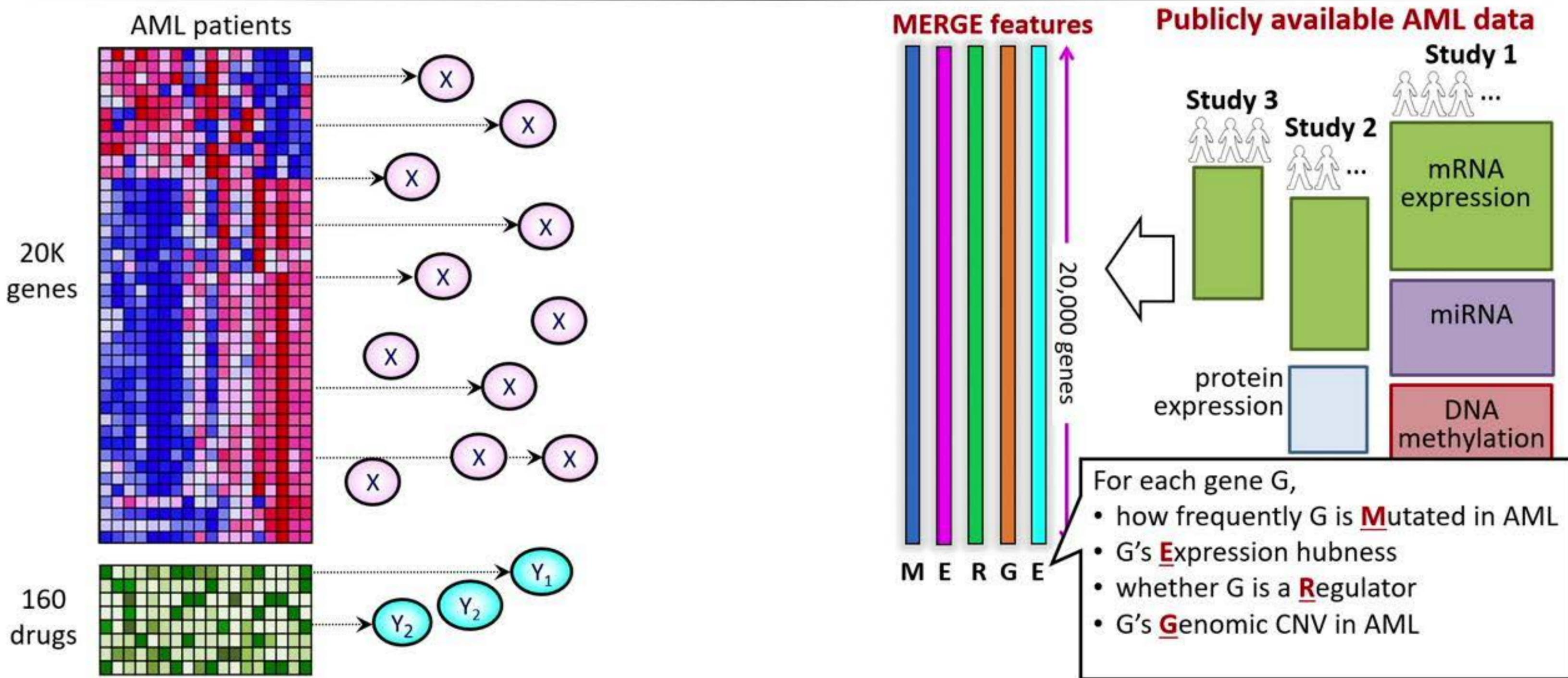
Safiye



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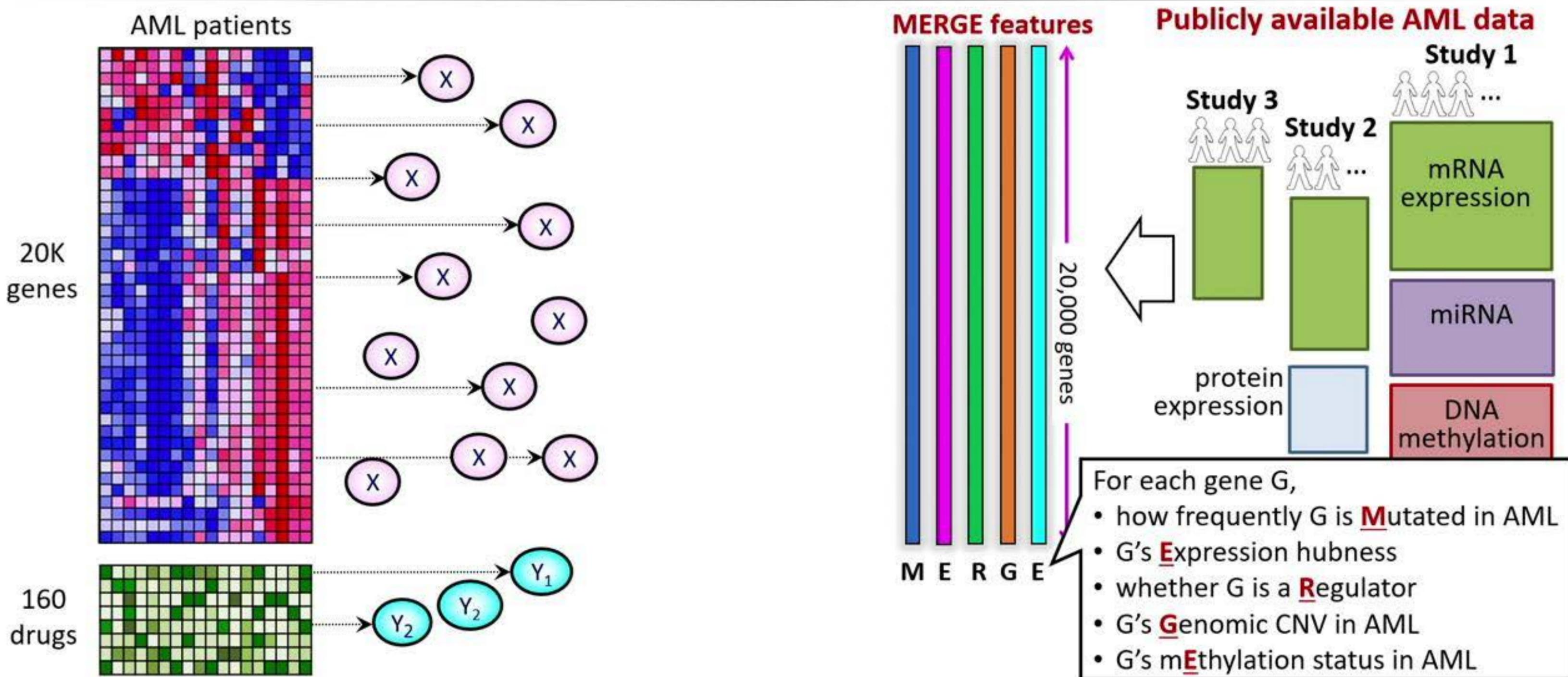
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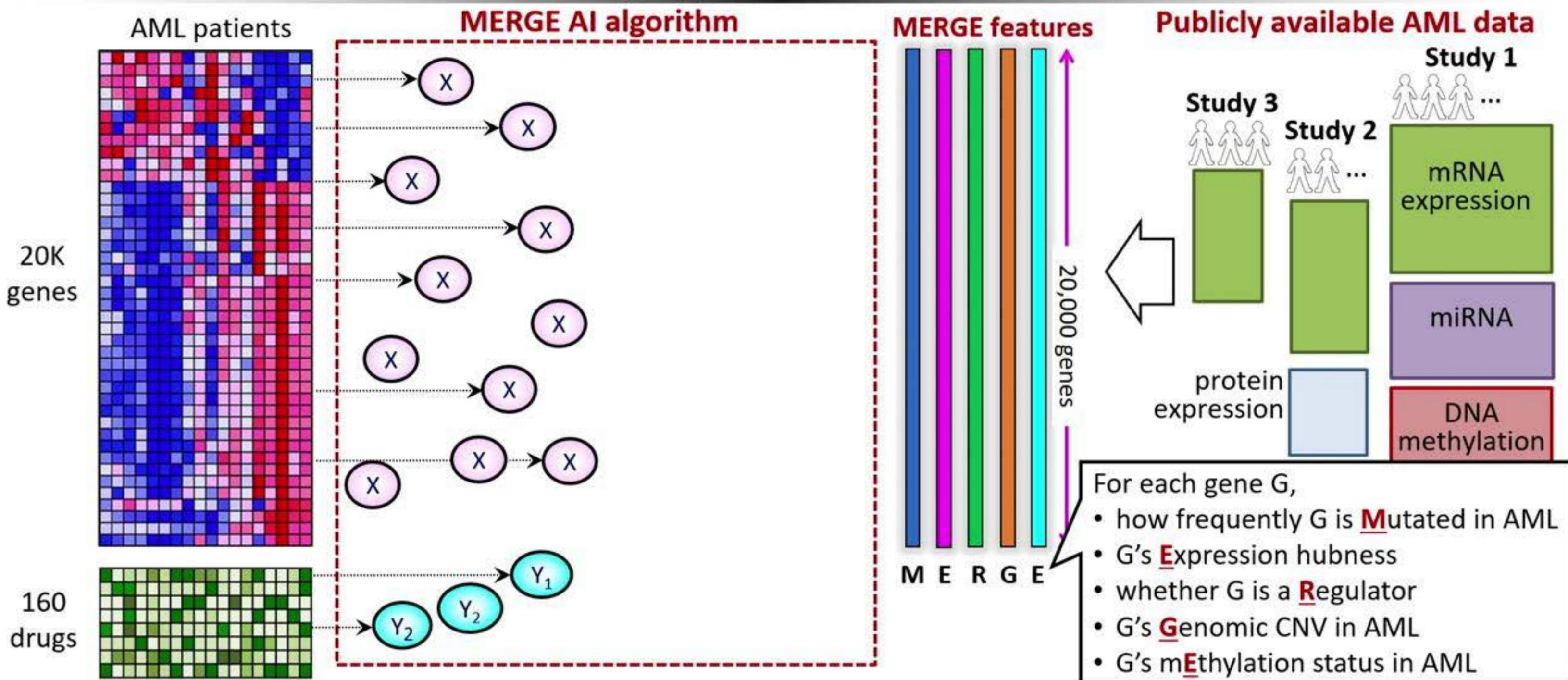
Safiye



MERGE: Machine learning approach to integrate big data to select robust expression markers



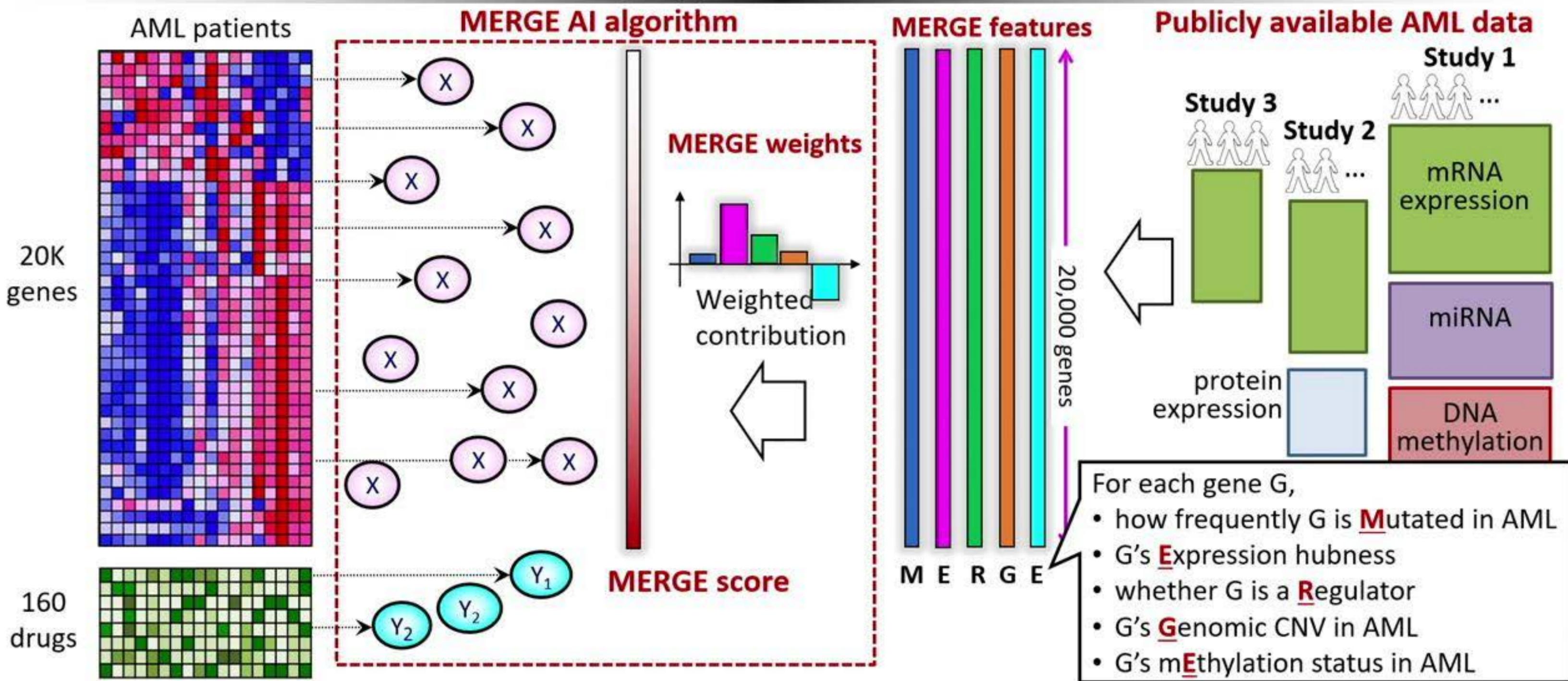
Safiye



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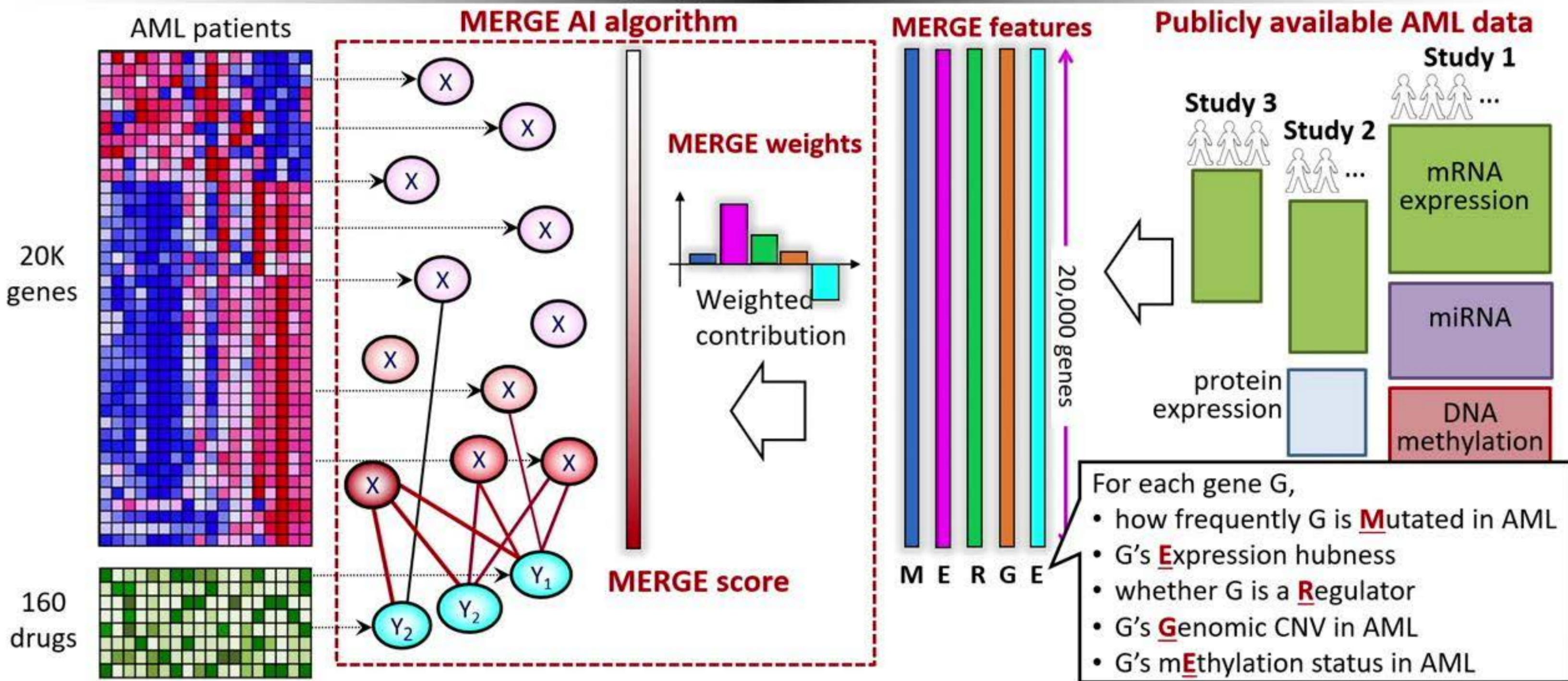
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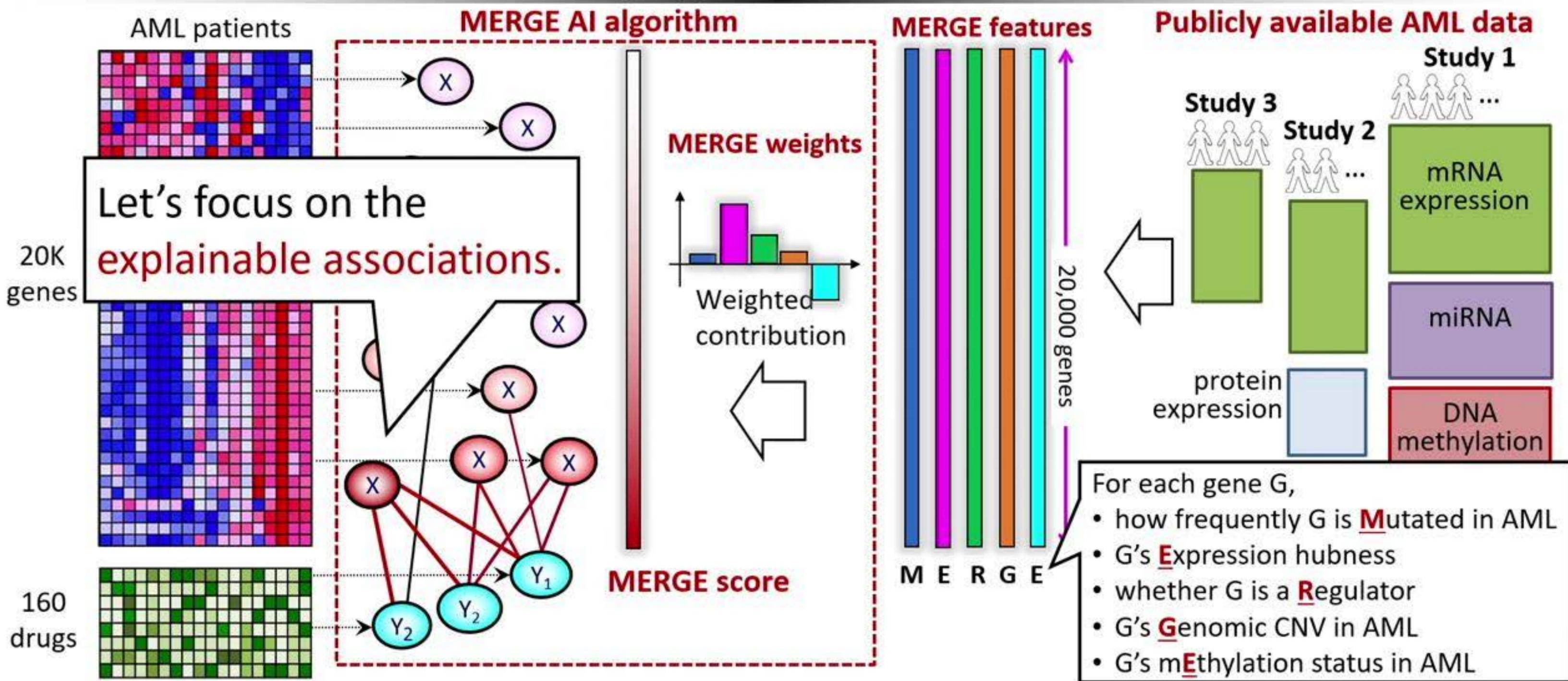
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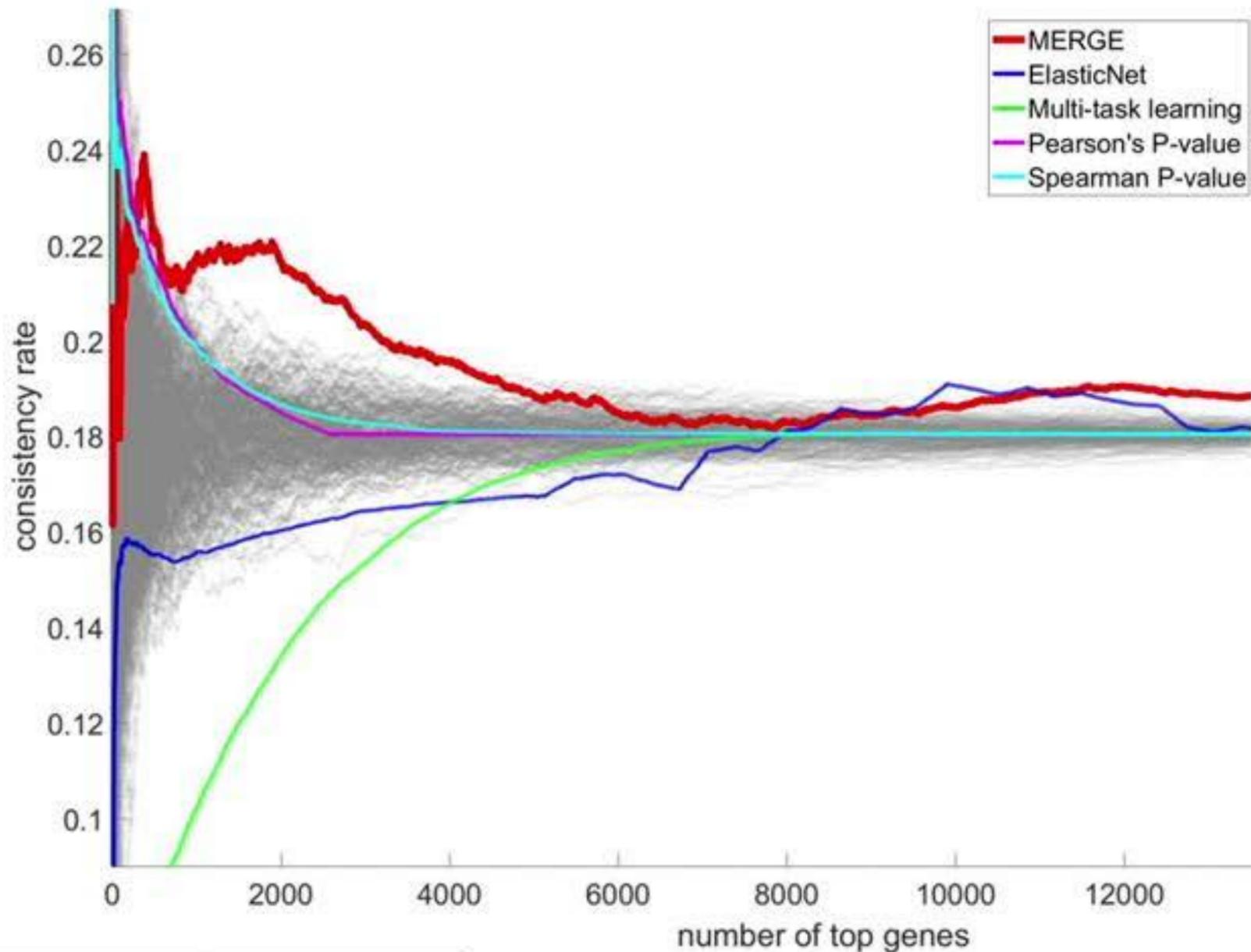
Safiye



