Asymmetric predictability

An information theoretic approach to causal inference

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2023 WNAR/IMS Annual Meeting
Anchorage, Alaska.

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Acknowledgements

“Asymmetry mirrors underlying causal structures*”

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*Postulates and assumptions apply

Does $X \to Y$ or $Y \to X$?

Introduction

- Inferring $X \to Y$ or $Y \to X$ from observations $(x_1, y_1), \ldots, (x_n, y_n)$ from f_{XY} is challenging.

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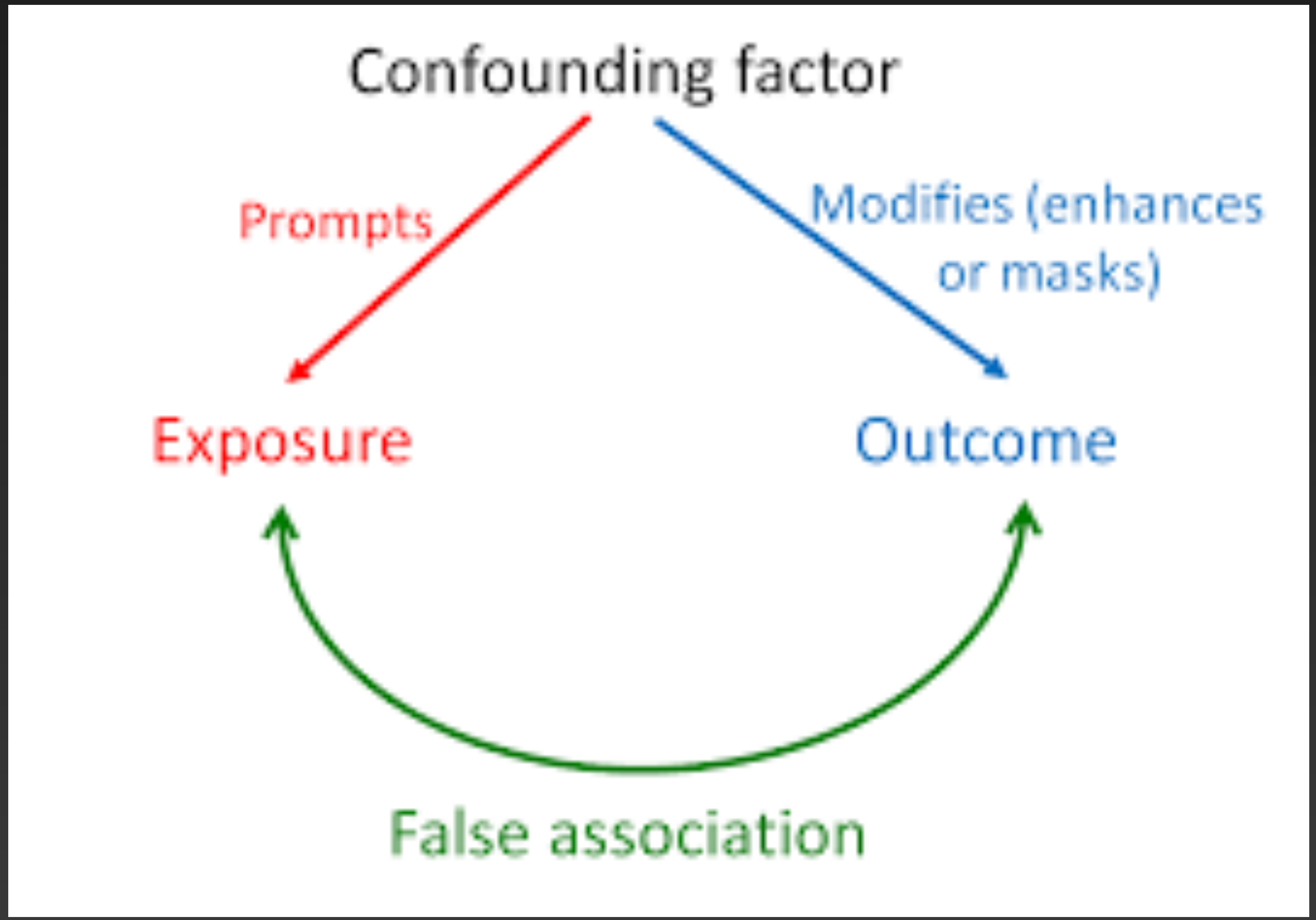
  - Common confounders:



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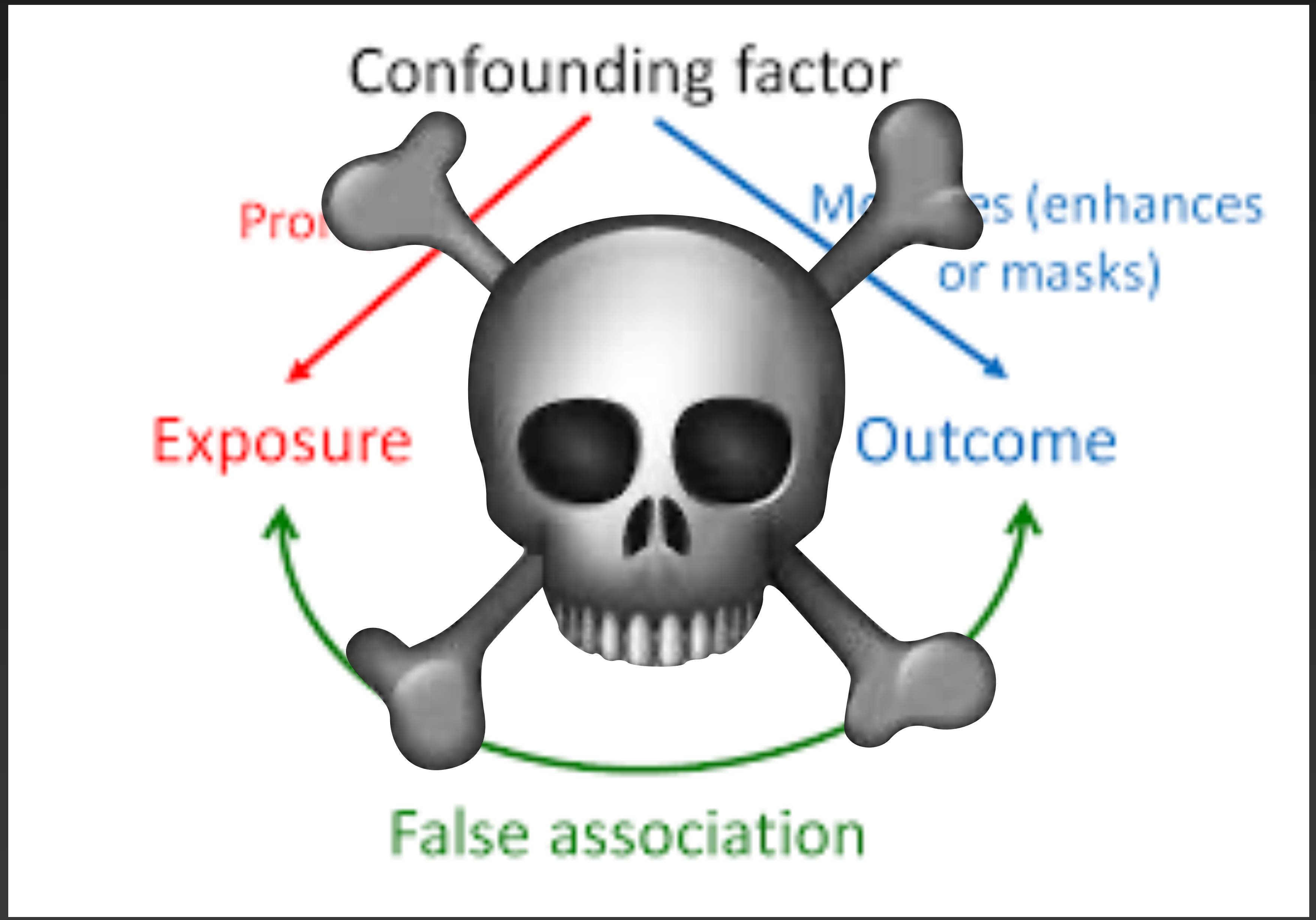

