

Supplemental Health, DI & LTC Conference

**Evolve with Epigenetics
in DI, LTC & CI
Risk Assessment**



ENGAGE

EVOLVE

ELEVATE

2023



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Welcome to the World of Epigenetics!

Agenda

- Review the human genome & epigenome
- Explain the history & science of epigenetics
- Describe epigenetic modulation in normal development, the environment & due to lifestyle behaviors
- Describe how smoking affects the epigenome & causes disability
- Explain how epigenetic testing can measure the impact of excess alcohol use, which leads to increased disability risk
- Review how coronary heart disease, a leading cause of long-term disability, can be discovered through epigenetic blood testing



Genome v. Epigenome



Genome (Genetics is the biologic study of genes, variation & heredity)

- Entire genetic code across all cell types
- Heritable
- Can be damaged by radiation
- Can be edited through gene therapy (e.g., CRISPR)

Epigenome (Epigenetics is the biologic study of the epigenome)

- Entire epigenetic code across all cells in the body
- Can be reprogrammed due to normal development, environmental exposures, diseases & medications that target epigenetic regulators



Sir Conrad Waddington was a pioneer!

- First defined epigenetics in the early 1940s as: “The branch of biology which studies causal interactions between genes and their products, which bring the phenotype into being.”
- What’s a **phenotype**? **Phenotype**: Observable physical characteristics of an organism (e.g., appearance, behavior, development)
- Later in the 1940s, a type of epigenetic change called **DNA methylation** was described.
- In 1975, Allfrey et al. demonstrated DNA methylation & **histone modification** contributed to **gene expression control**.