MERGE outperforms its competitors on consistency rate and drug sensitivity prediction accuracy



Safiye

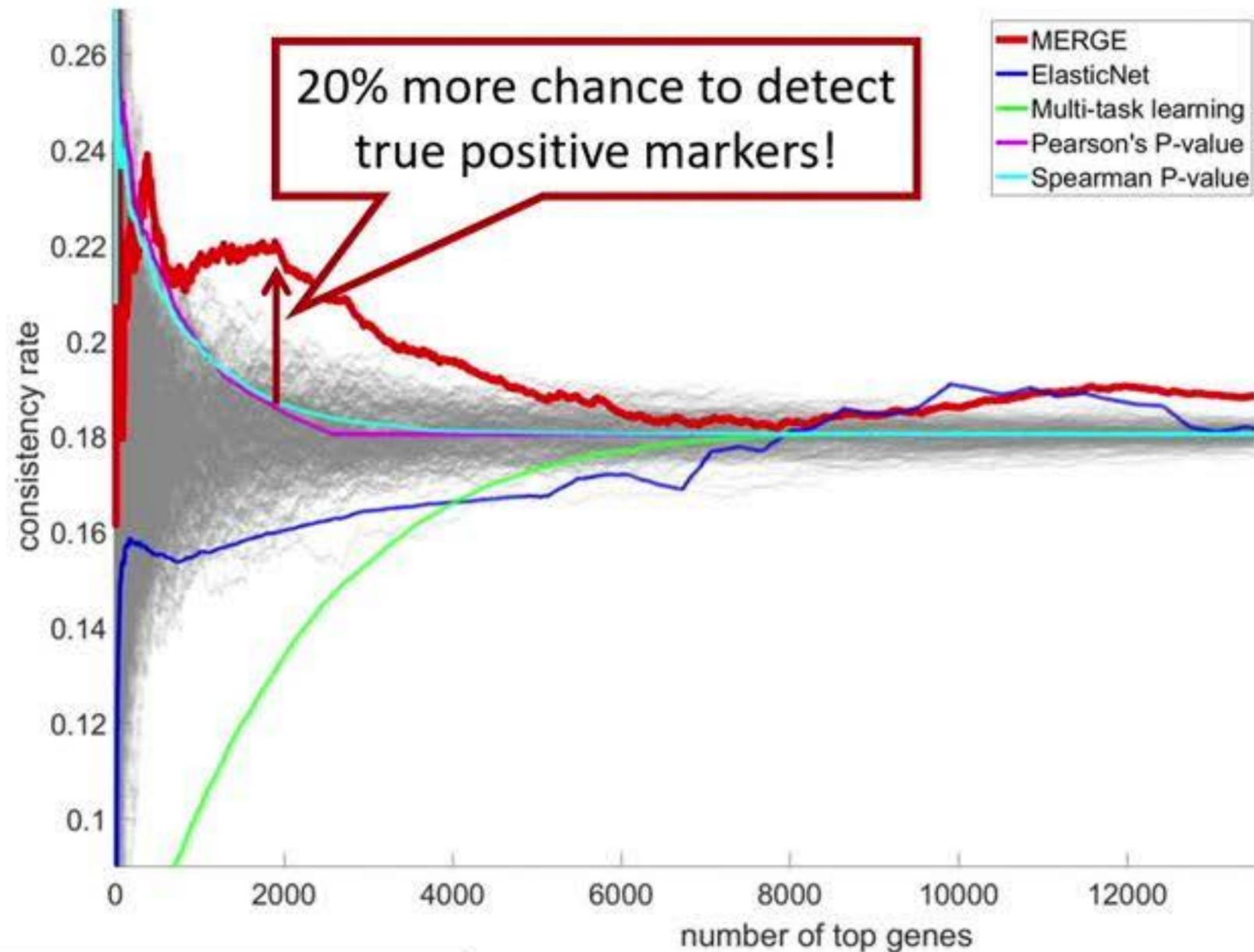


Lee*, Celik*, et al. (2018)
Nature Communications

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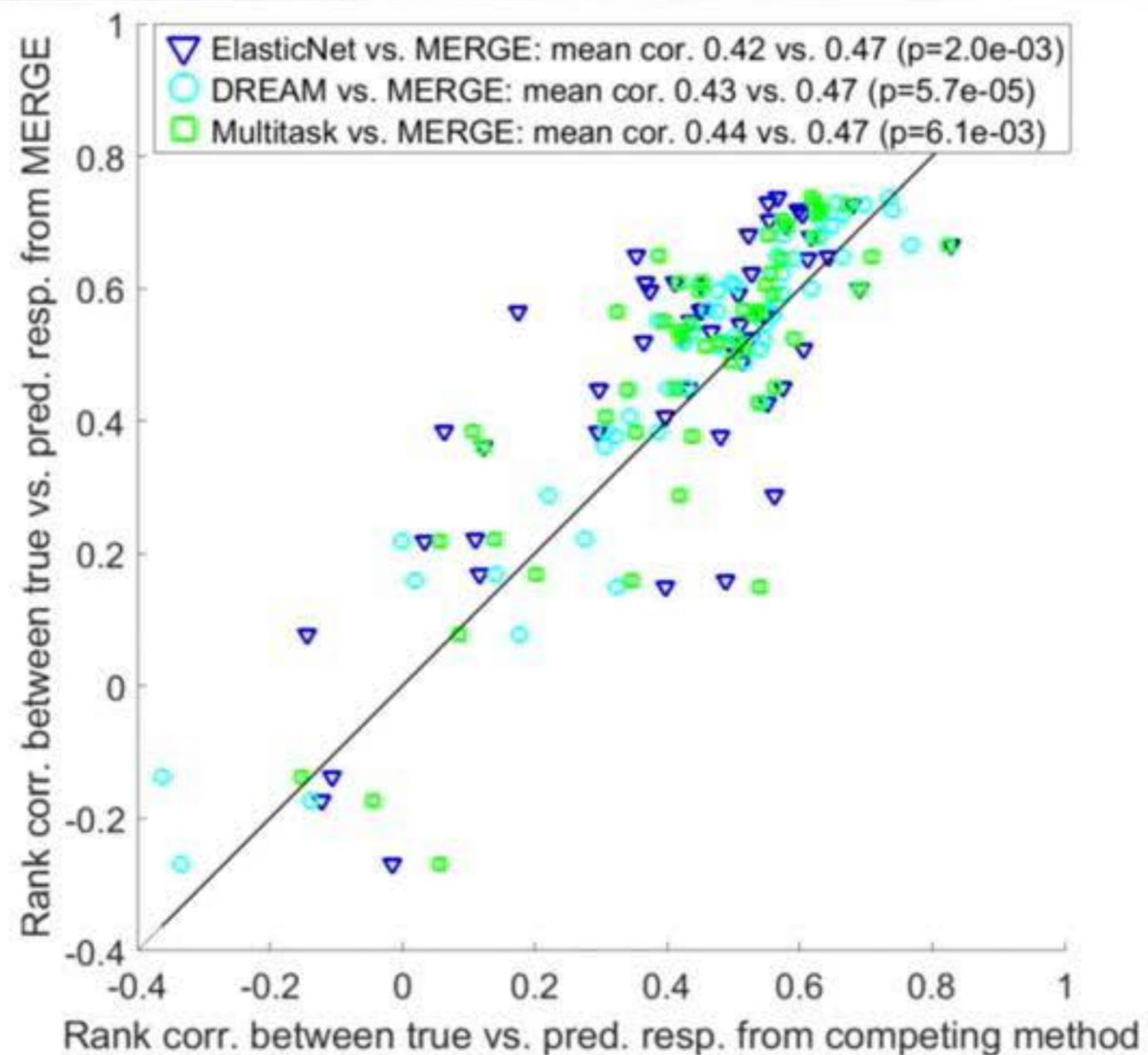
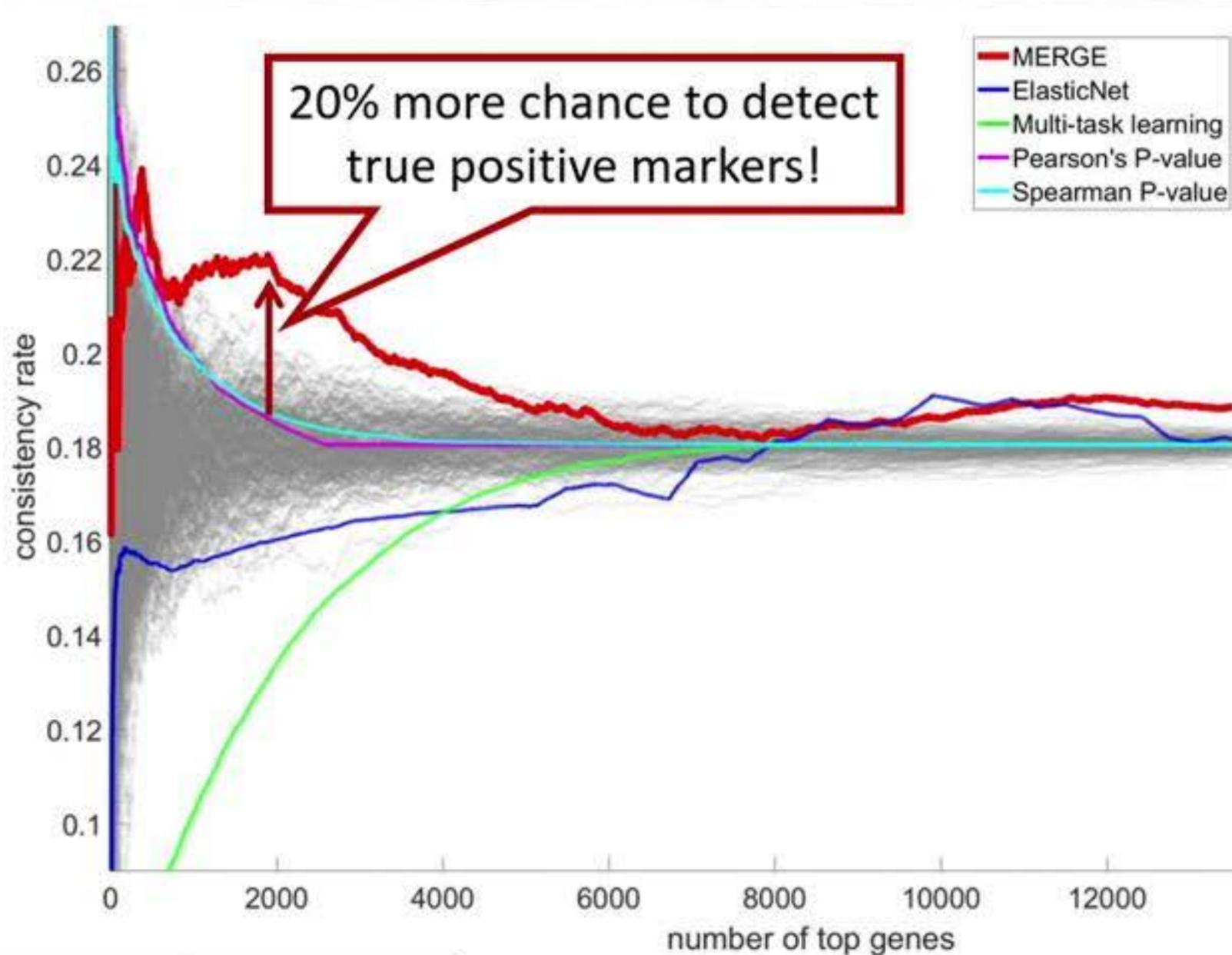