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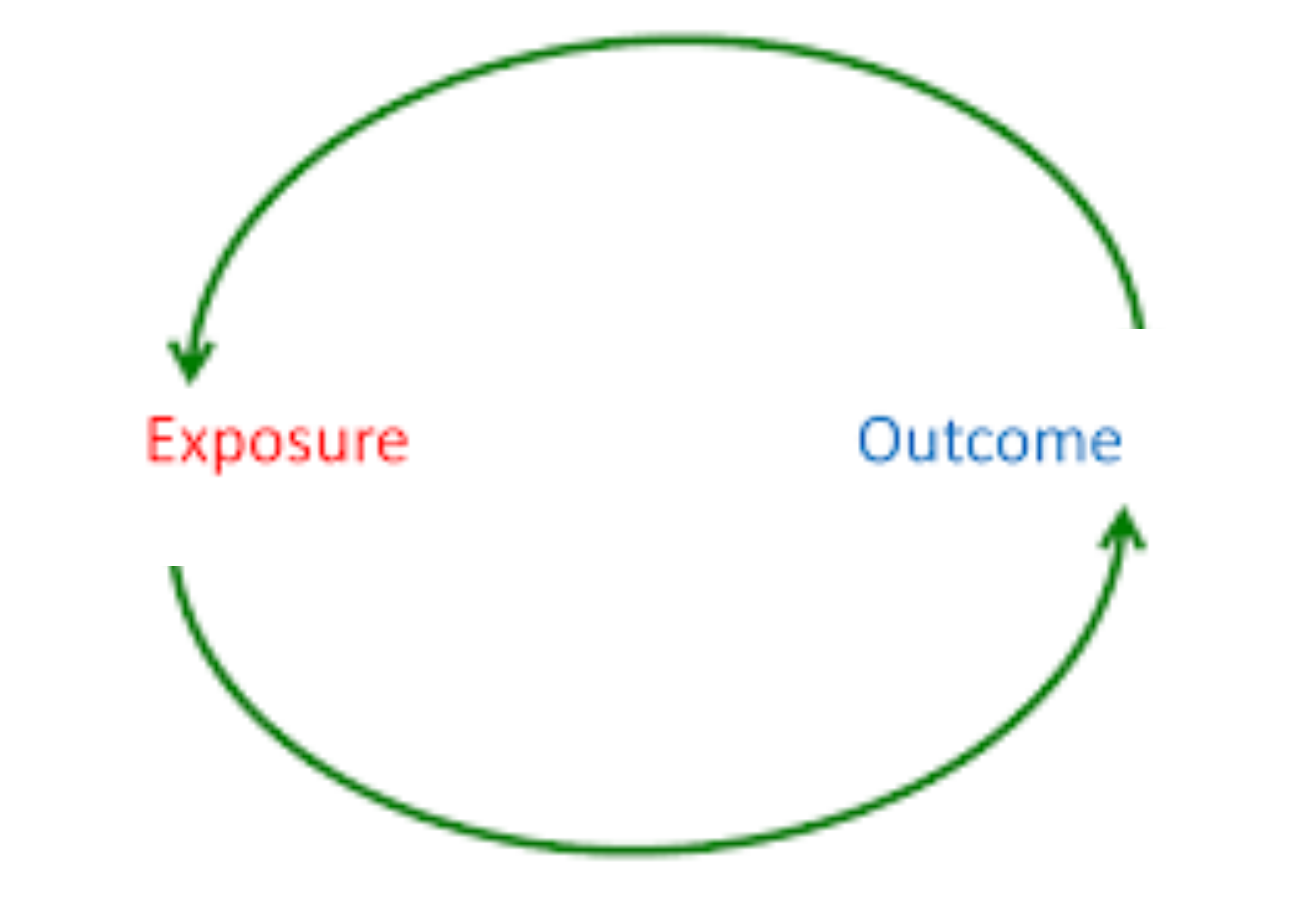

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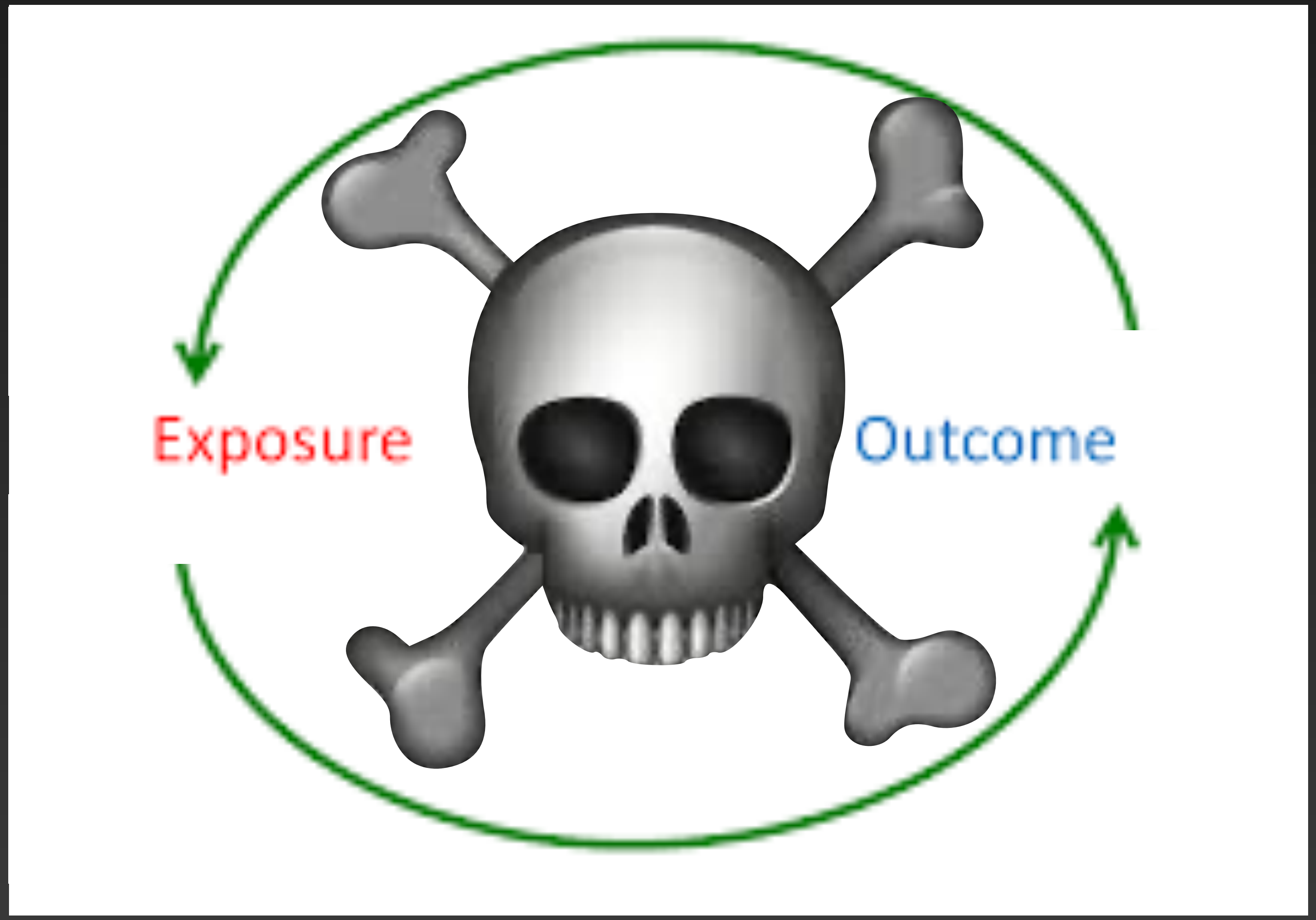
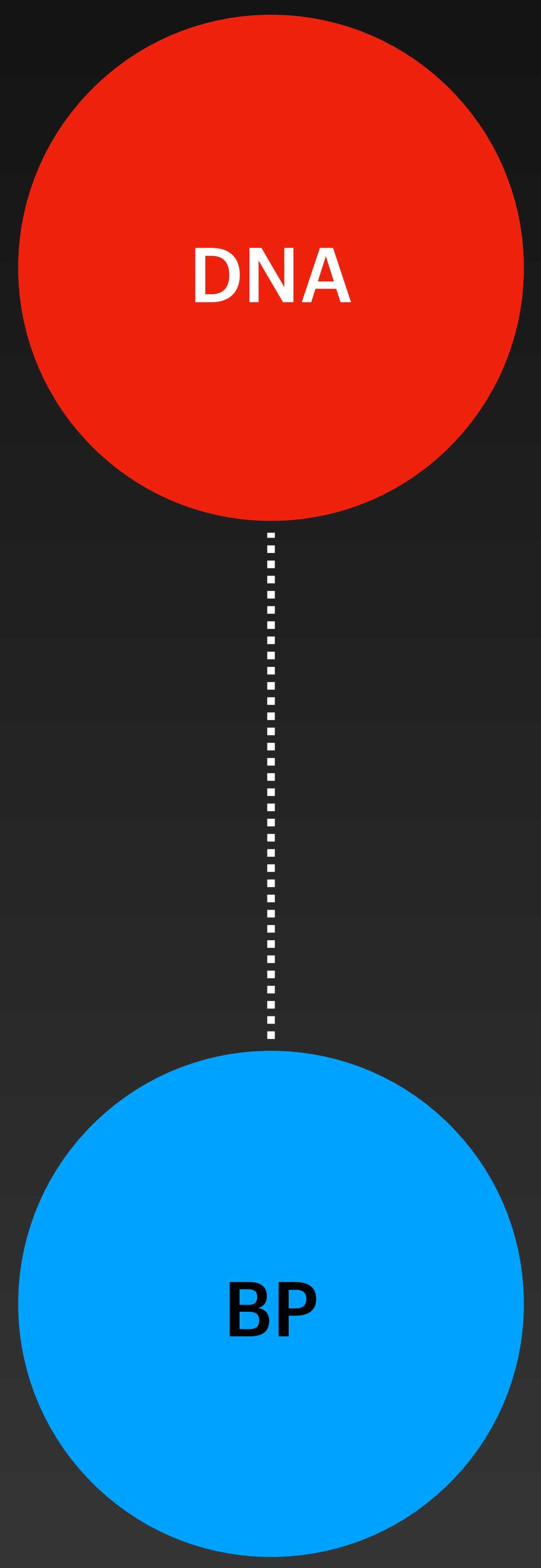