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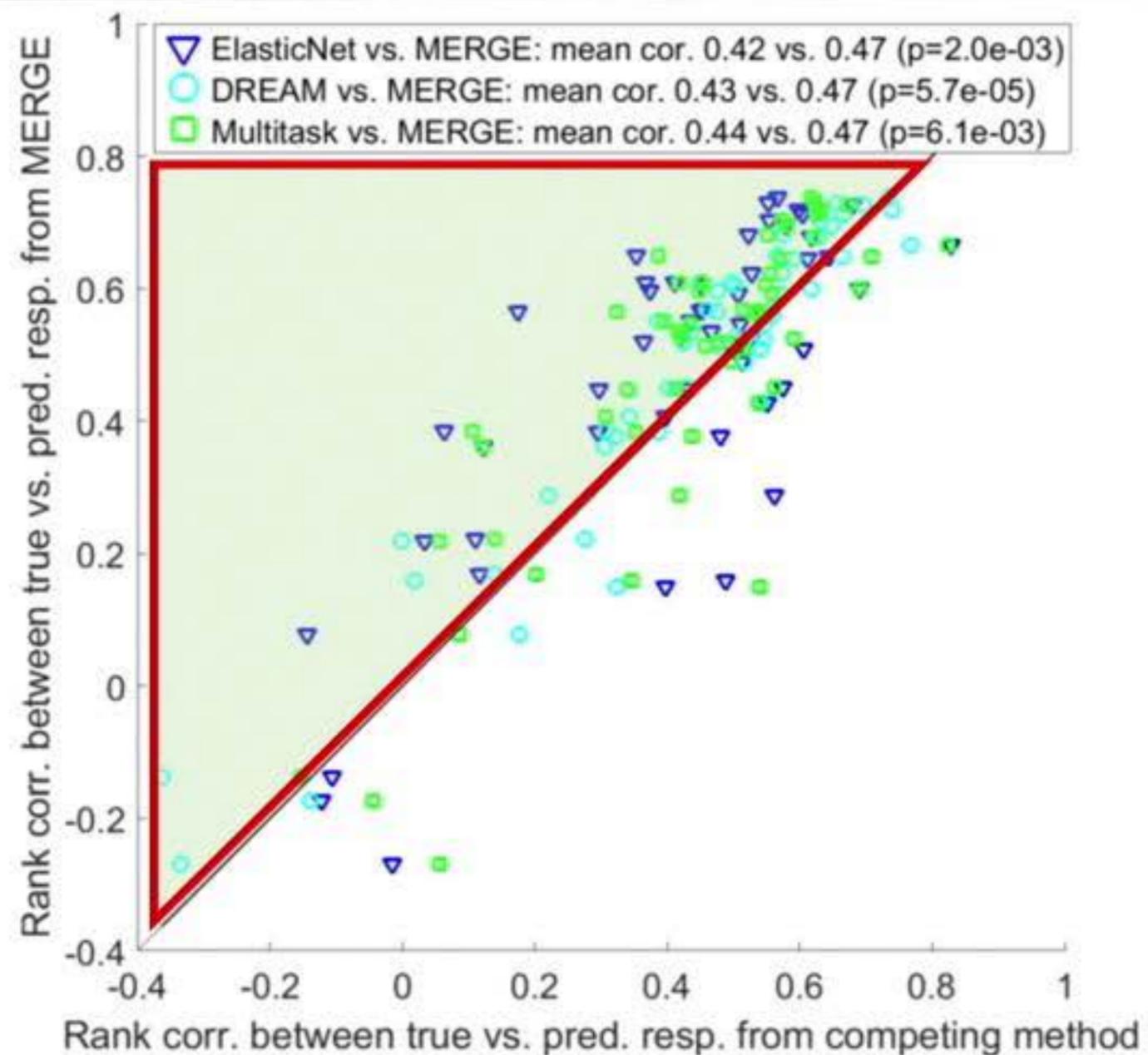
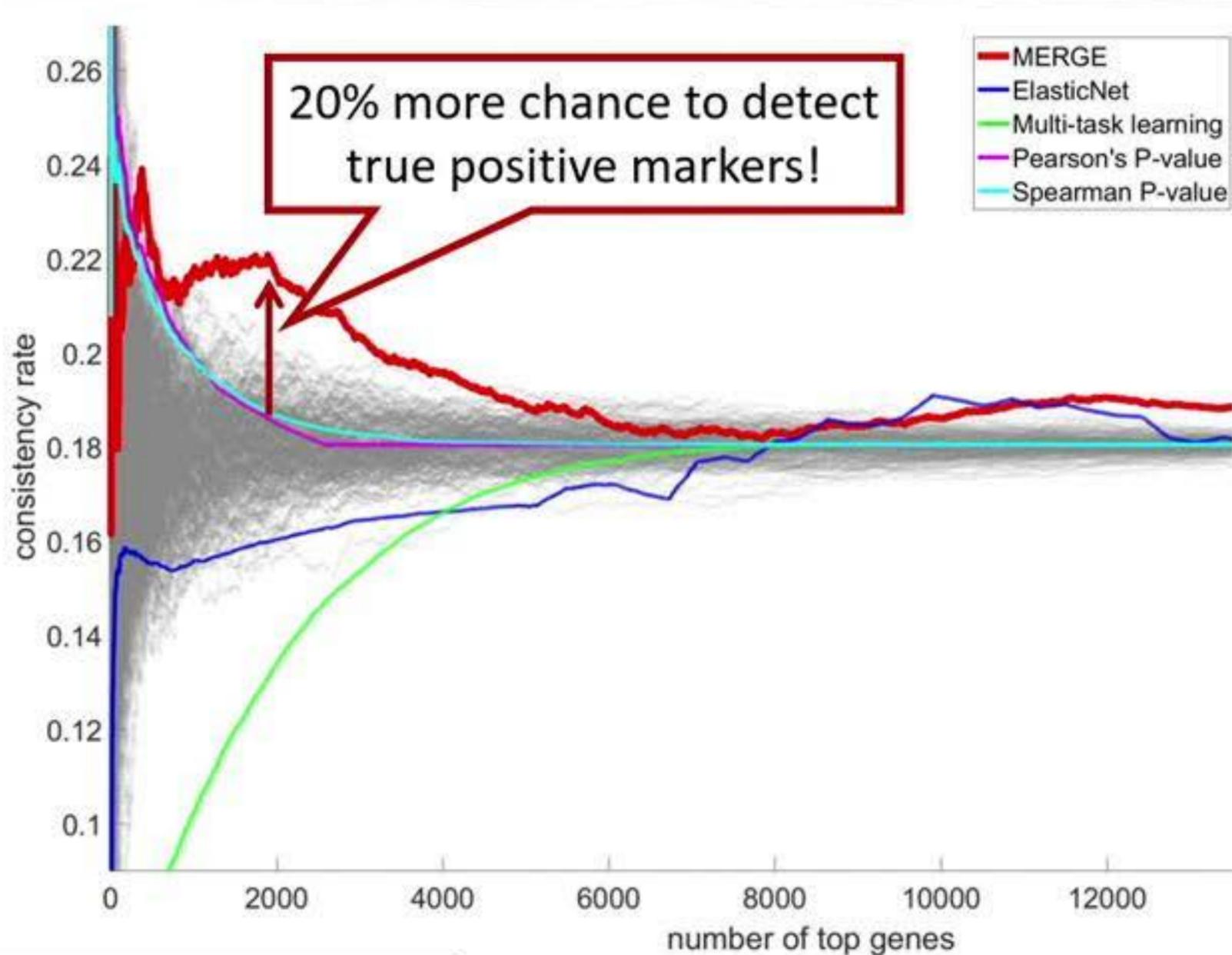


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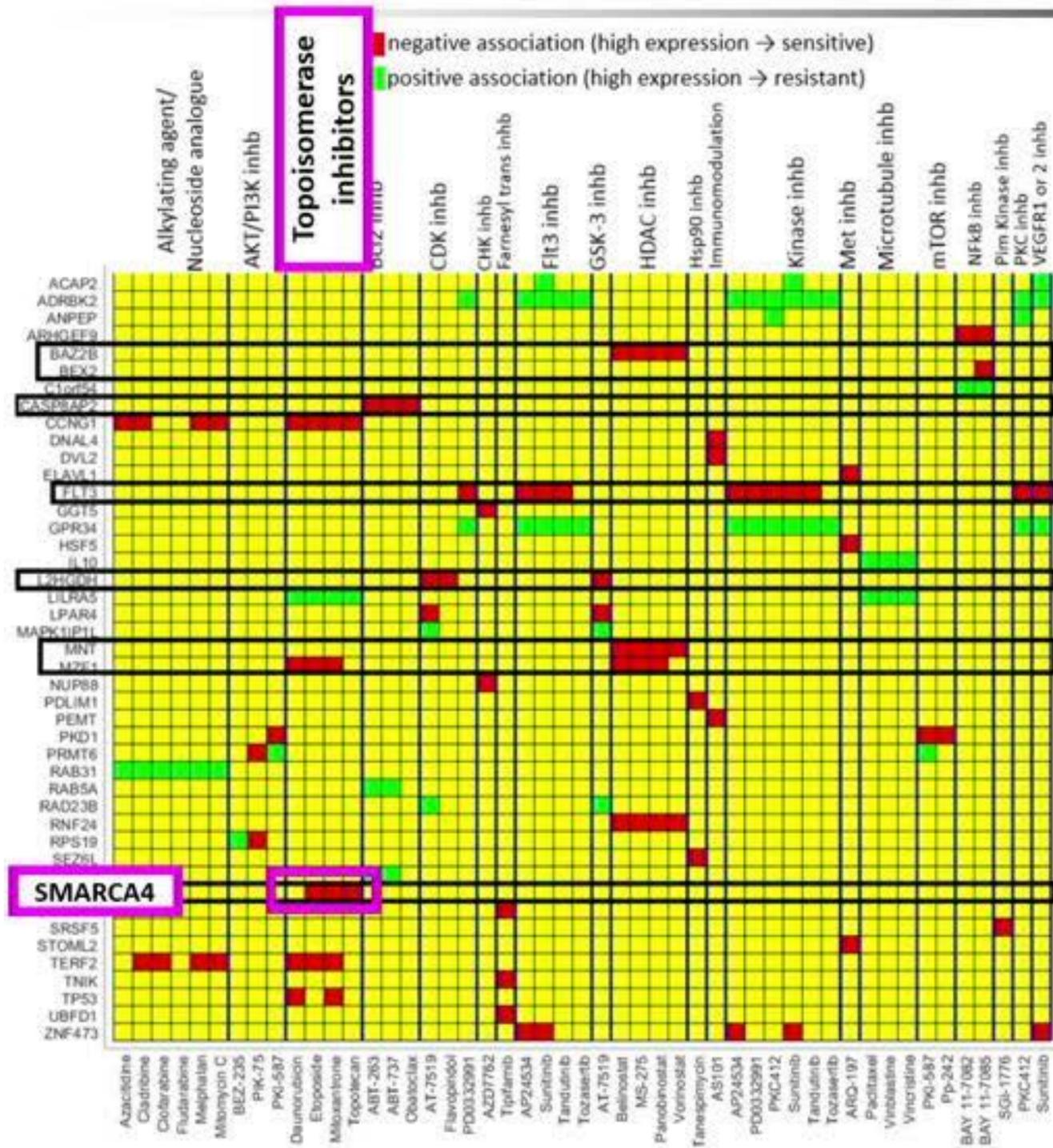
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Example novel gene-drug associations captured by the learned marker potential



Safiye

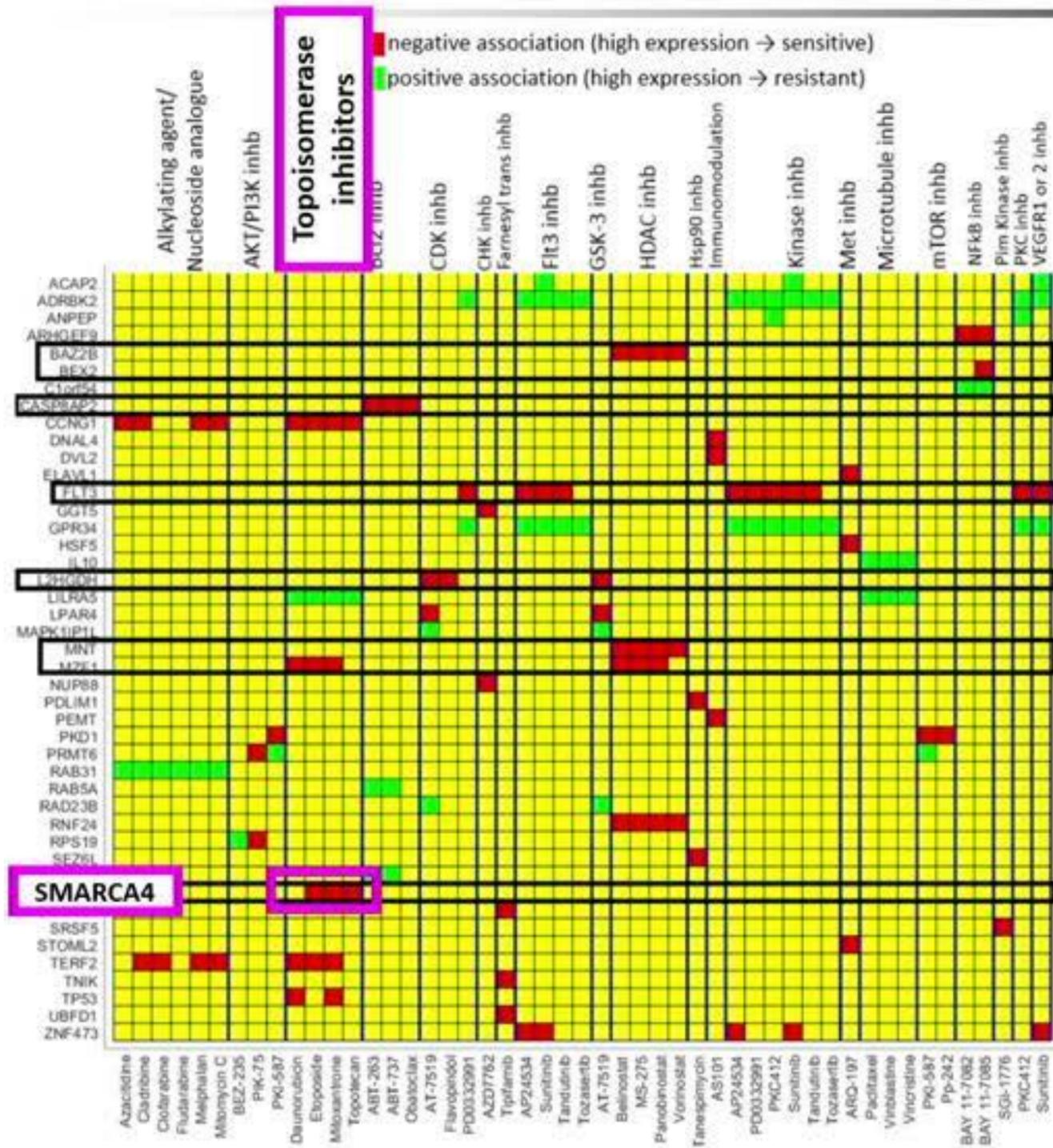
- High expression of *SMARCA4* is associated with increased sensitivity of *mitoxantrone* and *etoposide*



Example novel gene-drug associations captured by the learned marker potential



Safiye



- High expression of *SMARCA4* is associated with increased sensitivity of *mitoxantrone* and *etoposide*
- Clinical importance:**
 - Mitoxantrone – included in nearly all first line AML treatment
 - Etoposide, mitoxantrone – 2 of the 3 drugs used in the MEC regimen, a common therapy for relapsed AML
 - This finding can have immediate impact.



Hematology
 Dr. Pamela Becker

Experimental validation – SMARCA4 over-expression drives sensitivity to etoposide & mitoxantrone

Hematology
Dr. Pamela Becker





Experimental validation – SMARCA4 over-expression drives sensitivity to etoposide & mitoxantrone

- We considered an AML cell line
 - **KG-1: low** SMARCA4



Experimental validation – SMARCA4 over-expression drives sensitivity to etoposide & mitoxantrone

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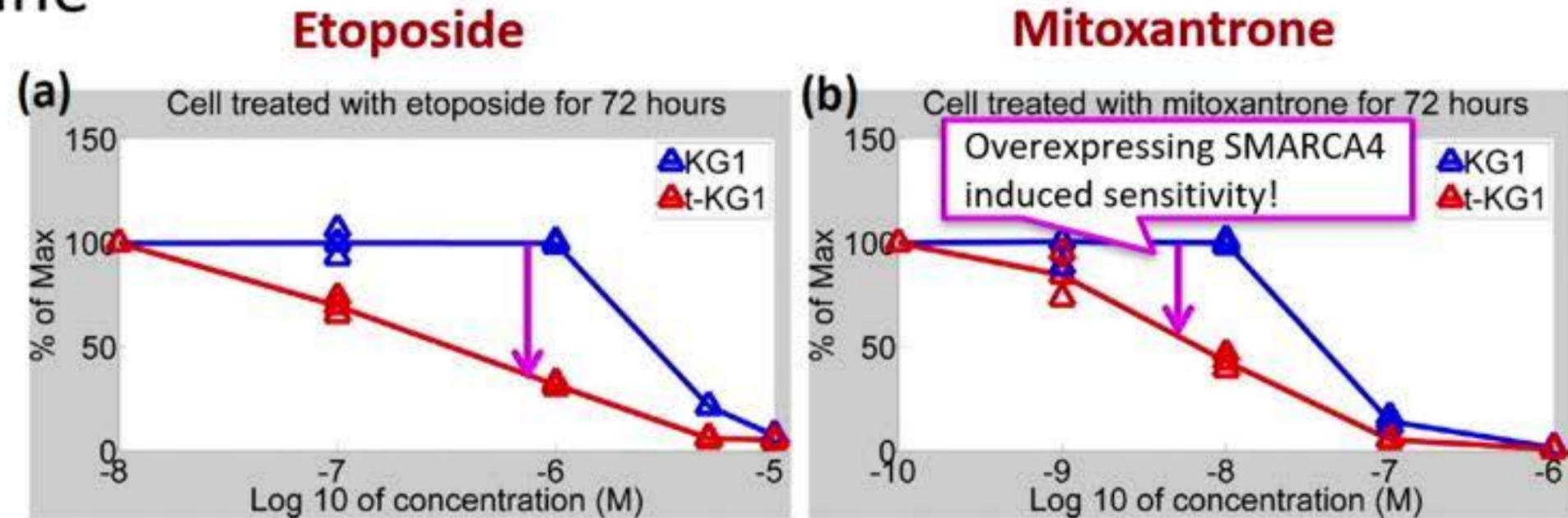
Etoposide

Mitoxantrone



Experimental validation – SMARCA4 over-expression drives sensitivity to etoposide & mitoxantrone

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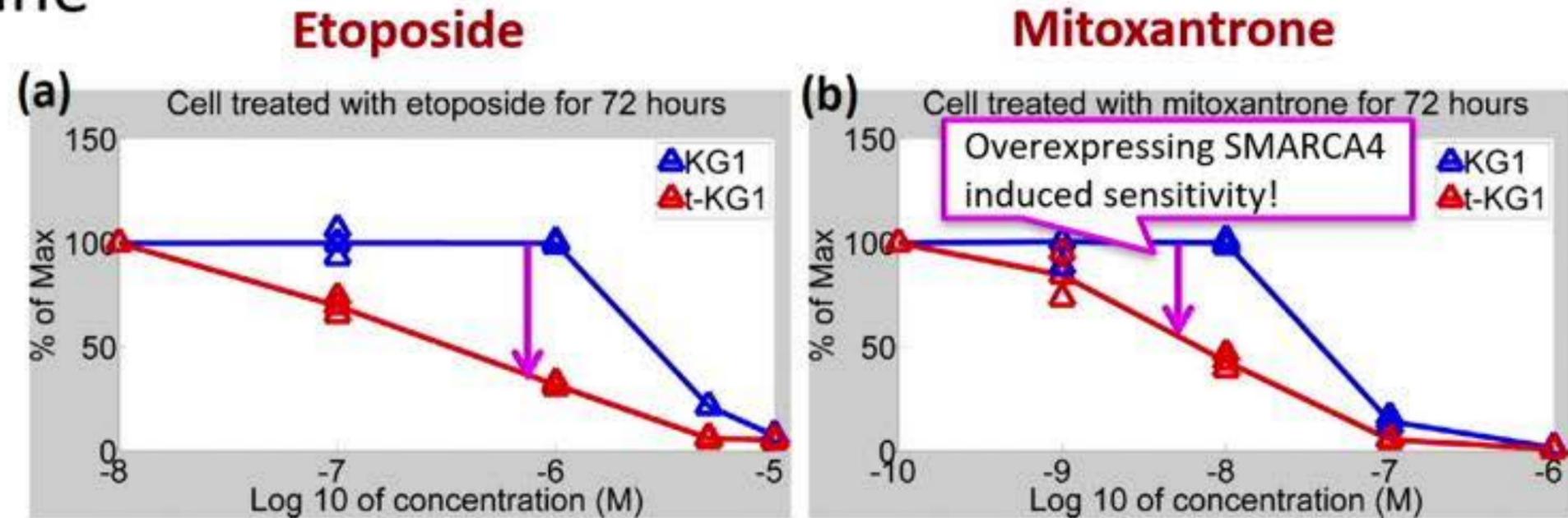




Experimental validation – SMARCA4 over-expression drives sensitivity to etoposide & mitoxantrone

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 - **Transfected KG-1: high**