Methodology motivated by an epigenetic question

Does *DNAm* → *BP* or *BP* → *DNAm*?

Early Life Exposures in Mexico to Environmental Toxicants (*ELEMENT*) cohort study



- Genes associated with blood pressure: ***ATP2B1***, ***FGF5***, and ***PRDM8***.

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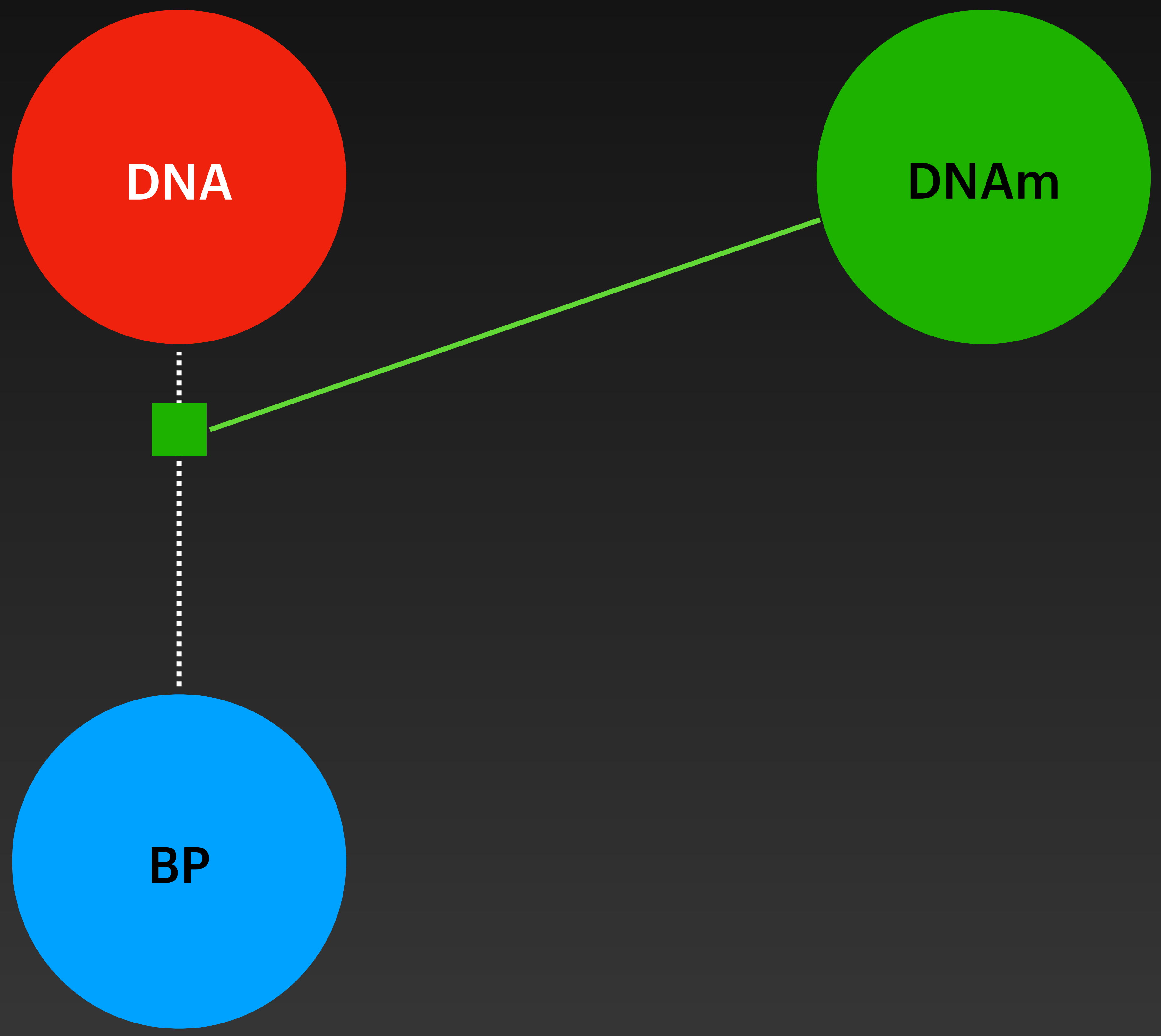