- Another AML cell line
 - **U937: high** SMARCA4

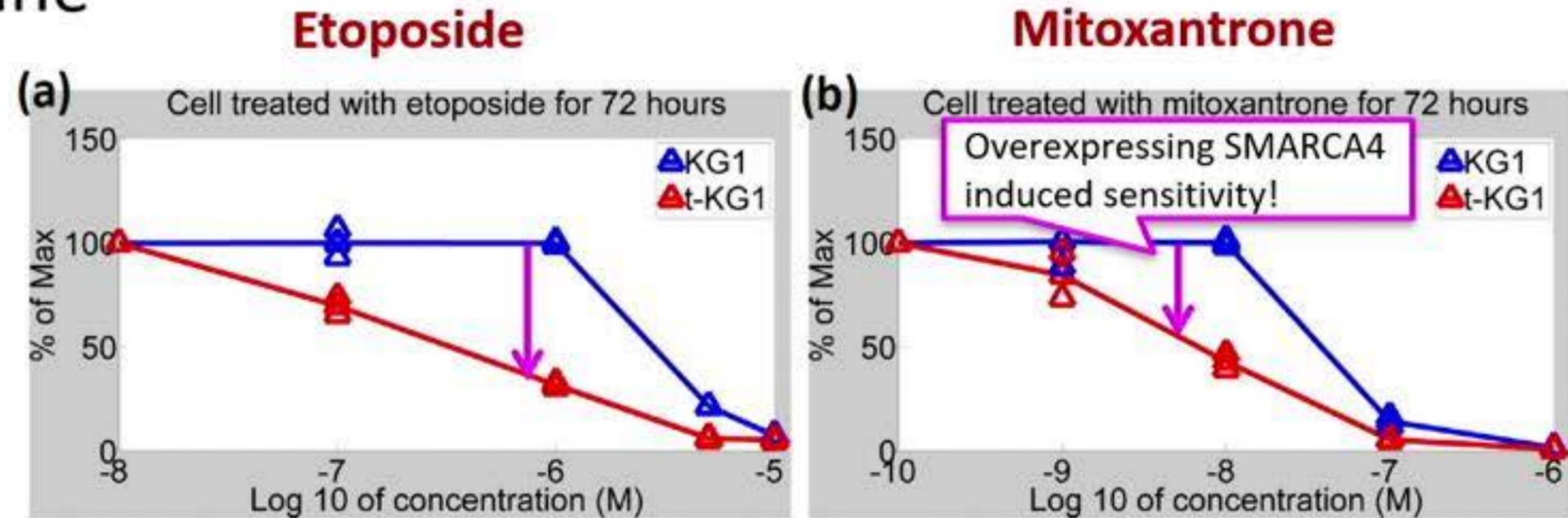




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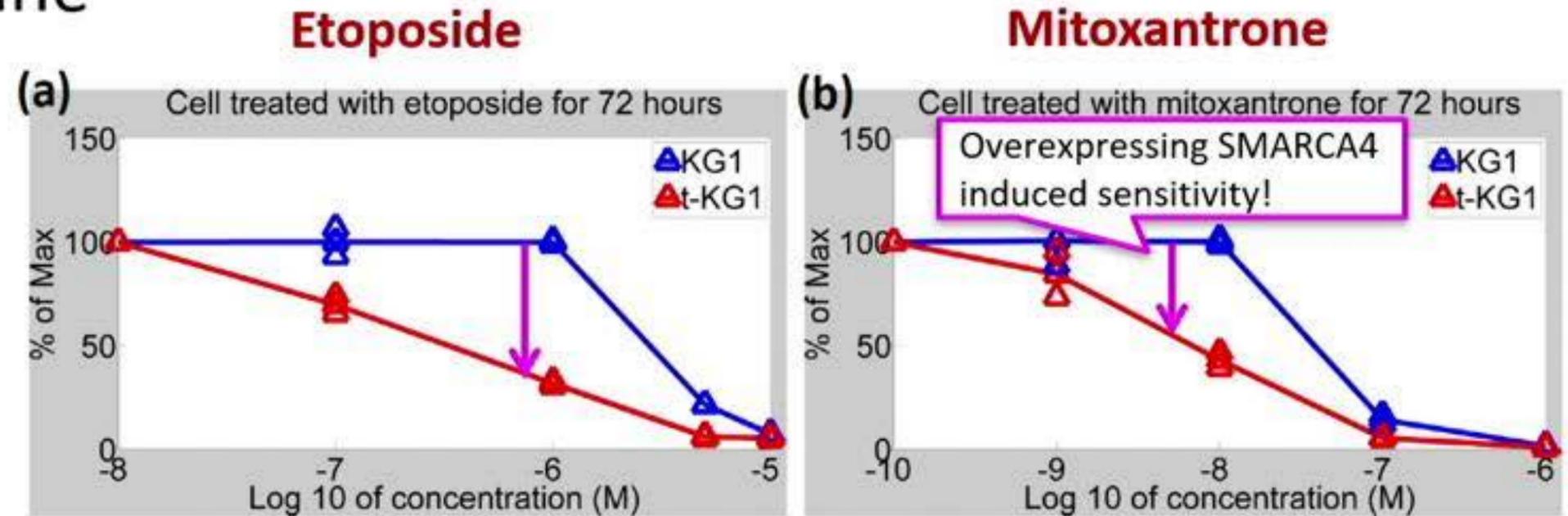
- Another AML cell line
 - **U937: high** SMARCA4
 - **Transfected U937: high**



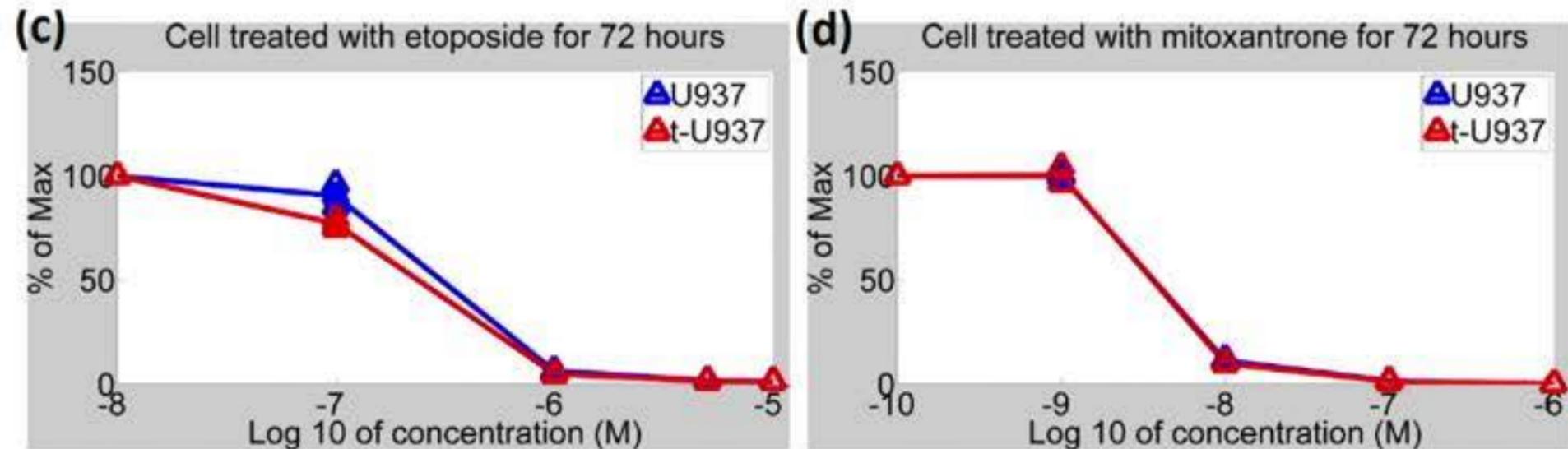


Experimental validation – SMARCA4 over-expression drives sensitivity to etoposide & mitoxantrone

- We considered an AML cell line
 - **KG-1: low** SMARCA4
 - **Transfected KG-1: high**



- Another AML cell line
 - **U937: high** SMARCA4
 - **Transfected U937: high**



Interpretable ML can transform important areas of medicine

Prediction & decision support systems in hospitals

- Make interpretable predictions from complex models.

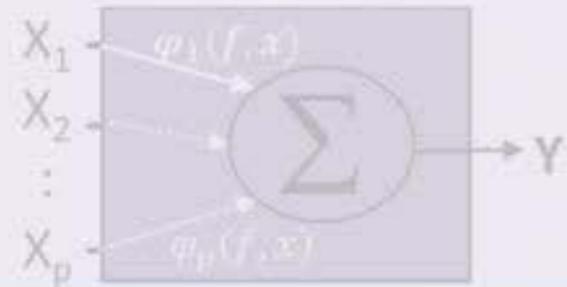
Cancer precision medicine

- Learn interpretable feature representations.

Alzheimer's disease therapeutic target discovery

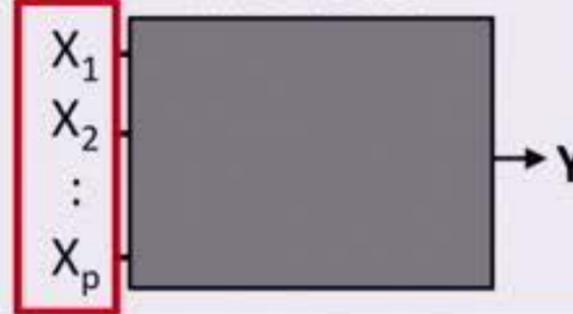
- Integrate data sets for statistical power and interpretability.

Black Box

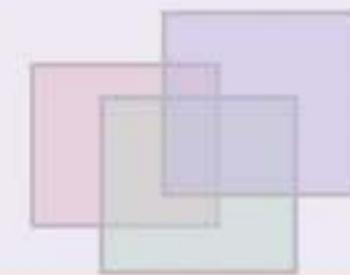


General ML techniques

ML model



Data integration



Bedside applications



Basic science



Interpretable ML can transform important areas of medicine

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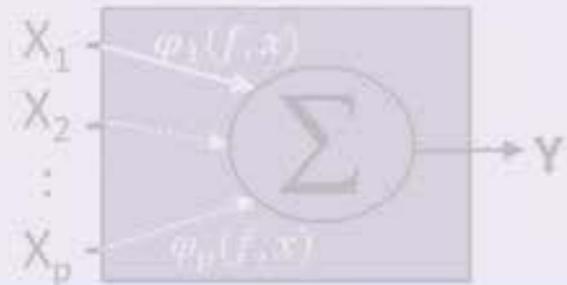
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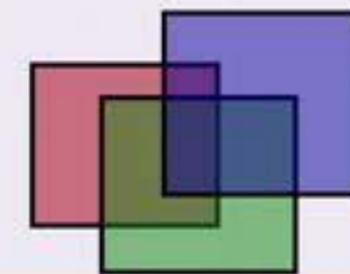


General ML techniques

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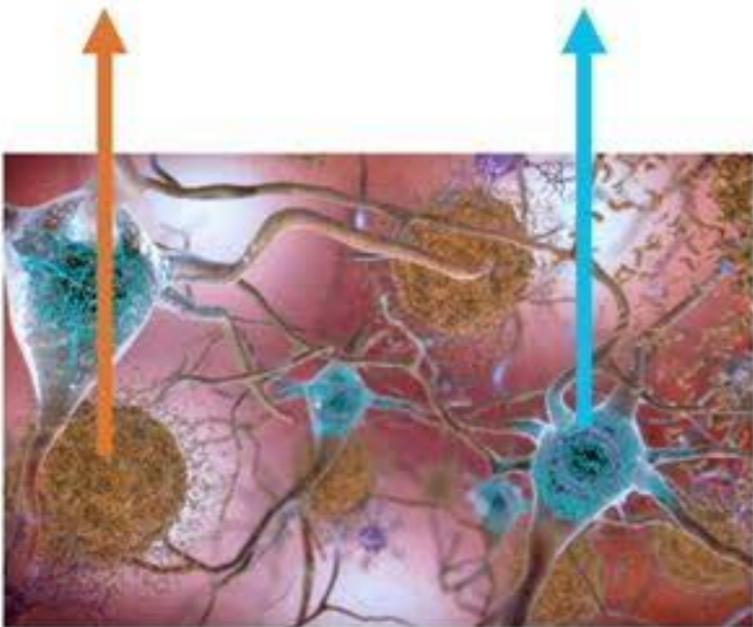


Alzheimer's disease (AD)

- 6th most common cause of death in the US
- No effective therapy exists to delay or prevent onset of progression
- Only disease that cannot be cured or even slowed down among the top 10 deadly diseases in the US

Alzheimer's disease (AD)

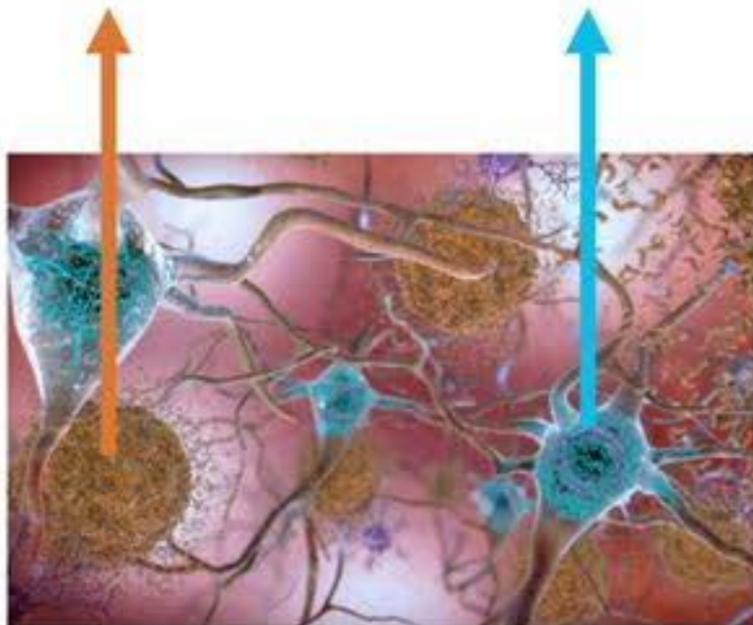
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Alzheimer's disease (AD)

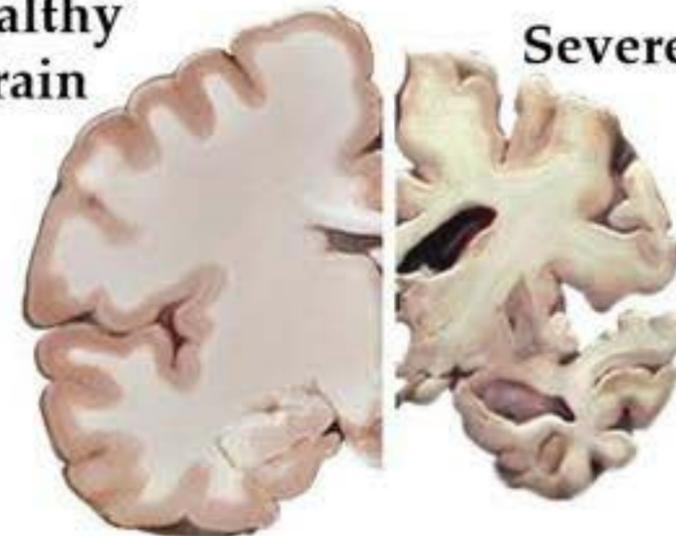
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Amyloid- β
(A β)



Tau

Healthy
brain



Severe AD

What do we need to identify the molecular basis of A β or tau level?

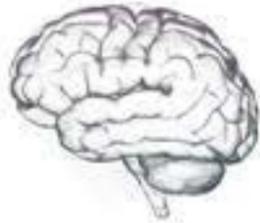
INPUT



- We need expression and phenotype data.

What do we need to identify the molecular basis of A β or tau level?

INPUT



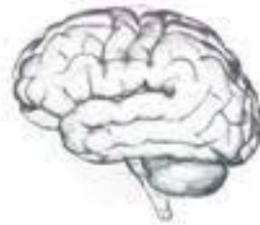
brain

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What do we need to identify the molecular basis of $A\beta$ or tau level?

INPUT

Phenotype
($A\beta$ level) ■



brain

- We need expression and phenotype data.

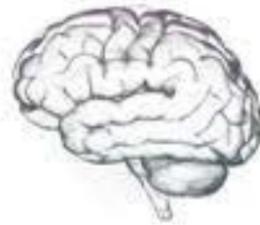
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Gene
expression
levels



brain

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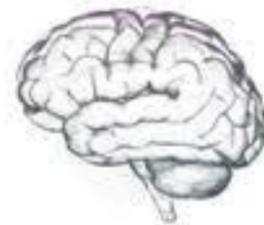
Phenotype
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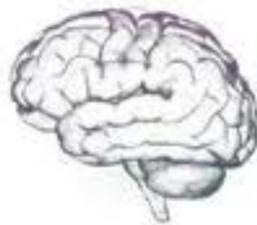
Gene
expression
levels



Samples



brain

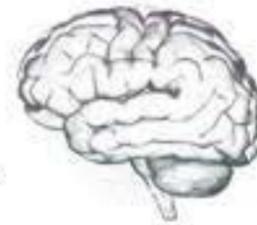


brain



brain

...



brain

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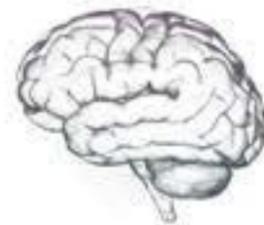
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Phenotype
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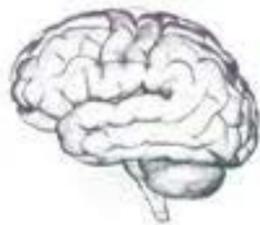


Gene
expression
levels

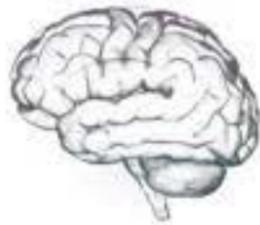
Samples



brain

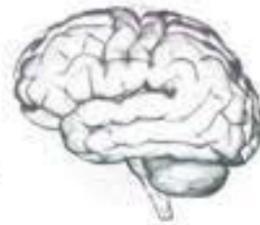


brain



brain

...



brain

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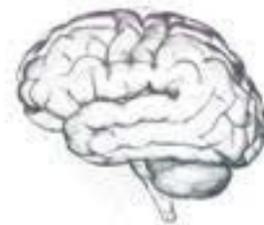
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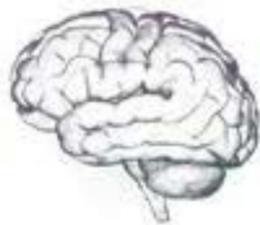
Gene
expression
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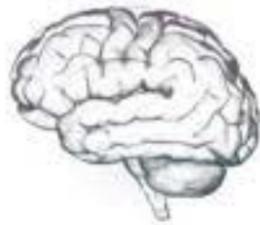
Samples



brain

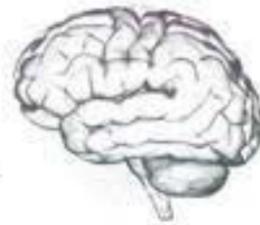


brain



brain

...



brain

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 - Statistical association between the phenotype and each gene expression level

What do we need to identify the molecular basis of A β or tau level?

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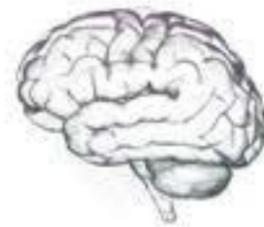
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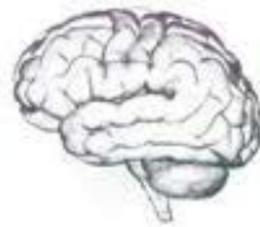
Gene
expression
levels



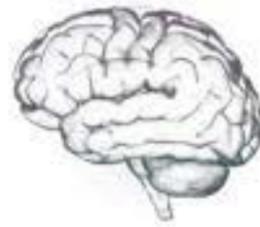
Samples



brain

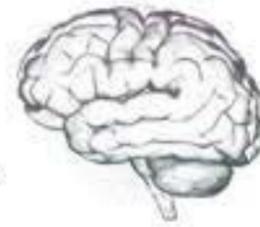


brain



brain

...



brain

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AD expression data is limited and discrepancies across studies post challenges



Safiye

Neuropathology
Internal Medicine
AD Research Center



Dirk Keene



Paul Crane



Joey Mukherjee

AD expression data is limited and discrepancies across studies post challenges



Safiye

- Expression and neuropathology measured in **1,742 samples from 9 brain regions.**

Region acronym	Brain region	Sample size
ACT-TCx	Temporal cortex	85
ACT-PCx	Parietal cortex	79
ACT-HIP	Hippocampus	80
ACT-FWM	Forebrain white matter	81
ROSMAP-DPFCx	Dorsolateral prefrontal cortex	538
MSBB-BM10	Brodmann area 10 (frontopolar cortex)	244
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- Different brain regions have different cell type compositions, functions, and relevance to AD.

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- Different tools and methods are used to quantify neuropathology

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- Different subject compositions or experimental procedures (batch effects, and confounders)

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- Different brain regions have different cell type compositions, functions, and relevance to AD.
- Different tools and methods are used to quantify neuropathology
- Different subject compositions or experimental procedures (batch effects, and confounders)
- We need a powerful ML algorithm that can incorporate reliable prior knowledge to help us focus on true signals.**

Neuropathology
Internal Medicine
AD Research Center



Dirk Keene



Paul Crane



Joey Mukherjee

EMBARKER (EMpowering Big data with prior Knowledge for Expression marker discovery)



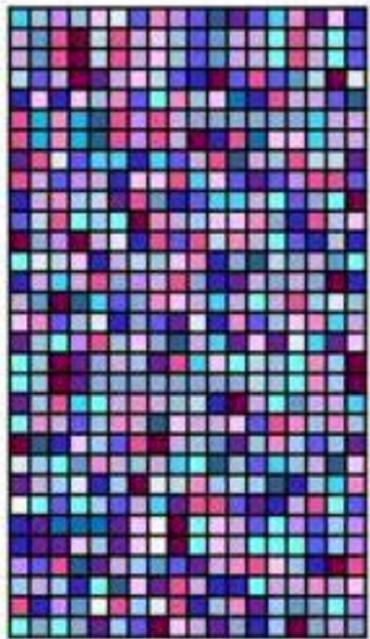
Safiye

INPUT

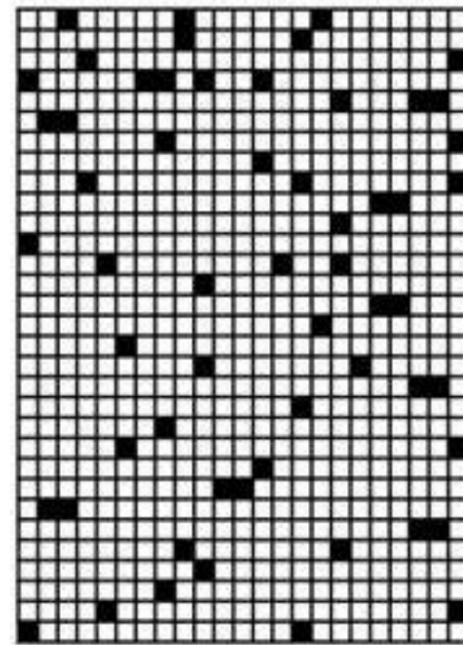
Phenotype
(A β level)



Gene
expression
levels



Samples



Pathways

674 REACTOME pathways from
the current version of MSigDB C2

EMBARKER (EMpowering Big data with prior Knowledge for Expression marker discovery)



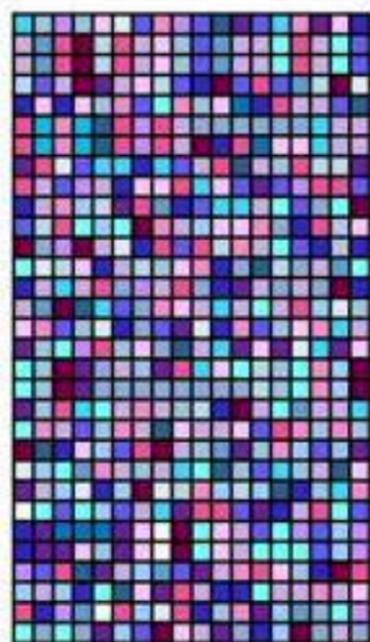
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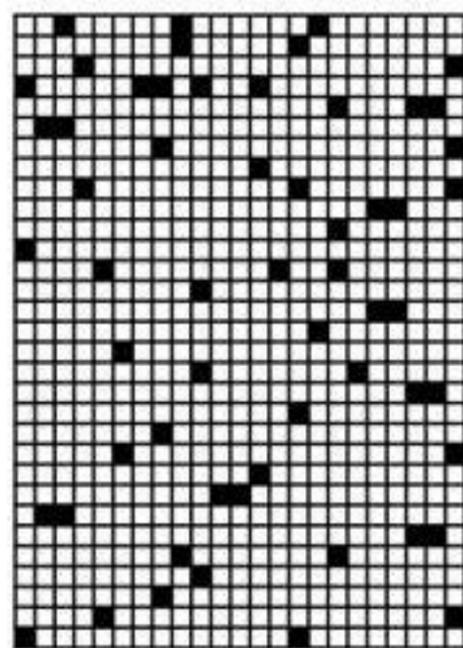
Phenotype
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Gene
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Samples



Pathways

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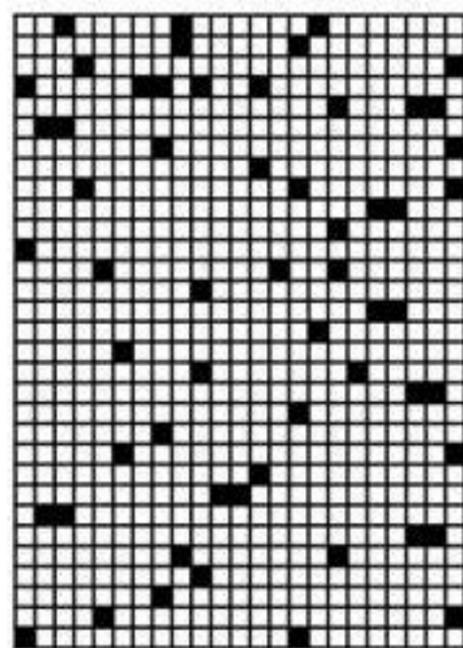
Phenotype
($A\beta$ level)



Gene
expression
levels



Samples



Pathways

EMBARKER

$$\alpha = (1 - \gamma)C + \gamma A\beta$$

$$\beta_p = \frac{\sum_i (A_{ip} \alpha_i)}{\sum_i A_{ip}}$$

OUTPUT

α
(gene weights)



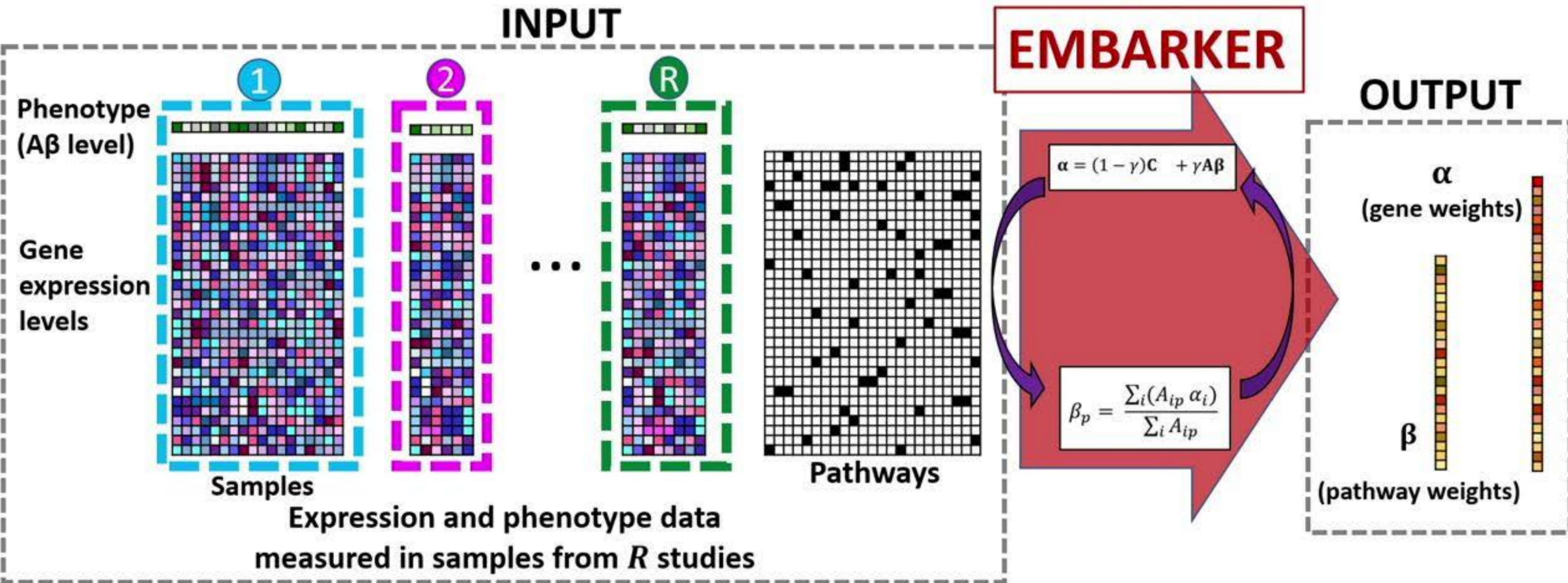
β

(pathway weights)

EMBARKER (EMpowering Big data with prior Knowledge for Expression marker discovery)



Safiye

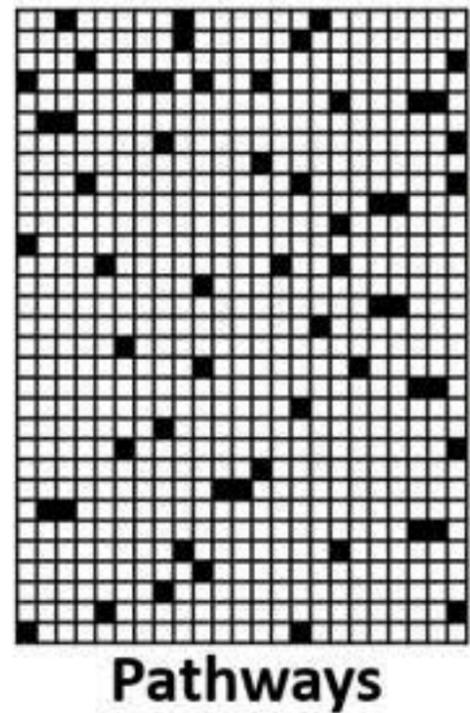
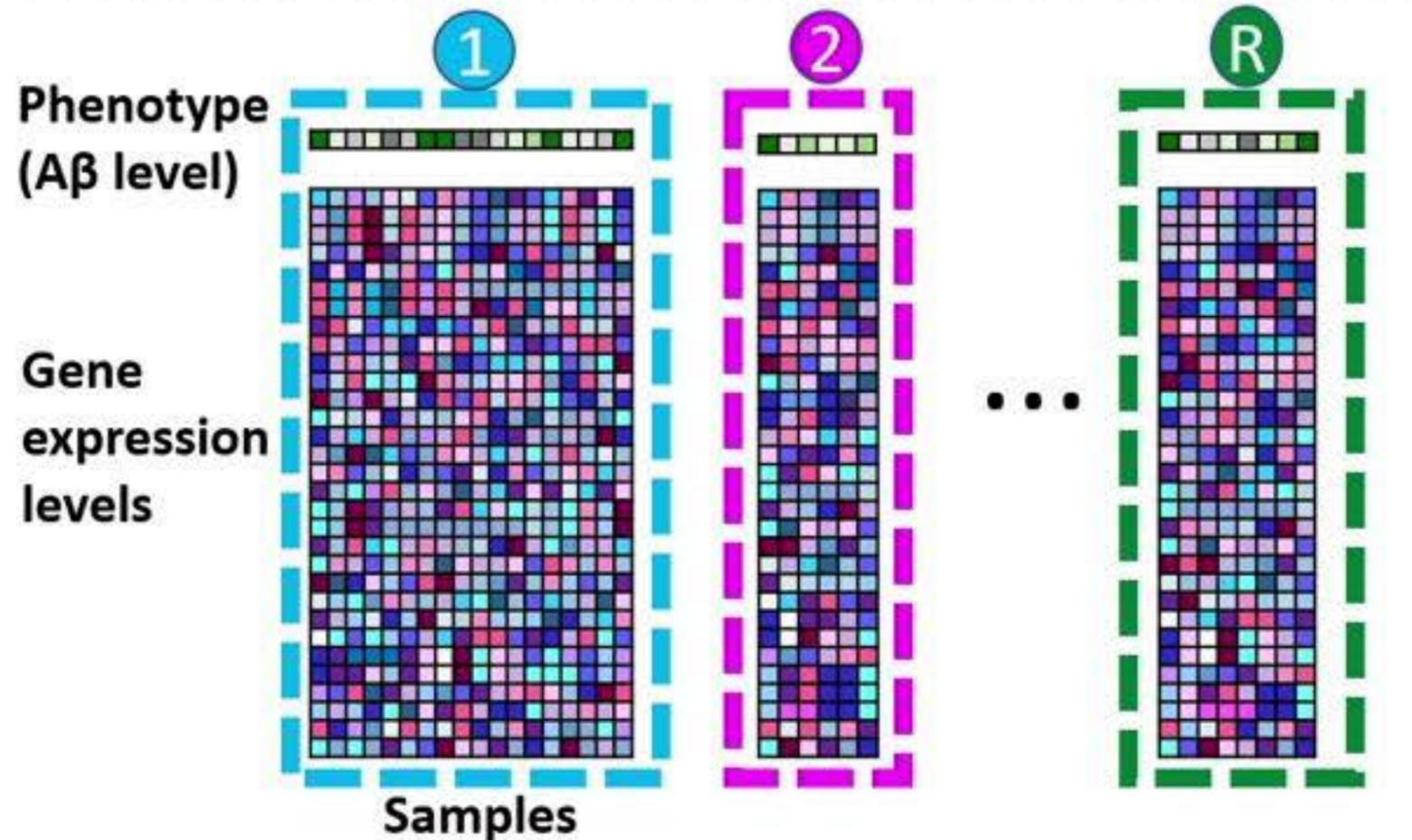


EMBARKER (EMpowering Big data with prior Knowledge for Expression marker discovery)