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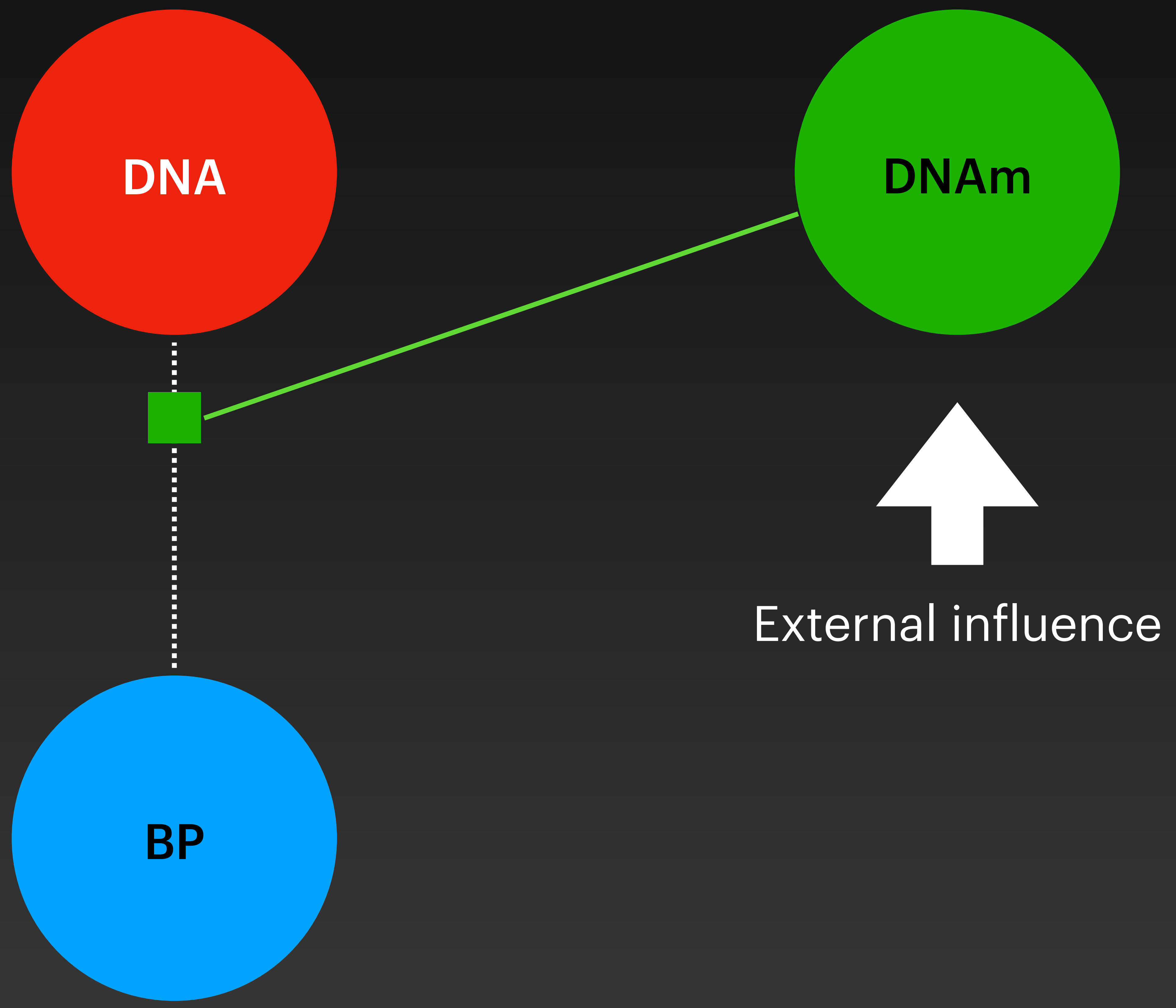

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- Methylation influenced by external features.

Does *DNAm → BP or BP → DNAm?*

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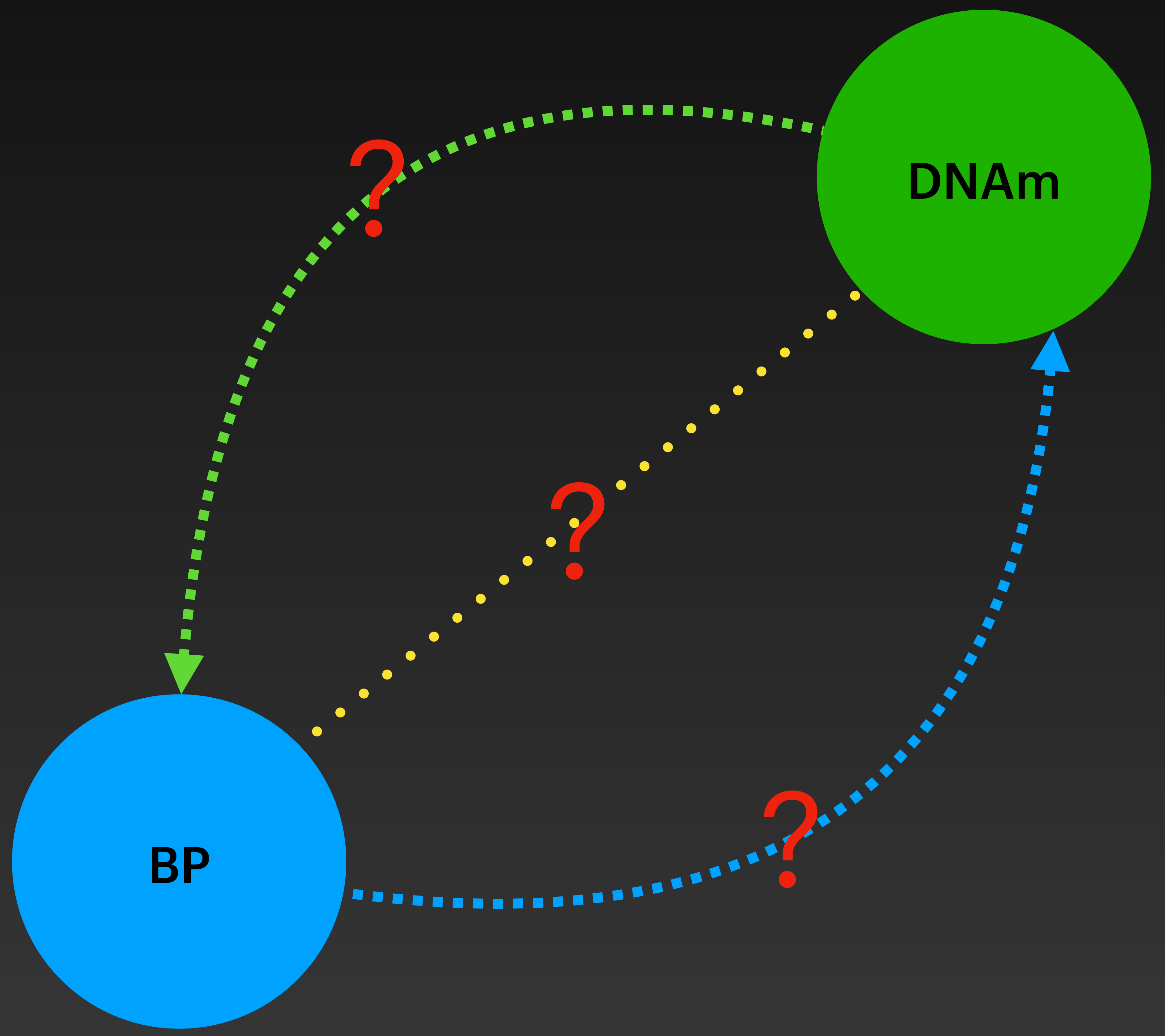

- Genes associated with blood pressure: ***ATP2B1***, ***FGF5***, and ***PRDM8***.
- Gene expression controlled by methylation.
- Methylation influenced by external features.
- ***Questions:***

  1. ***EpiGWAS for BP?***
  2. ***DNAm → BP or BP → DNAm?***

Deliverables

Does $X \to Y$ or $Y \to X$?

Directed Mutual Information (DMI)

1. **Asymmetric predictability**: well-justified framework for studying statistical asymmetries between cause and effect.

Does $X \to Y$ or $Y \to X$?

Directed Mutual Information (DMI)

1. **Asymmetric predictability**: well-justified framework for studying statistical asymmetries between cause and effect.

2. New information theory-based measure: **Directed Mutual Information** (DMI).

   A. DMI can test for independence.

   B. DMI can quantify and estimate "asymmetries" between cause and effect.

Asymmetric predictability

Some information theoretic concepts

Entropy decomposition equation:

$$H(X, Y) = MI(X, Y) + H(X \mid Y) + H(Y \mid X)$$

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Mutual information:

$$MI(X, Y) = E_{XY}\left[\log c_{XY}\right]$$

$$MI = 0 \iff X \perp Y$$

Symmetric!