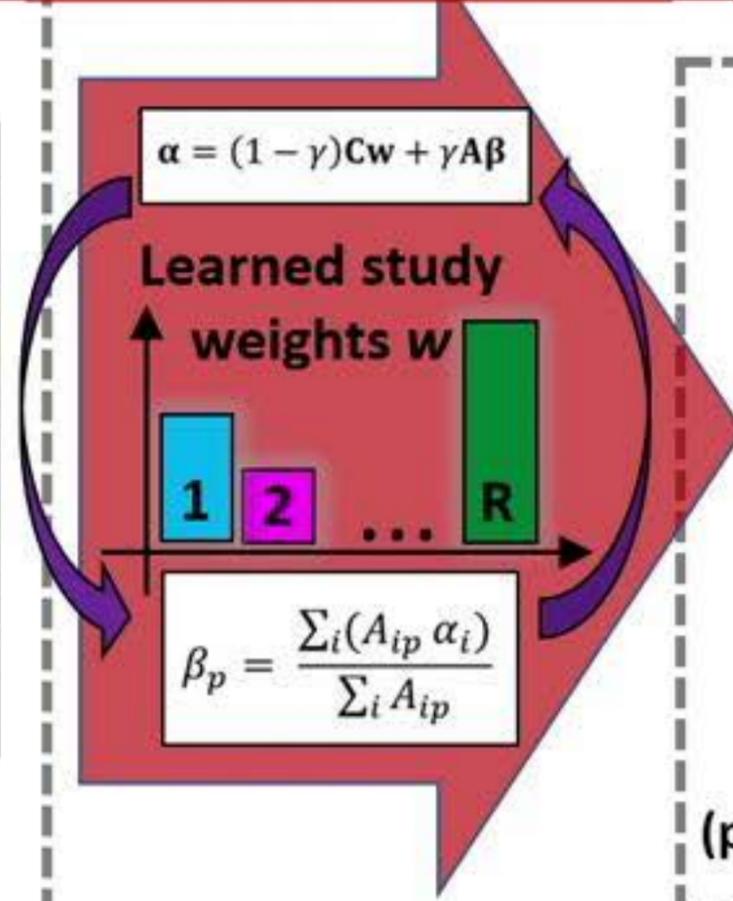


Safiye

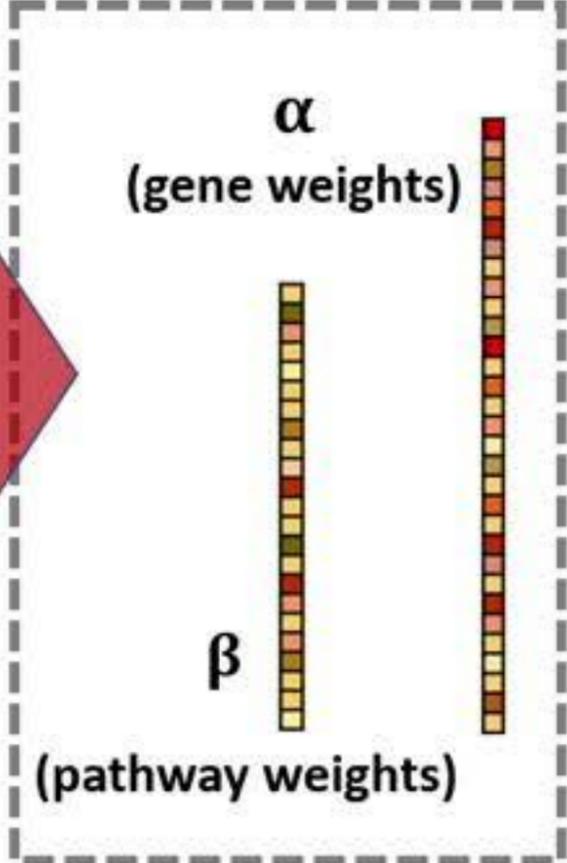
INPUT



EMBARKER-M



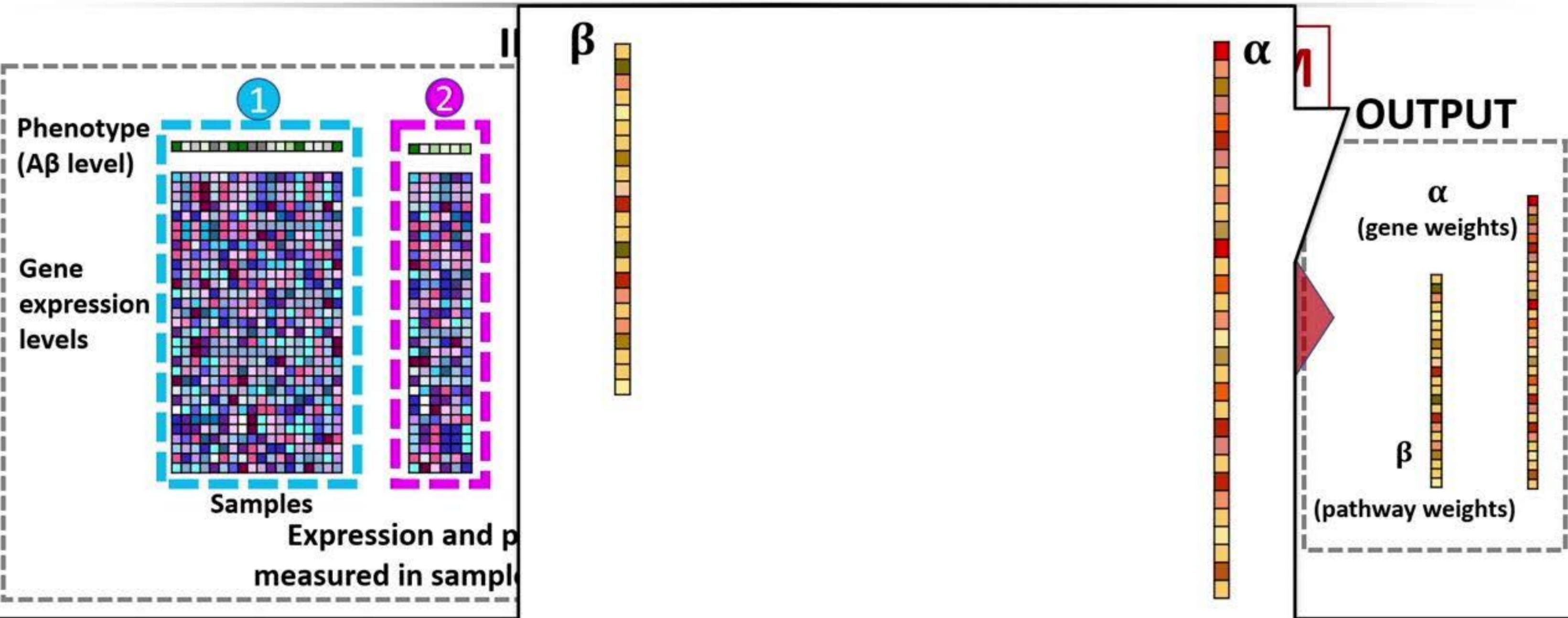
OUTPUT



EMBARKER (EMpowering Big data with prior Knowledge for Expression marker discovery)



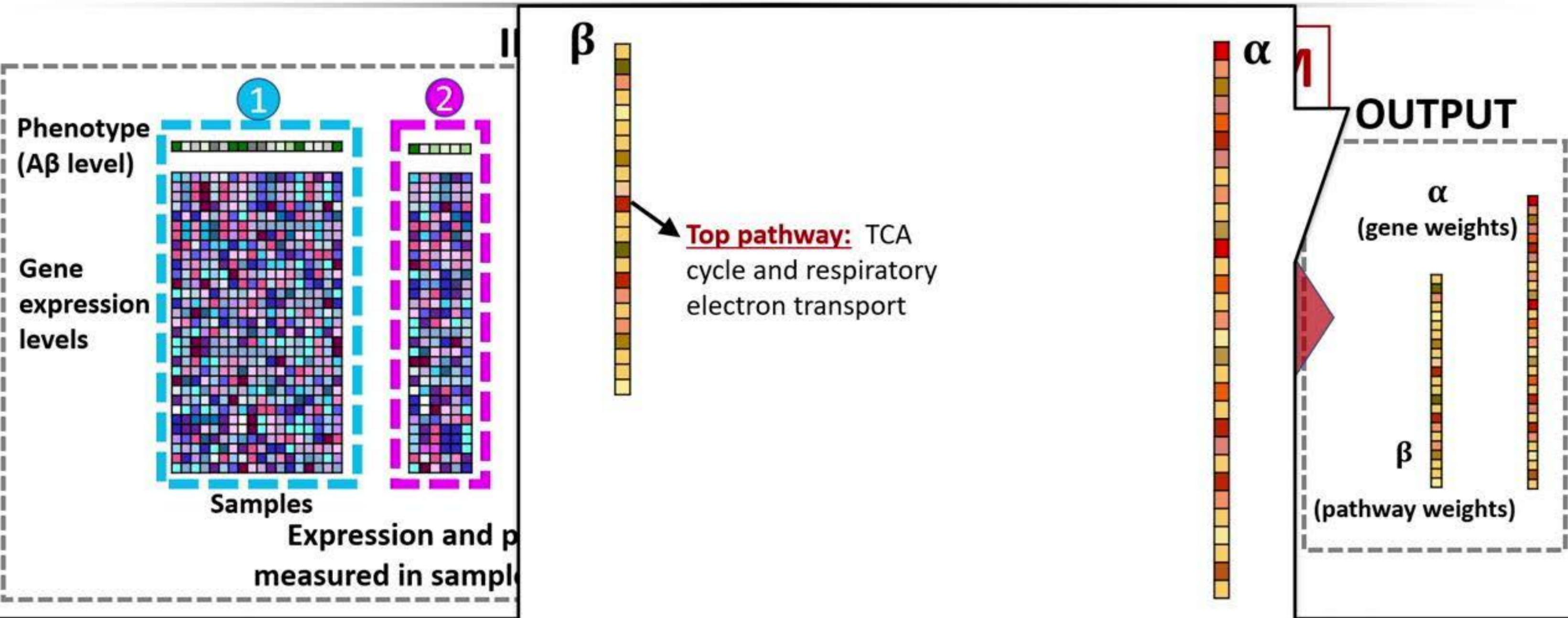
Safiye



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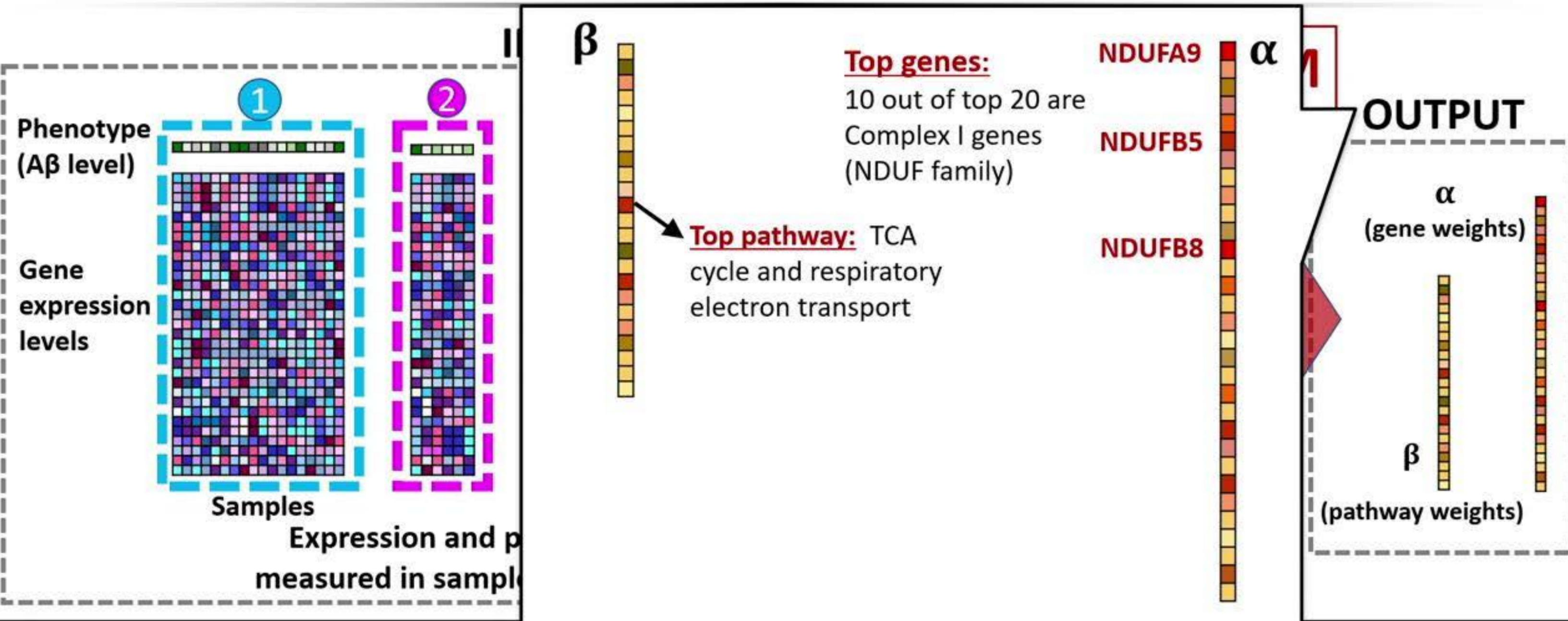
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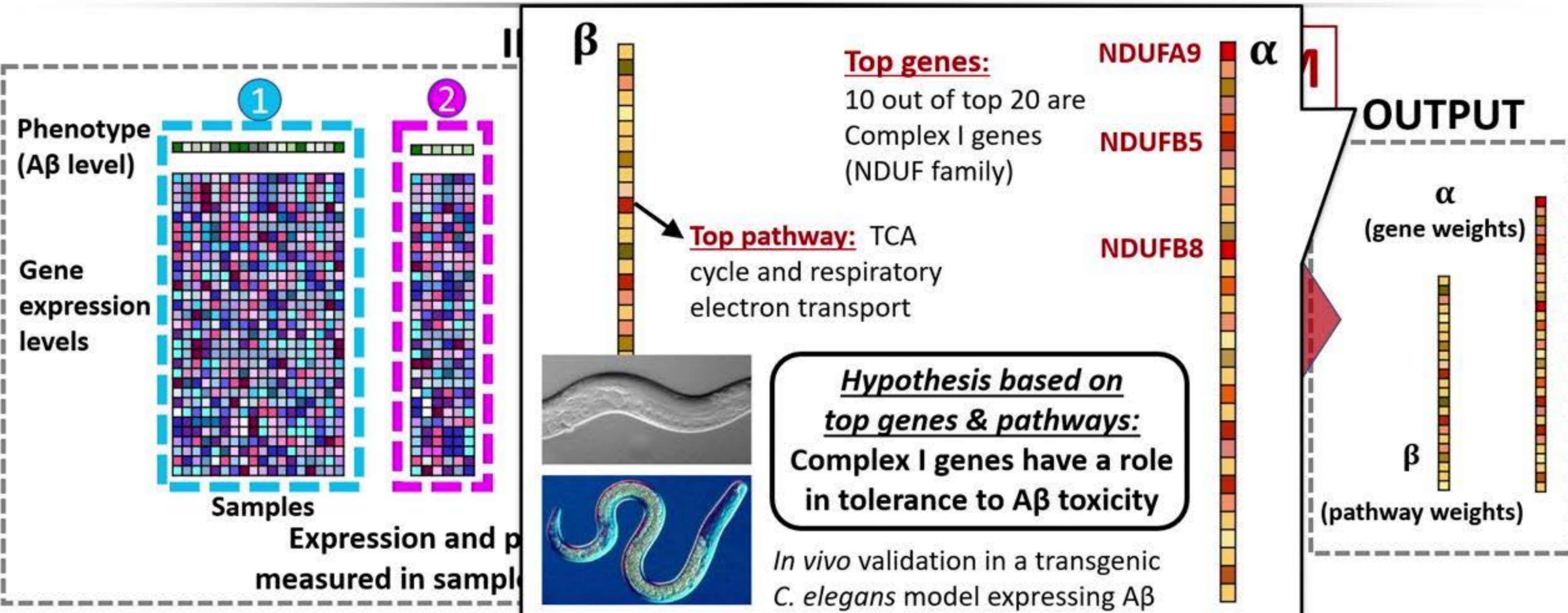
Safiye



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Safiye



***In vivo* validation – Inhibition of mitochondrial complex I subunit NDUFA9 leads to tolerance to A β toxicity**



Josh Russell



Matt
Kaeberlein

- If we knock down the worm homolog of NDUFA9, would we see delay in paralysis?

In vivo validation – Inhibition of mitochondrial complex I subunit NDUFA9 leads to tolerance to A β toxicity

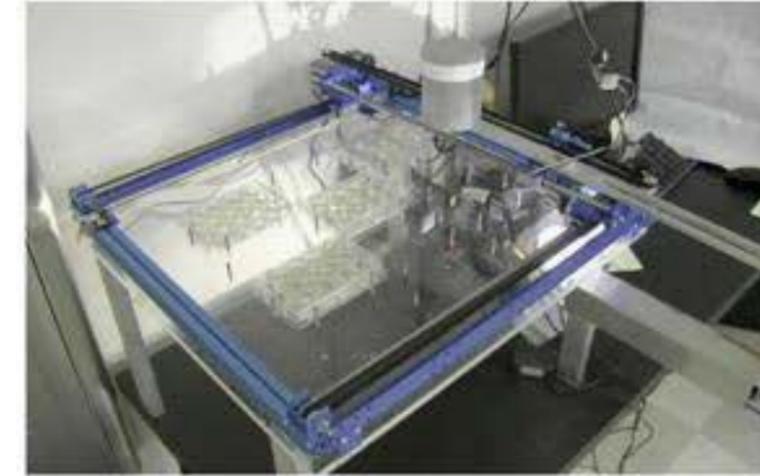


Josh Russell



Matt Kaeberlein

- If we knock down the worm homolog of NDUFA9, would we see delay in paralysis?
- Paralysis assay using the WormBot in Kaeberlein lab



Control



0:00.27

Treatment



0:00.64

- 144 experiments per run
- Automated software
- Time-lapse movies
- Efficiency (2 min vs. 3.5 hr)



Ben Blue



Jason Pitt

Pitt et al., unpublished

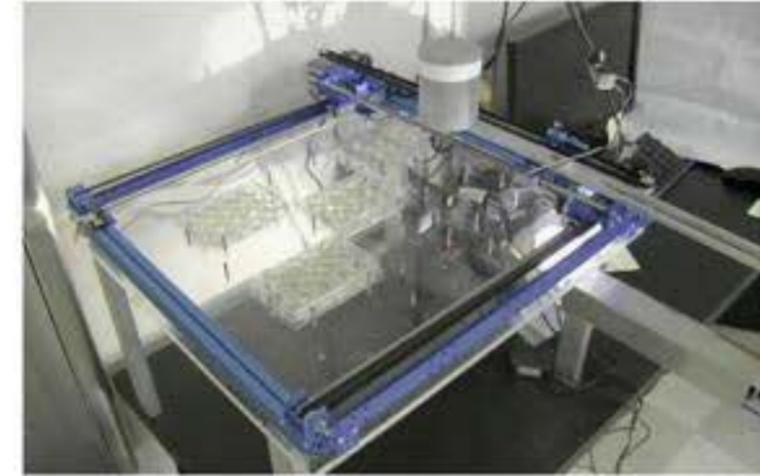
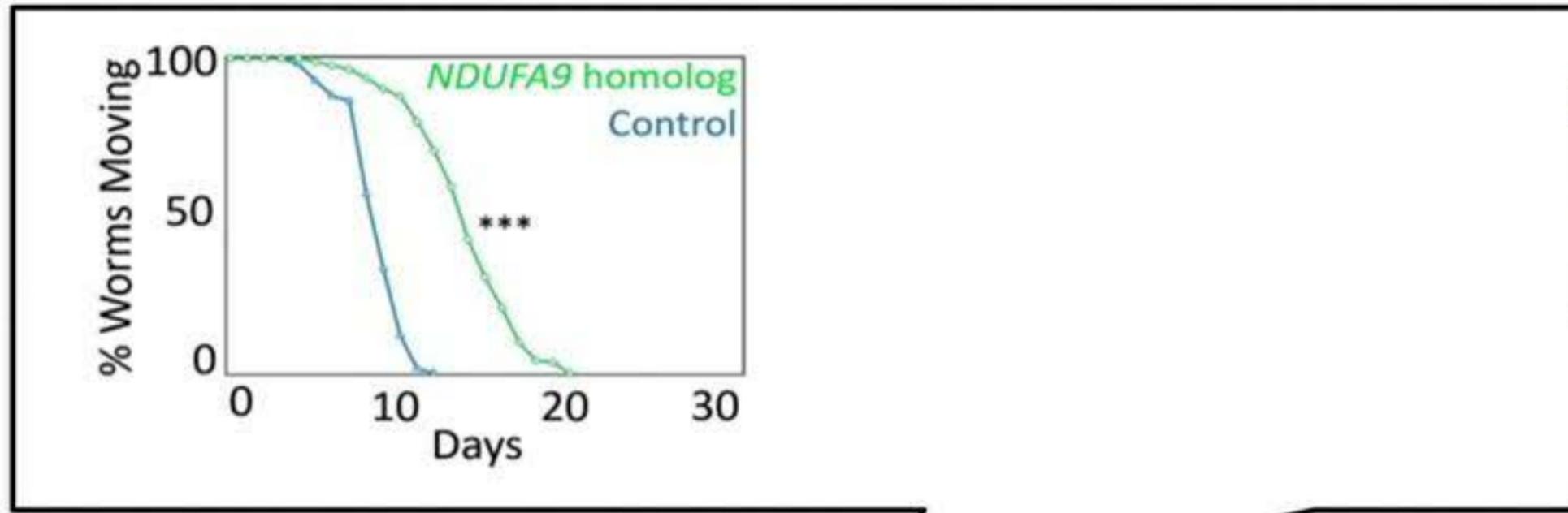
Mitochondrial complex I toxicity