Some information theoretic concepts

Entropy decomposition equation:

$$H(X,Y) = MI(X,Y) + H(X|Y) + H(Y|X)$$

Study independence with MI.

Depends only on copula c_{XY}

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Joint entropy:

$$H(X, Y) = E_{XY}\left[-\log f_{XY}\right]$$

Marginal entropies $H(X)$ and $H(Y)$

Symmetric!

Some information theoretic concepts

Entropy decomposition equation:

$$H(X,Y) = MI(X,Y) + H(X|Y) + H(Y|X)$$

Total information in (X, Y)

Joint entropy:

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Conditional entropy:

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Information needed to predict X if we know Y

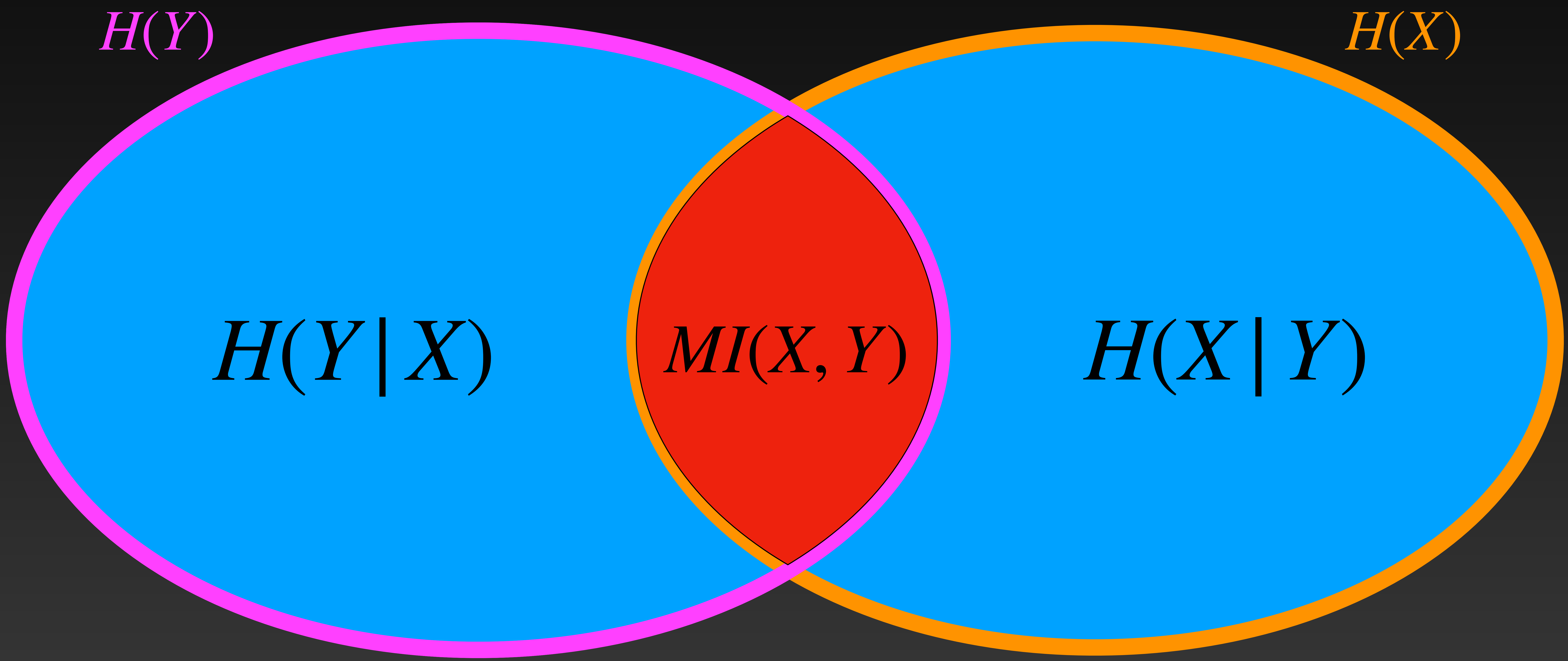
Conditional entropy:

$$H(X \mid Y) = E_{XY}\left[-\log \frac{f_{XY}}{f_X}\right]$$

Asymmetric!

Comparing conditional entropies

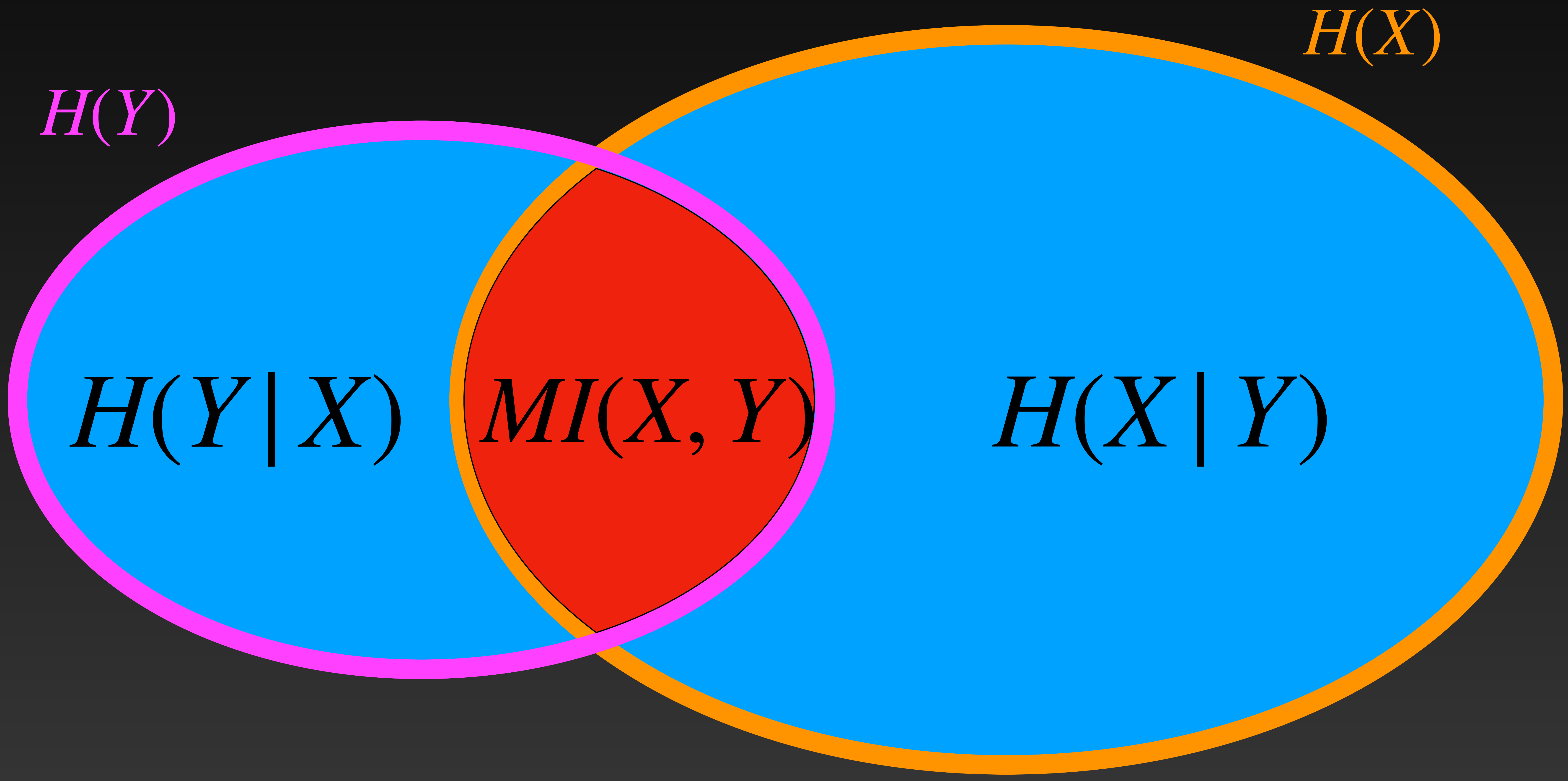
Symmetric entropy decomposition



Symmetric/balanced

Comparing conditional entropies

Asymmetric entropy decomposition



Asymmetry: “Less information needed to predict Y given X”

Asymmetric predictability

Causality in information space

Step 1: Consider $Y = g(X) + \epsilon$

Postulate: If $X \to Y$, the density f_X and the function g are "independent".

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$$\text{Cov}\left[\log\left(g'\right), f_X\right] = 0$$

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Step 3: after some more math...

If $X \to Y$, we have

$H(X \,|\, Y) = H(Y \,|\, X) +$ non-negative value

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References:

Janzing, D., et al. (2012). ***Information-geometric approach to inferring causal directions.***

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Towards defining DMI

Entropy ratio

Definition and properties

Entropy ratio compares $H(X\,|\,Y)$ and $H(Y\,|\,X)$:

$$ER(X\,|\,Y) = \frac{\exp\{H(X\,|\,Y)\}}{\exp\{H(X\,|\,Y)\} + \exp\{H(Y\,|\,X)\}}\,.$$

Entropy ratio

Definition and properties

$ER > 0$

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$ER > 0$

$ER(X \mid Y) > ER(Y \mid X)$
$\iff H(X \mid Y) > H(Y \mid X)$

Directed Mutual Information (DMI)

Definition and properties

$$DMI(X \mid Y) = MI(X, Y) \times ER(X \mid Y)$$

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Definition and properties

Test for independence

$$DMI(X|Y) = MI(X,Y) \times ER(X|Y)$$

Properties:

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2. $\Delta = DMI(X|Y) - DMI(Y|X) > 0 \iff H(X|Y) > H(Y|X) \iff X \to Y$

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Definition and properties

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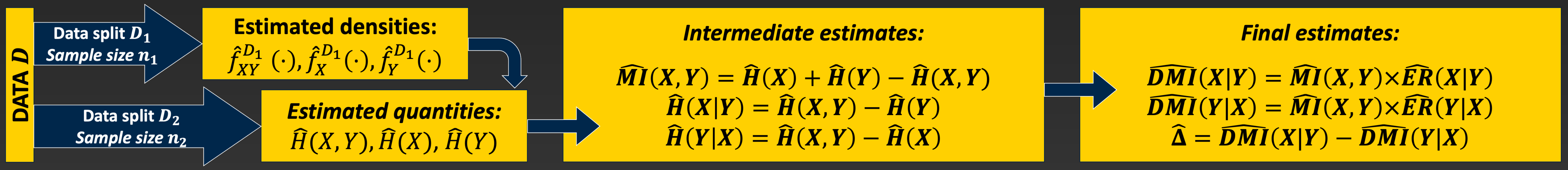
Estimation and inference using DMI

Directed Mutual Information (DMI)

Estimation and inference

1. Estimate density functions ("nuisance parameter") using one split
2. Evaluate entropy and mutual information using other split



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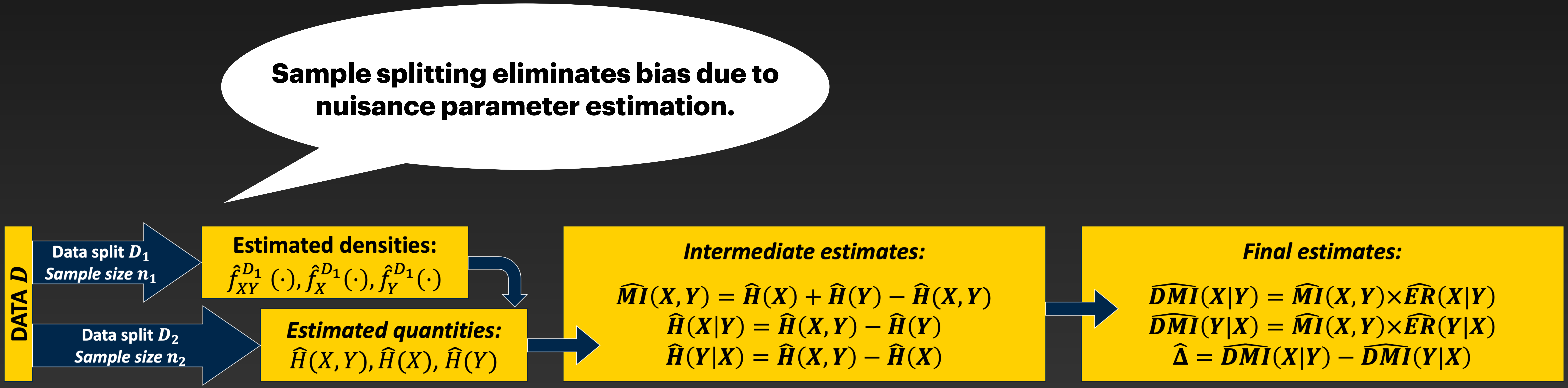

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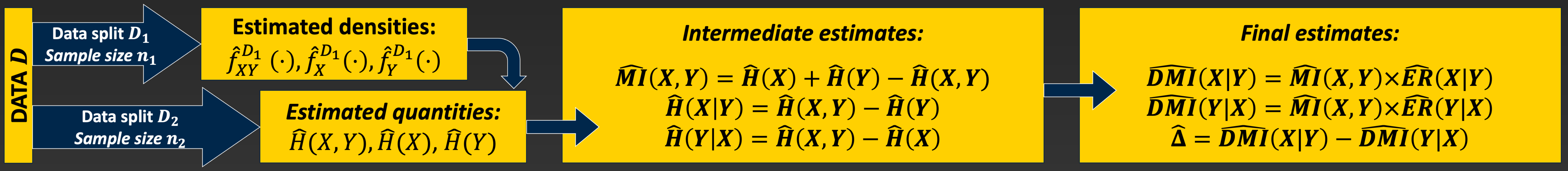
Cross-fitting yields improved empirical performance.



Directed Mutual Information (DMI)

Theoretical guarantees

1. Assuming the density functions are bounded, when $\min(n_1, n_2) \to \infty$, we have $\hat{DMI}(X \mid Y) \xrightarrow{p} DMI(X \mid Y)$.

2. Assuming $MI \neq 0$, $\min(n_1, n_2) \to \infty$, we have $\sqrt{n_2}\left(\hat{\Delta} - \Delta\right) \xrightarrow{D} N(0, \sigma_{\Delta}^2)$.

Directed Mutual Information (DMI)

Theoretical guarantees

Consistent estimates of DMI permit test of independence using permutation.

1. Assuming the density functions are bounded, when $\min(n_1, n_2) \to \infty$, we have $D\hat{M}I(X \mid Y) \xrightarrow{p} DMI(X \mid Y)$.

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Sign of $\hat{\Delta}$ informs $X \to Y$

(95%) CI allows for calibration

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New epigenetic insights using DMI

Does *DNAm* → BP or BP → *DNAm*

Application of DMI to methylation studies

- Cohort of 525 children of age 10 - 18 years in the ELEMENT cohort.

- 3 candidate genes: ***ATP2B1, FGF5,*** and ***PRDM8.***
  - Mildly correlated methylation sites: 21 for ***ATP2B1***, 21 for ***FGF5***, and 51 sites for ***PRDM8***.