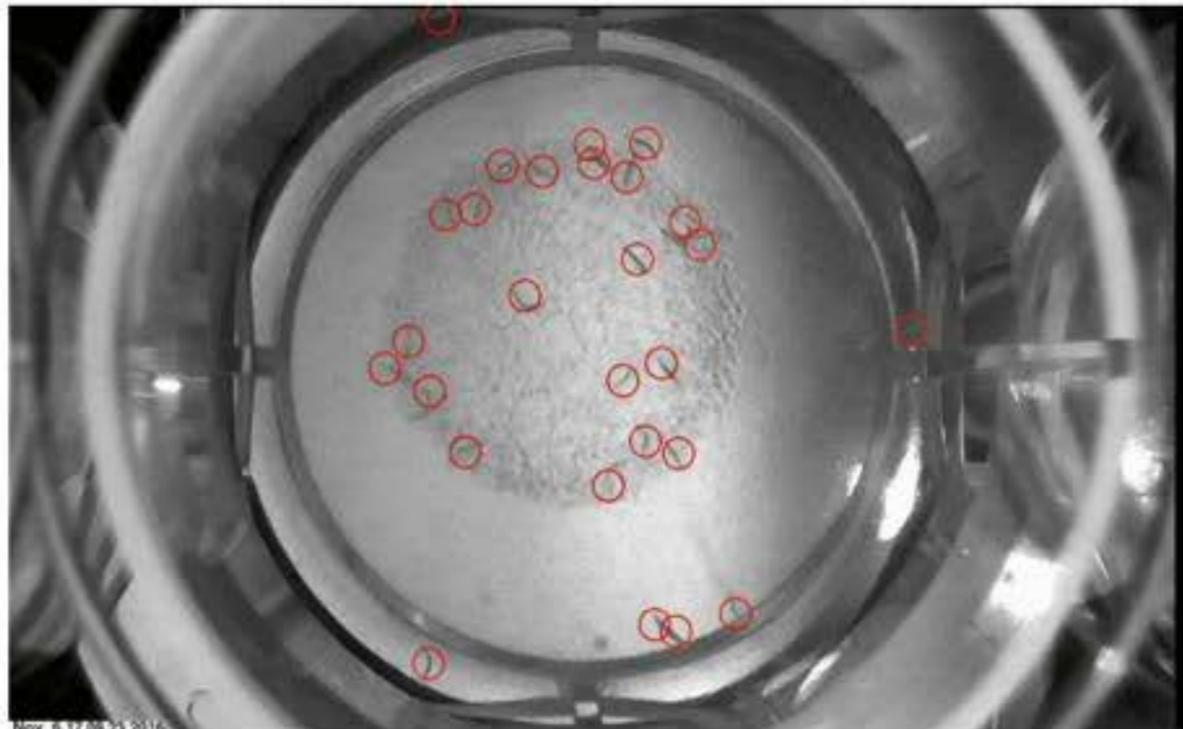
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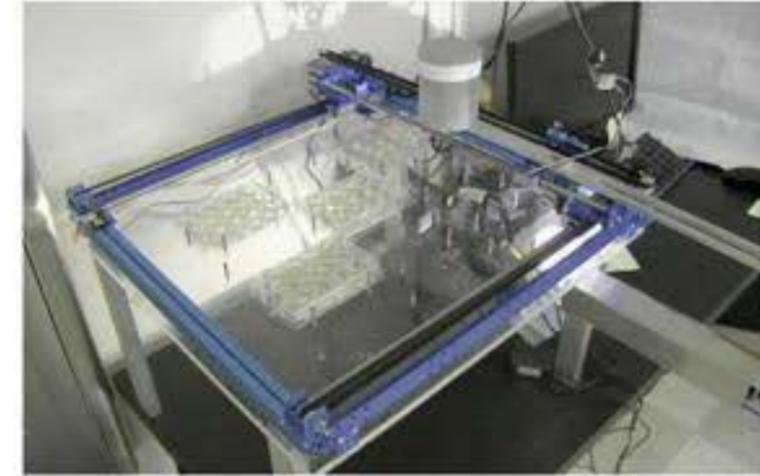
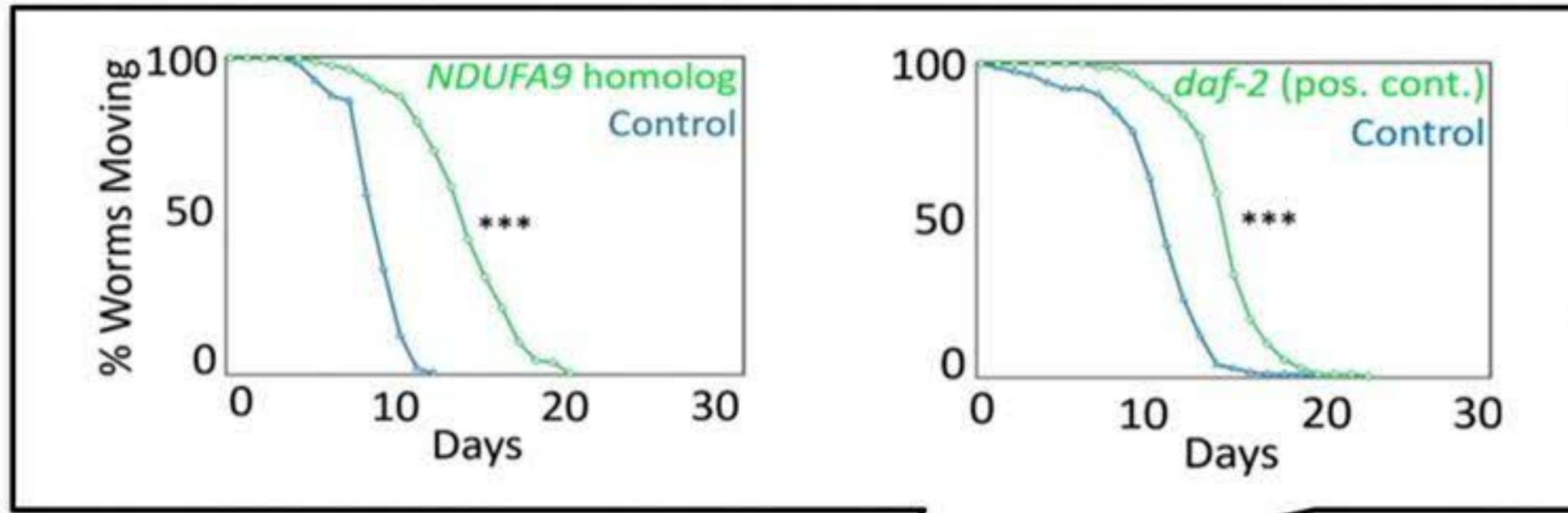
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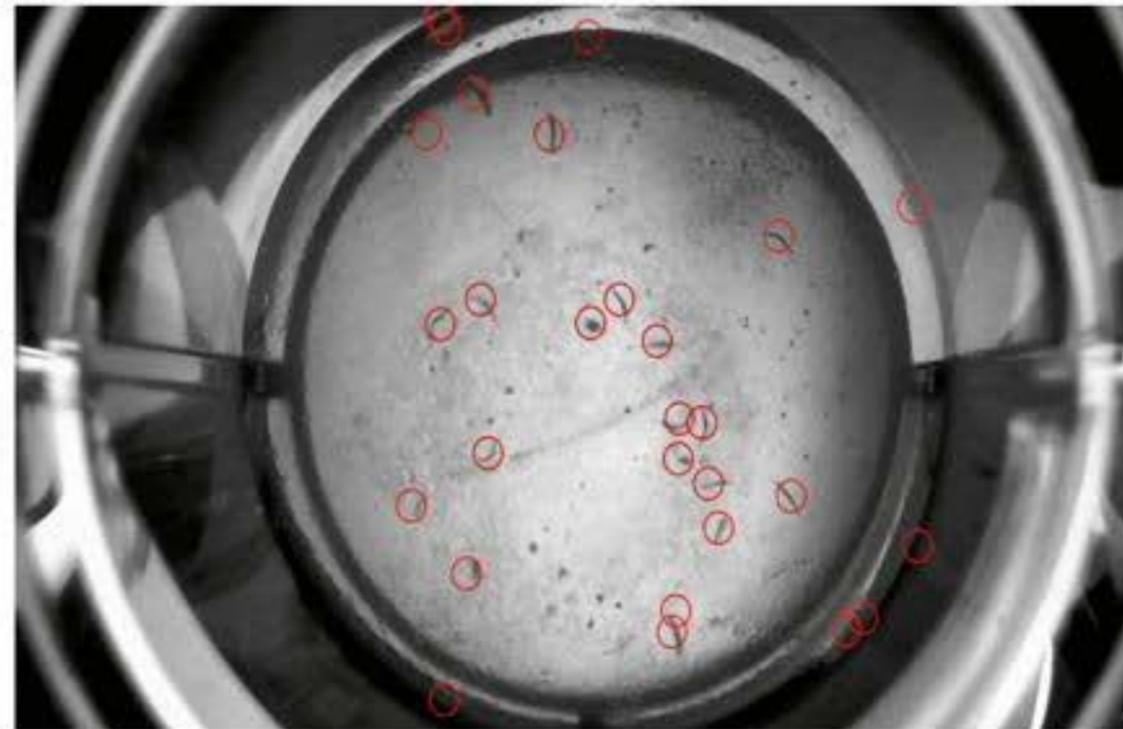
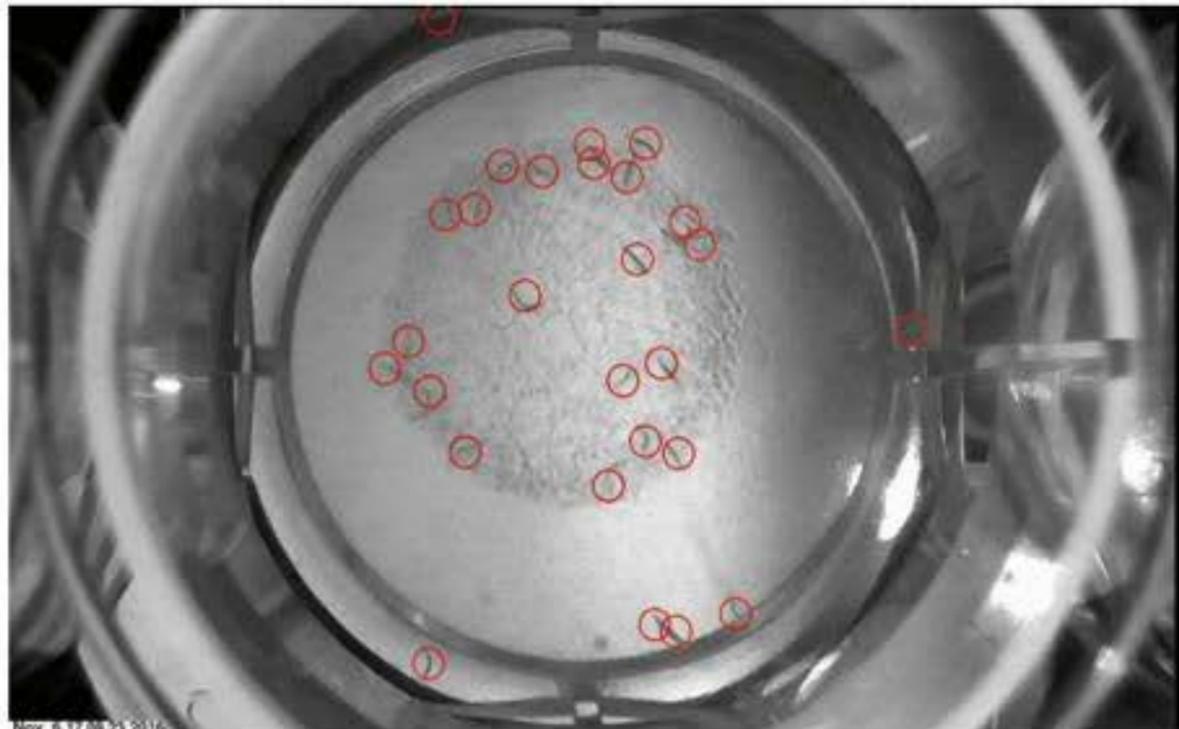


Matt Kaeberlein



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Treatment



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Ben Blue



Jason Pitt

Pitt et al., unpublished

Knockdown of 12 other Complex I genes also robustly protected against A β toxicity



Josh Russell Matt Kaeberlein

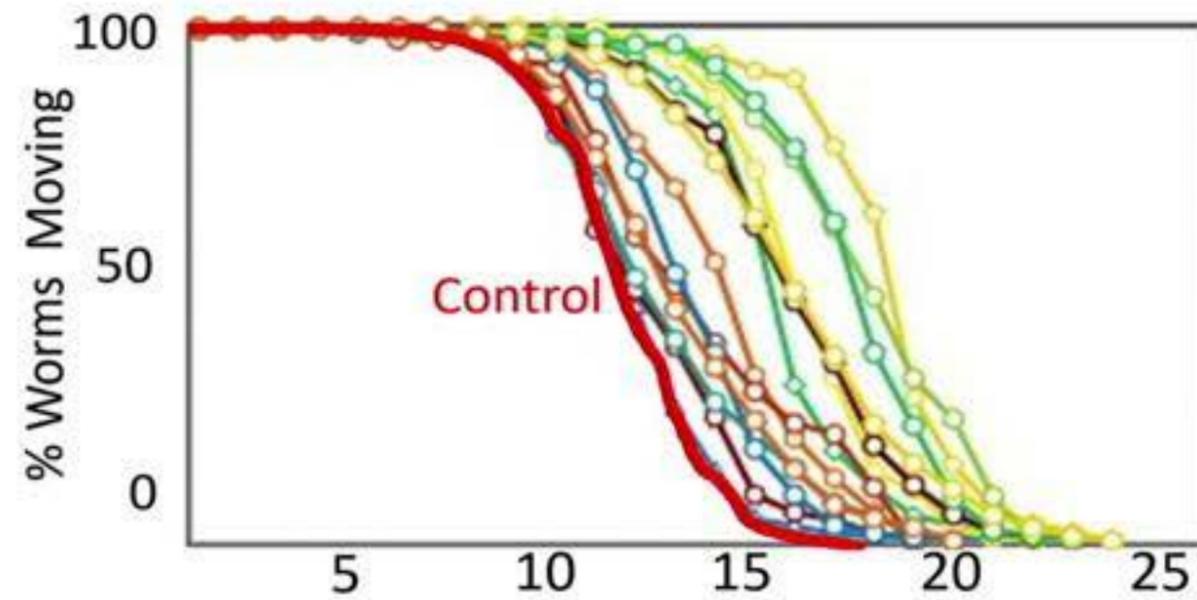
- 7 of top 10 (12 of top 20) EMBARKER-M genes are Complex I genes

Knockdown of 12 other Complex I genes also robustly protected against A β toxicity



Josh Russell Matt Kaeberlein

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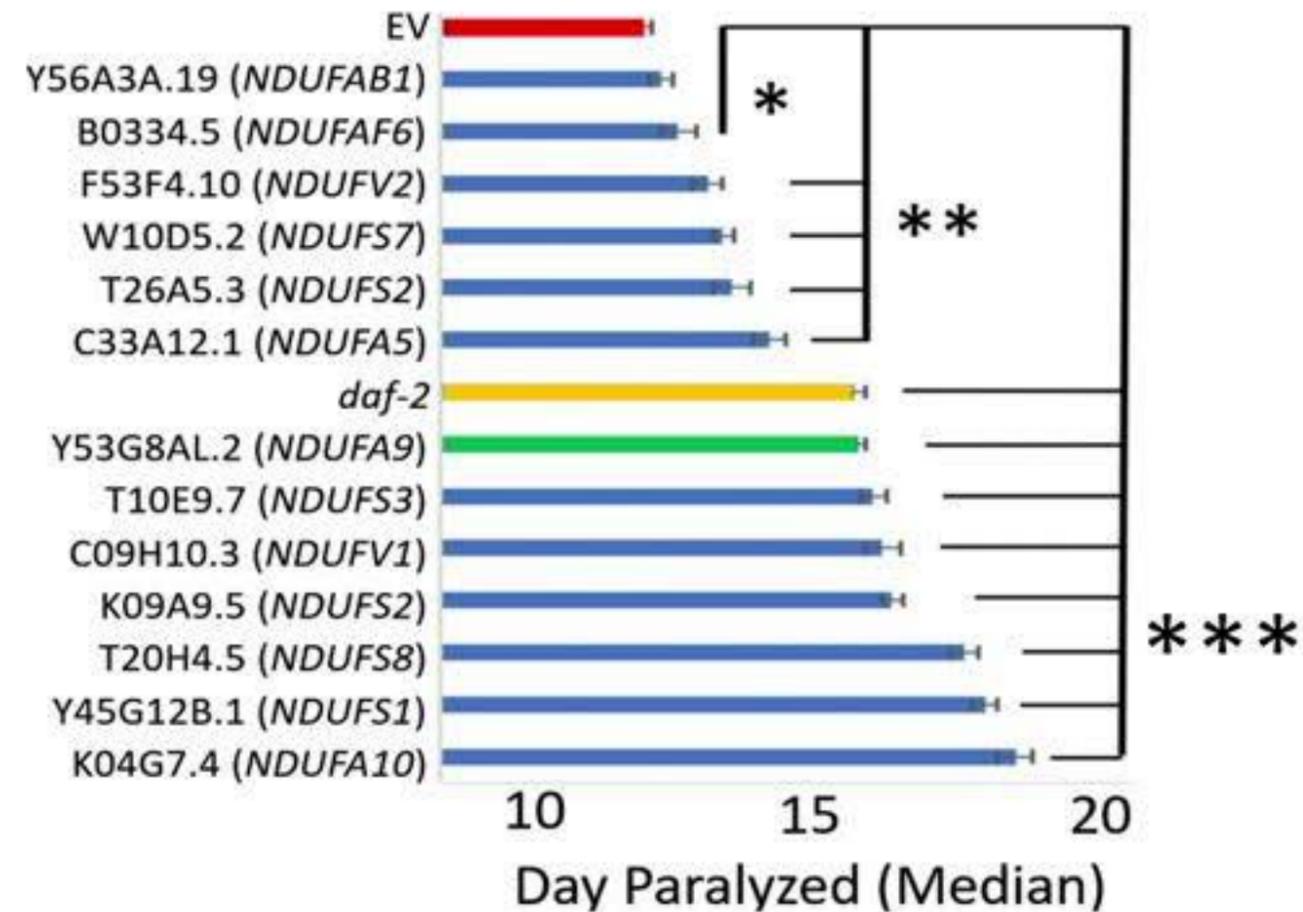
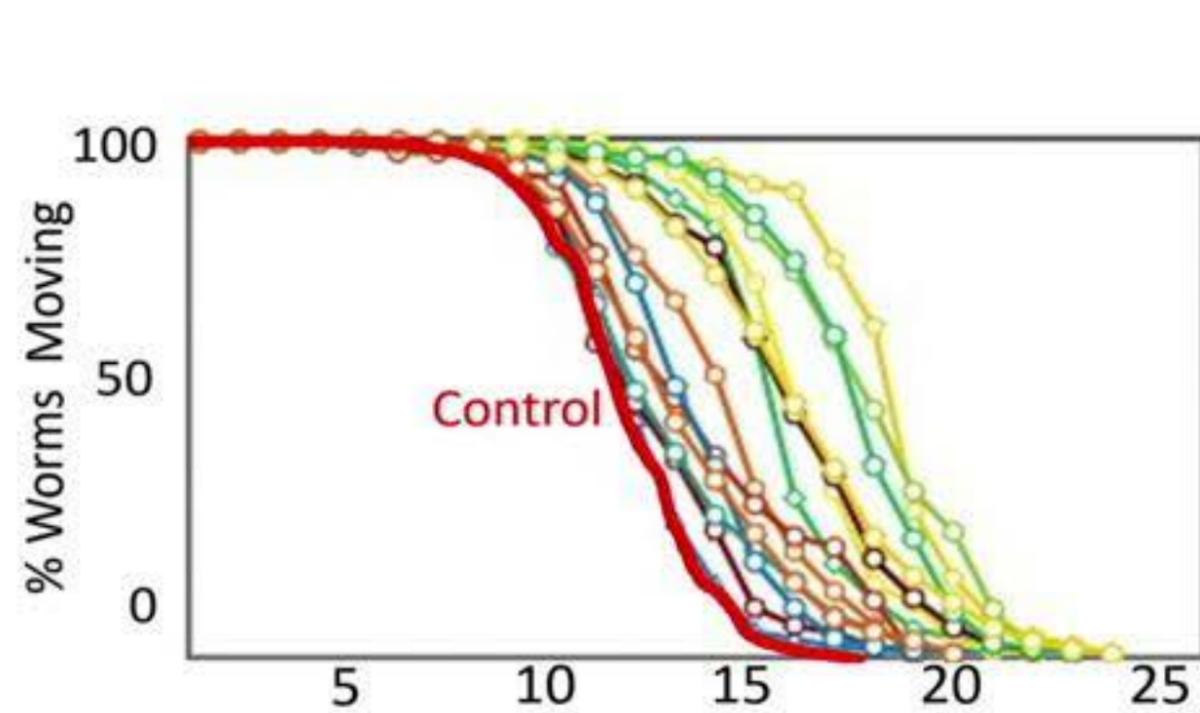