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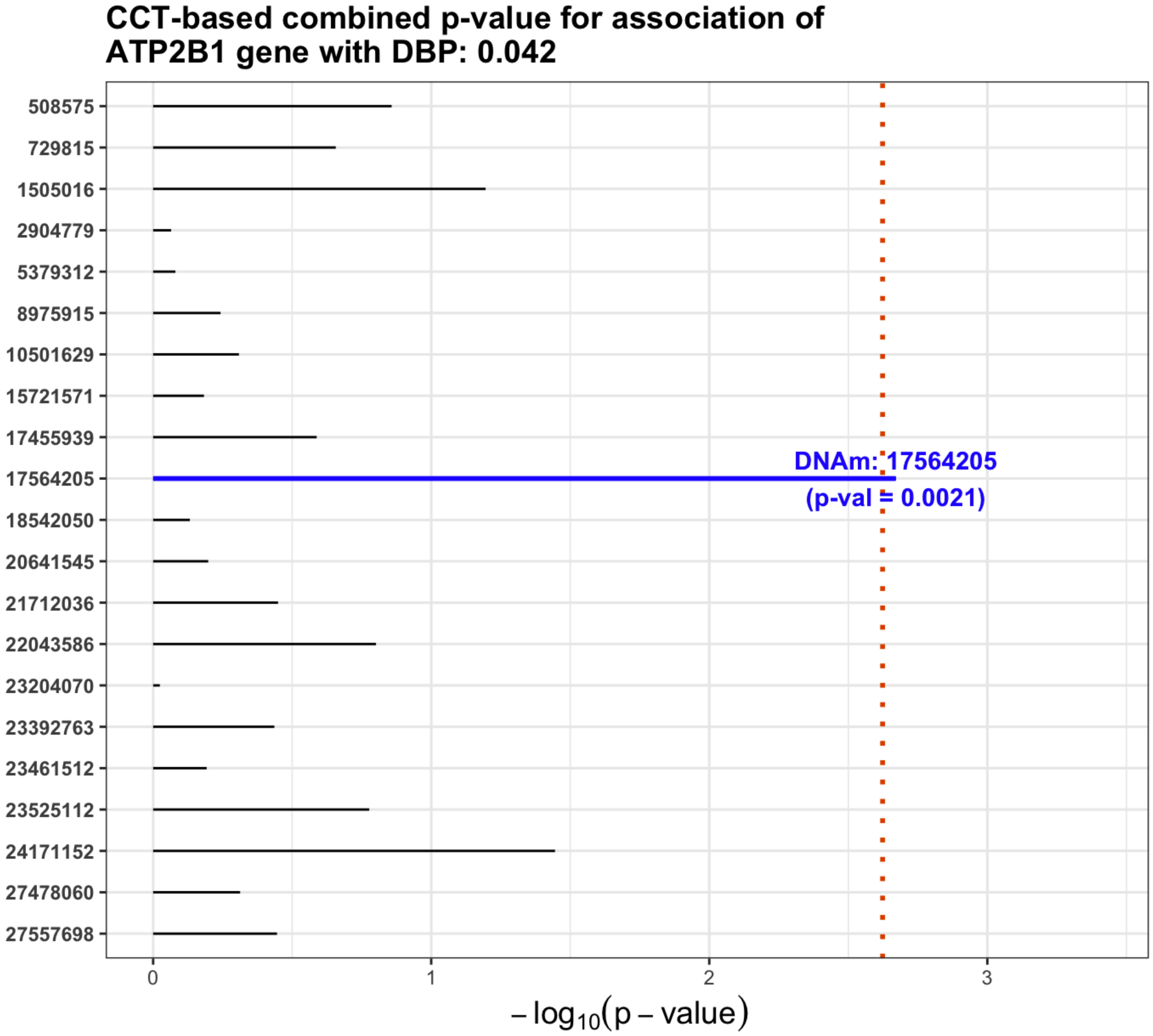
1. Test for association between *DNAm* site and BP for a given gene.
2. Aggregate all *DNAm*-findings using Cauchy combination test for each gene.
3. In *DNAm* sites associated with BP, check if *DNAm* → BP or BP → *DNAm*.

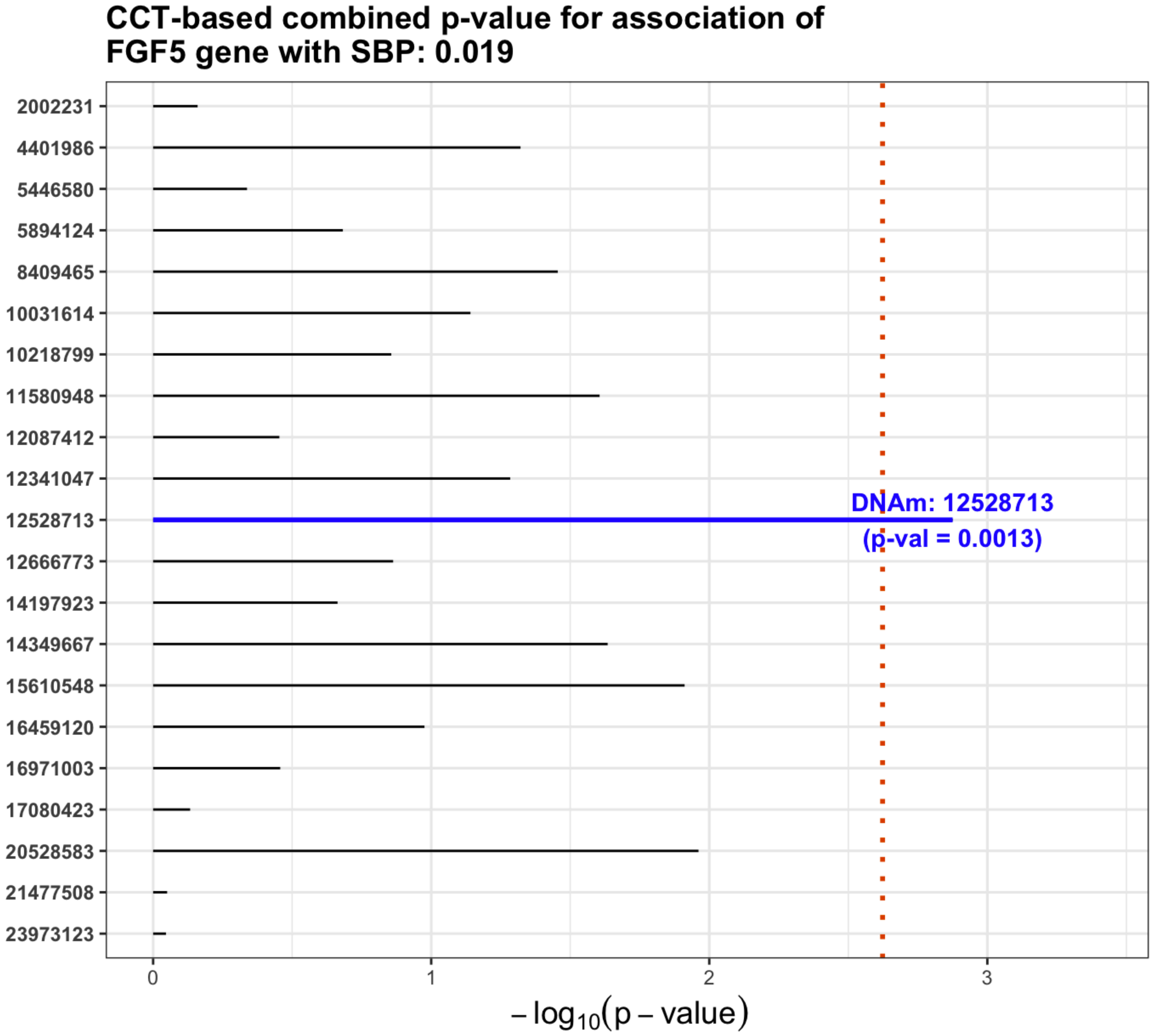
Finding 1: DNAm site #17564205 in *ATP2B1*

- Strongly associated with **diastolic** BP.
- Strong signal to drive gene-wide association with DBP.
- Next: check *DNAm* → BP or BP → *DNAm?*



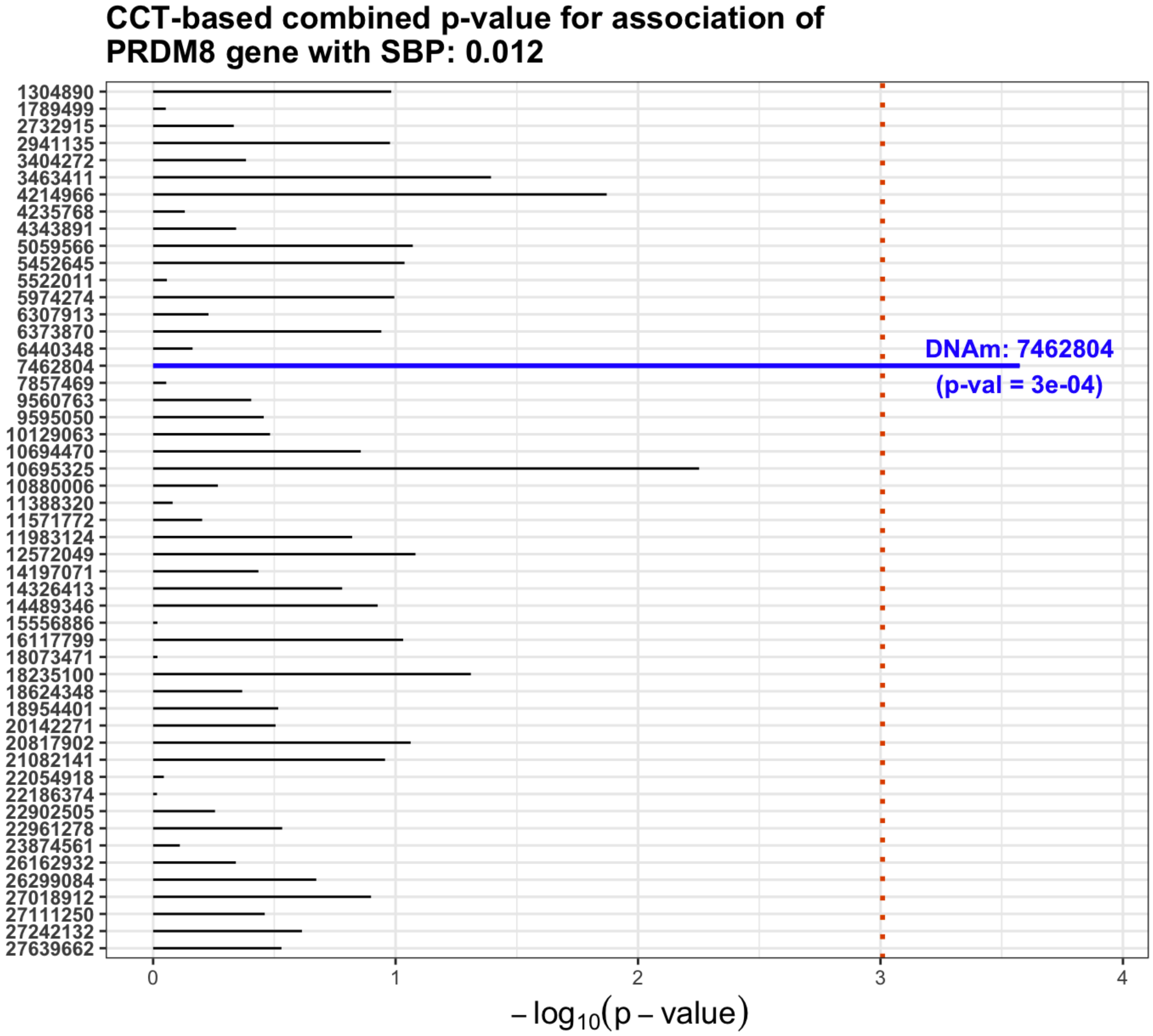
Finding 2: DNAm site #125287 in *FGF5*

- Strongly associated with **systolic** BP.
- Strong signal to drive gene-wide association with SBP.
- Next: check *DNAm* → BP or BP → *DNAm*?

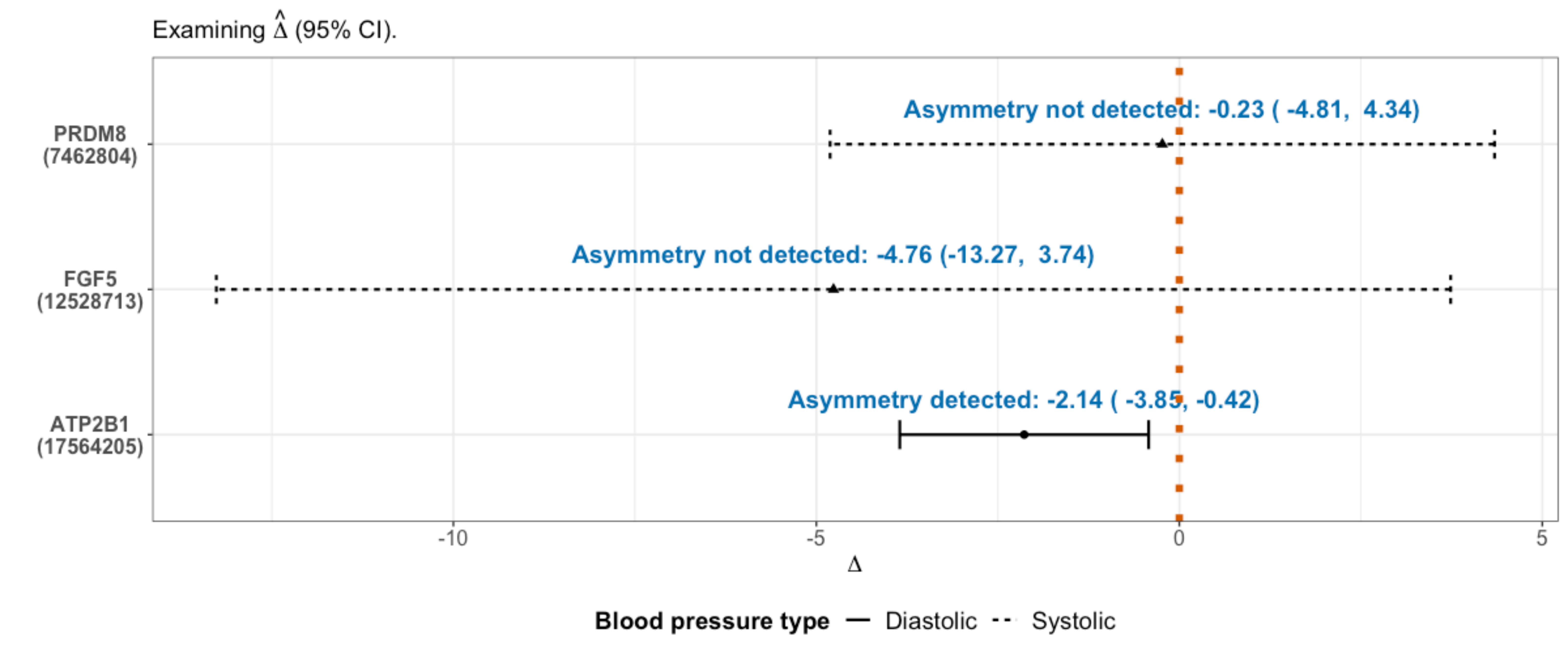


Finding 3: DNAm site #7462804 in *PRDM8*

- Strongly associated with **systolic** BP.
- Strong signal to drive gene-wide association with SBP.
- Next: check *DNAm* → BP or BP → *DNAm?*



Finding 4: DBP → #17564205 in *ATP2B1*



1. No asymmetry detected: ***#7462804*** (PRDM8) and ***#12528713*** (FGF5)
2. Asymmetry detected: **Diastolic BP** → **#17564205** in ***ATP2B1.***

Thank you for your time!

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References

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