Knockdown of 12 other Complex I genes also robustly protected against A β toxicity



Josh Russell Matt Kaeberlein

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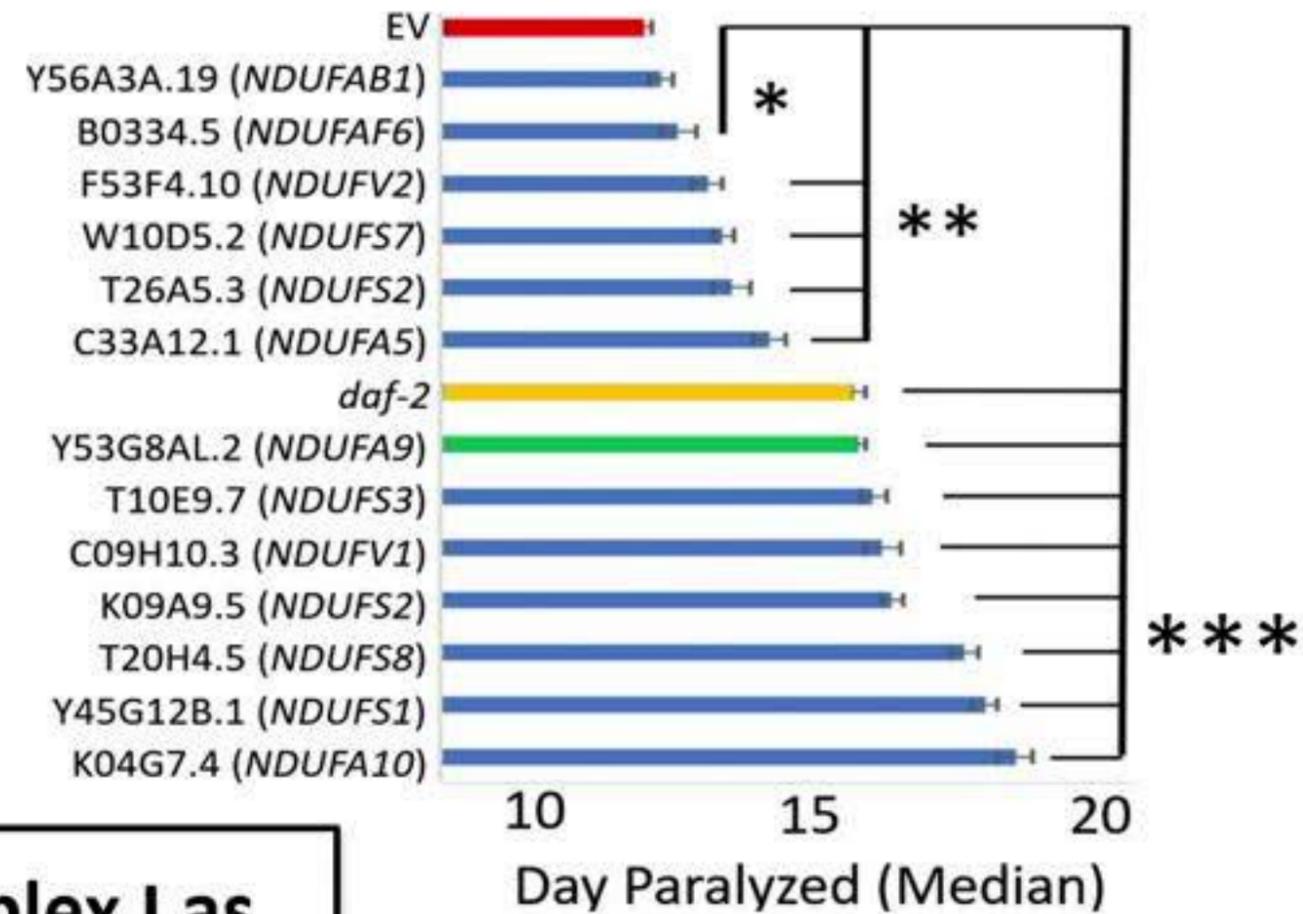
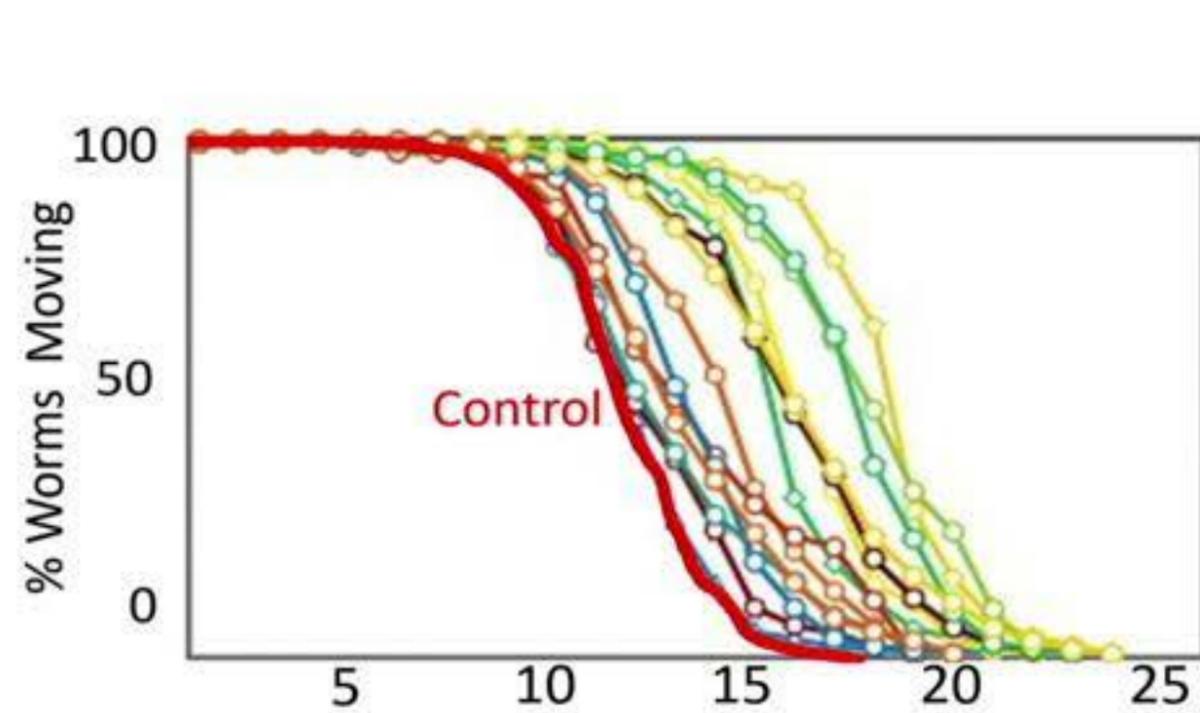


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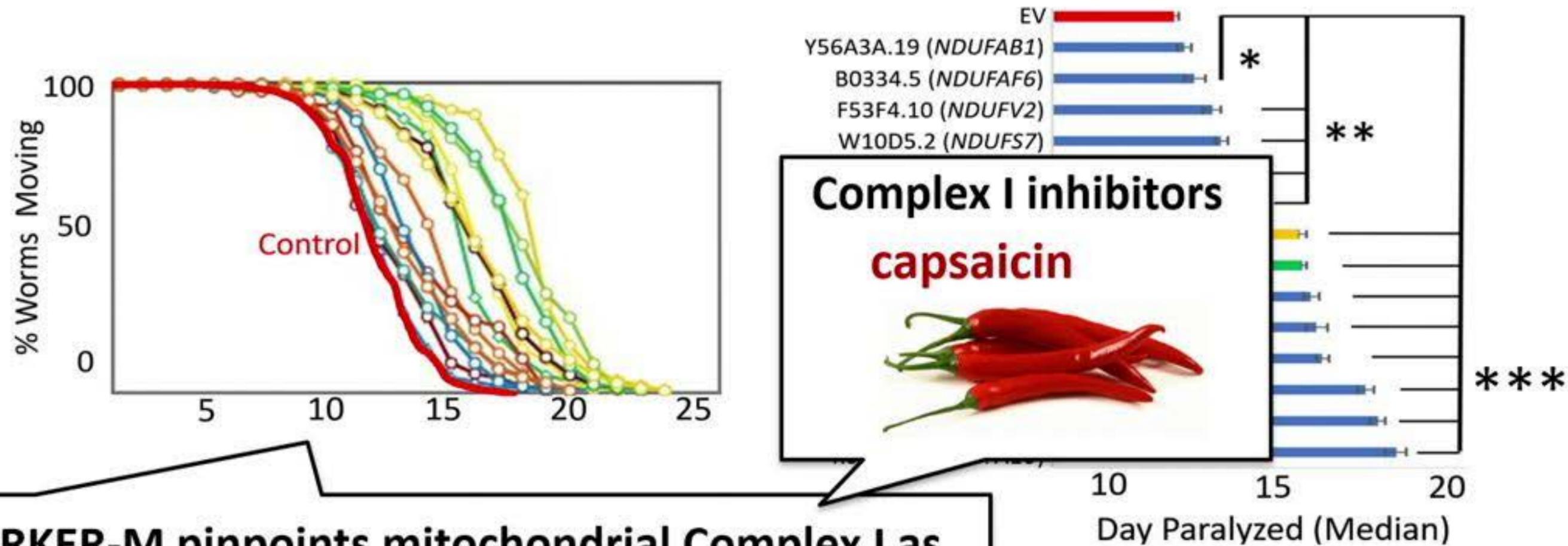
EMBARKER-M pinpoints mitochondrial Complex I as a critical mediator of proteostasis and a promising pharmacological avenue toward treating AD

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New AI/ML techniques can enable new ways to treat patients and to make biological discoveries from data

Prediction & decision support systems in hospitals

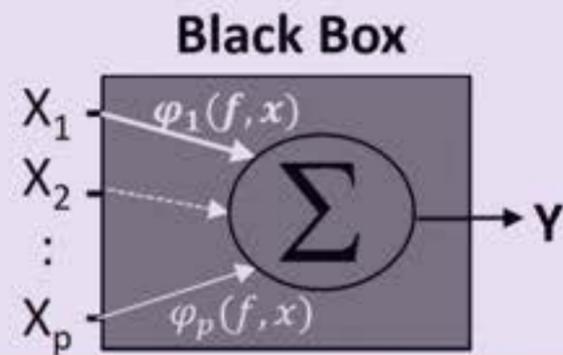
- Make interpretable predictions from complex models.

Cancer precision medicine

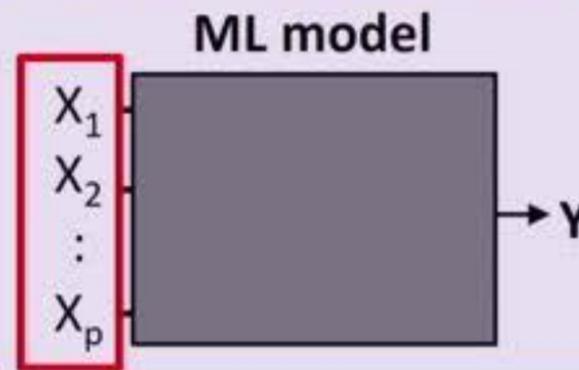
- Learn interpretable feature representations.

Alzheimer's disease therapeutic target discovery

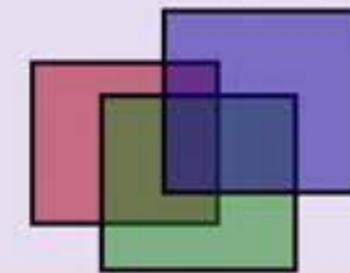
- Integrate data sets for statistical power and interpretability.



General ML techniques



Data integration



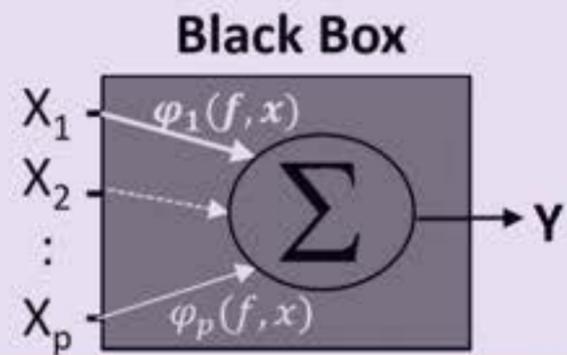
Bedside applications

Basic science

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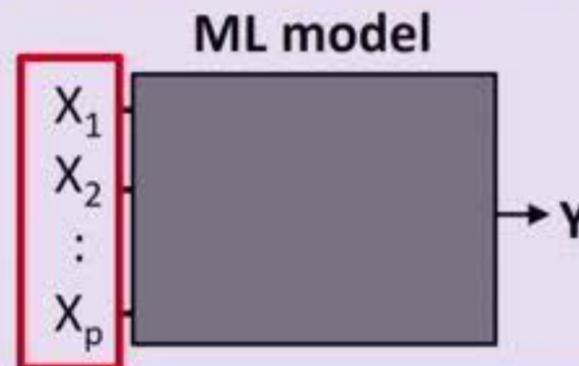
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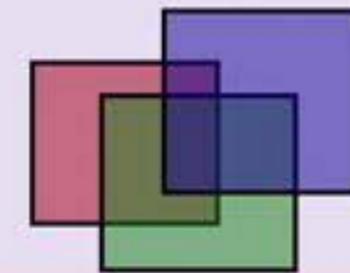
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SHAP, PHASE, Tree SHAP,
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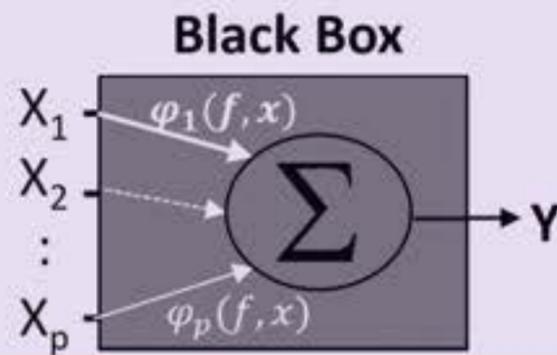
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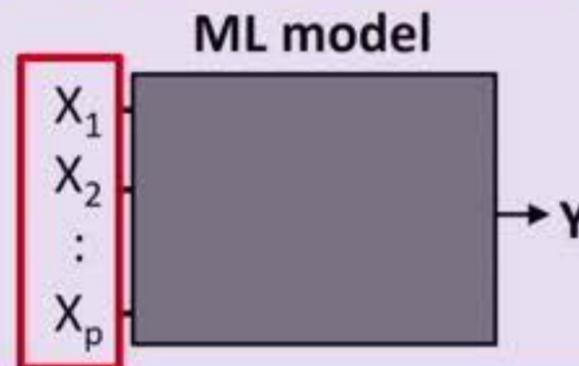
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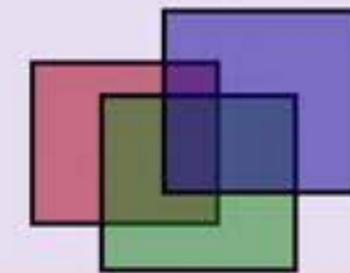
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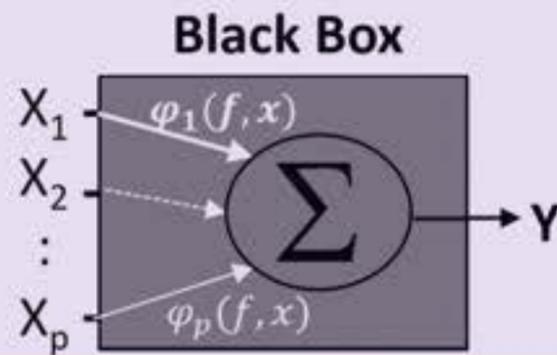
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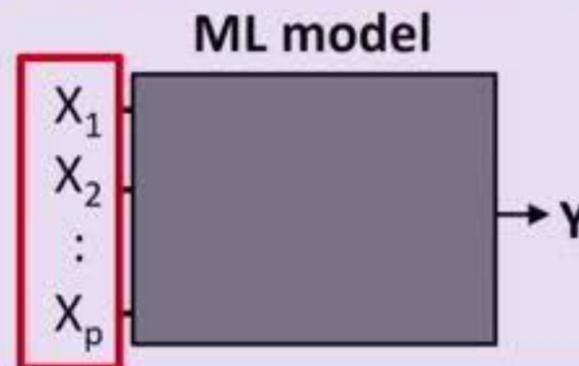
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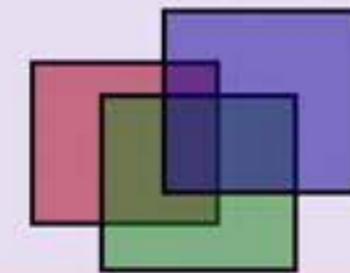
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EMBARKER

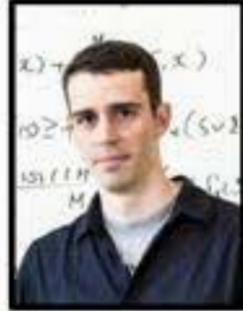
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Hematology



Tony Blau Pamela Becker

Emergency Medicine

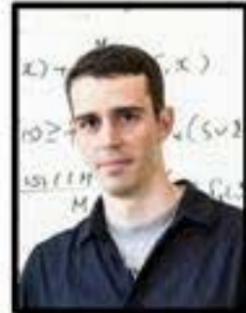


Nathan White

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Alex DeGrave



Pathology & neuropathology



Matt Kaeberlein



Dirk Keene

Internal Medicine

Alzheimer's disease research center



Paul Crane



Joey Mukherjee

Anesthesiology & Pain Medicine



Monica Vavilala



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Institute for Protein Design



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Safiye Celik



Hugh Chen Pasco

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NIH NIGMS R35 (PI: Lee)

NIH NLM R21 (MPI)

NSF ABI Innovation (PI: Lee)

NSF CAREER (PI: Lee)

American Cancer Society (PI: Lee)

NSF ABI Innovation (PI: Lee) – completed

NIH NIA R21 (PI: Lee) – completed

Hematology



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Emergency Medicine



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Pathology & neuropathology



Matt Kaeberlein



Dirk Keene

Internal Medicine

Alzheimer's disease
research center



Paul Crane



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