Conceptualizing Epigenetics

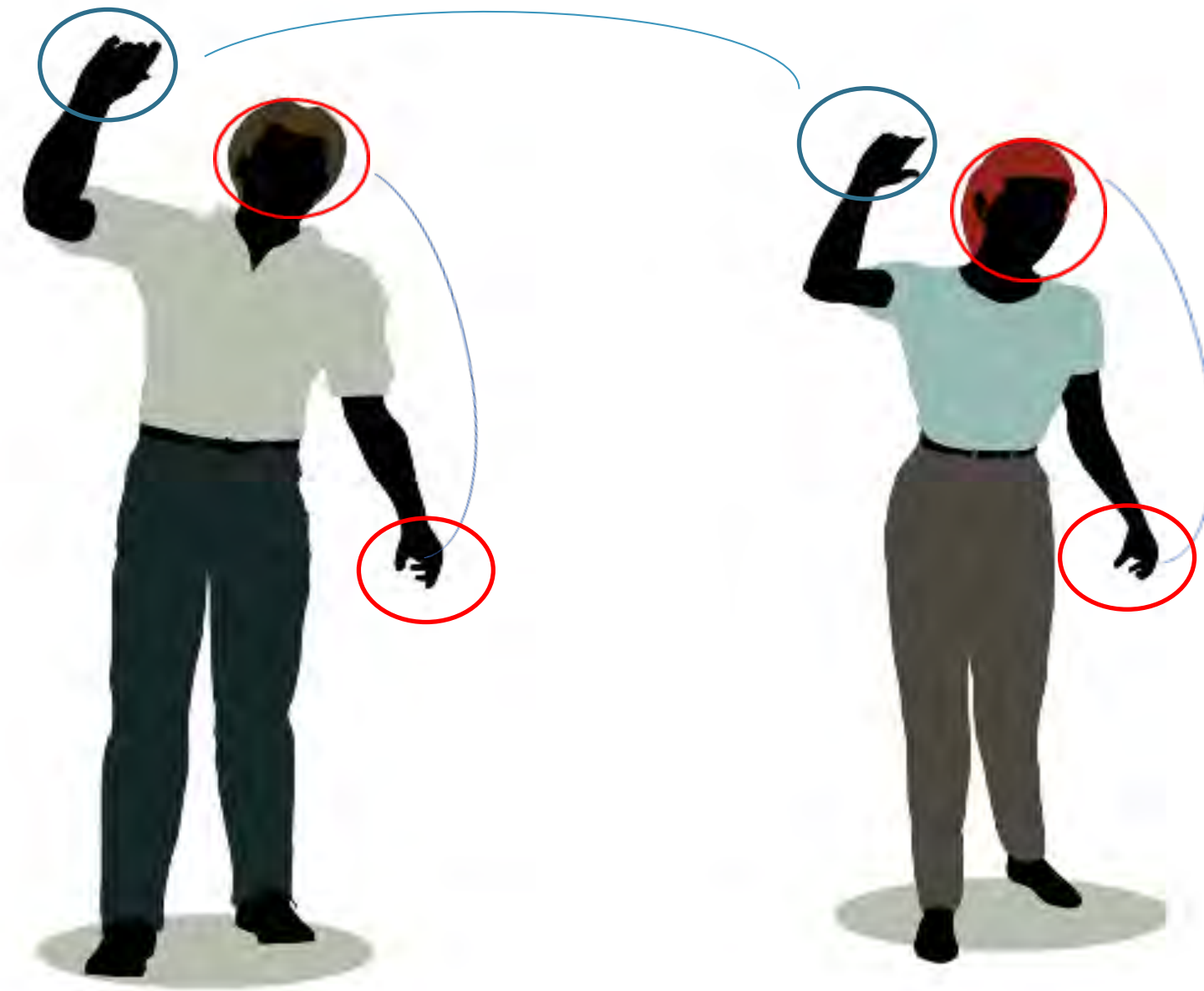
**We are alike but different...
why?**

Epigenetics!

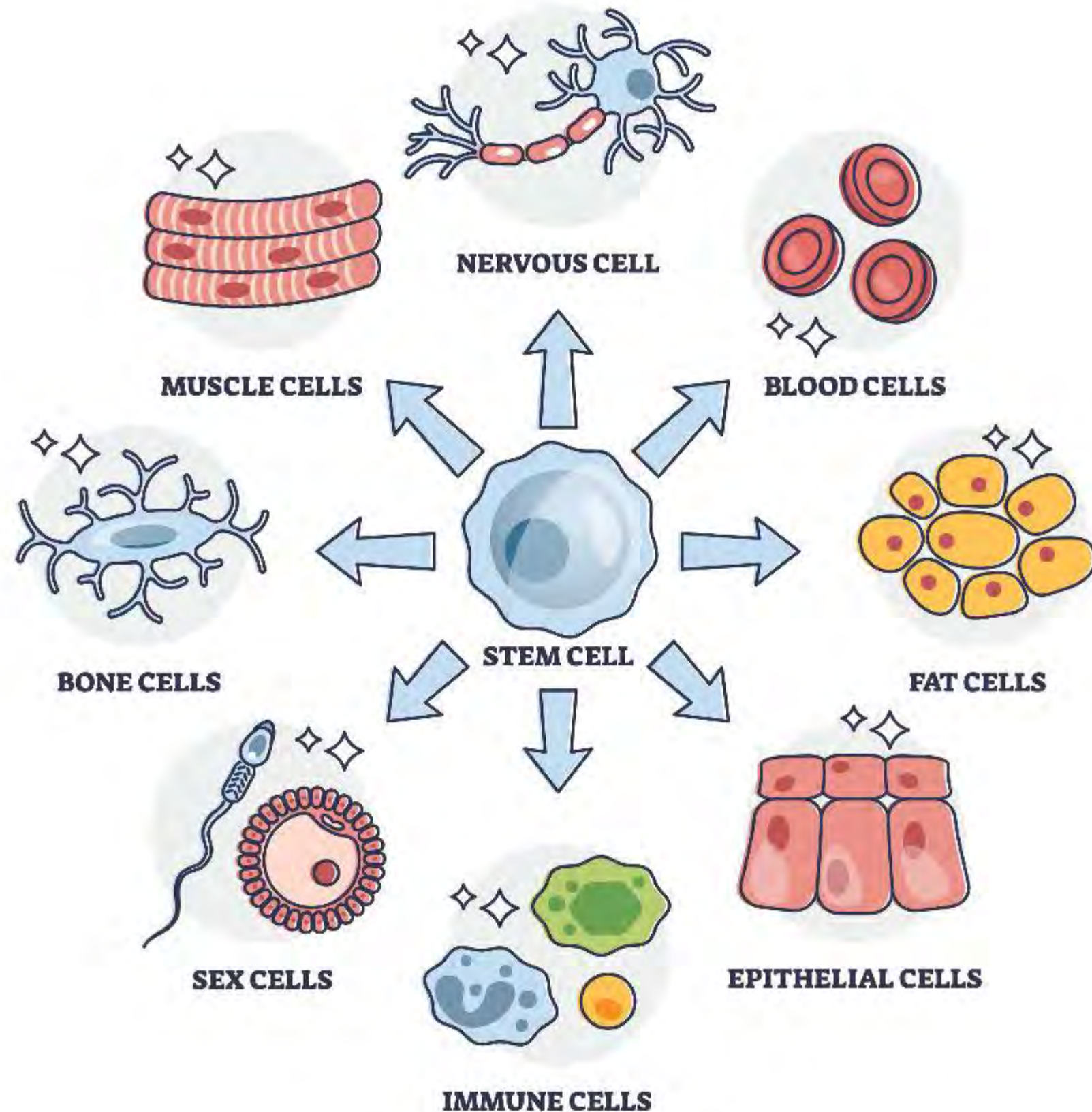
Epigenetic systems modulate gene transcription to:

- **Ensure proper cell fate.**
- Compensate for **differences in background genetic variation.**

Same in form, different in genotype



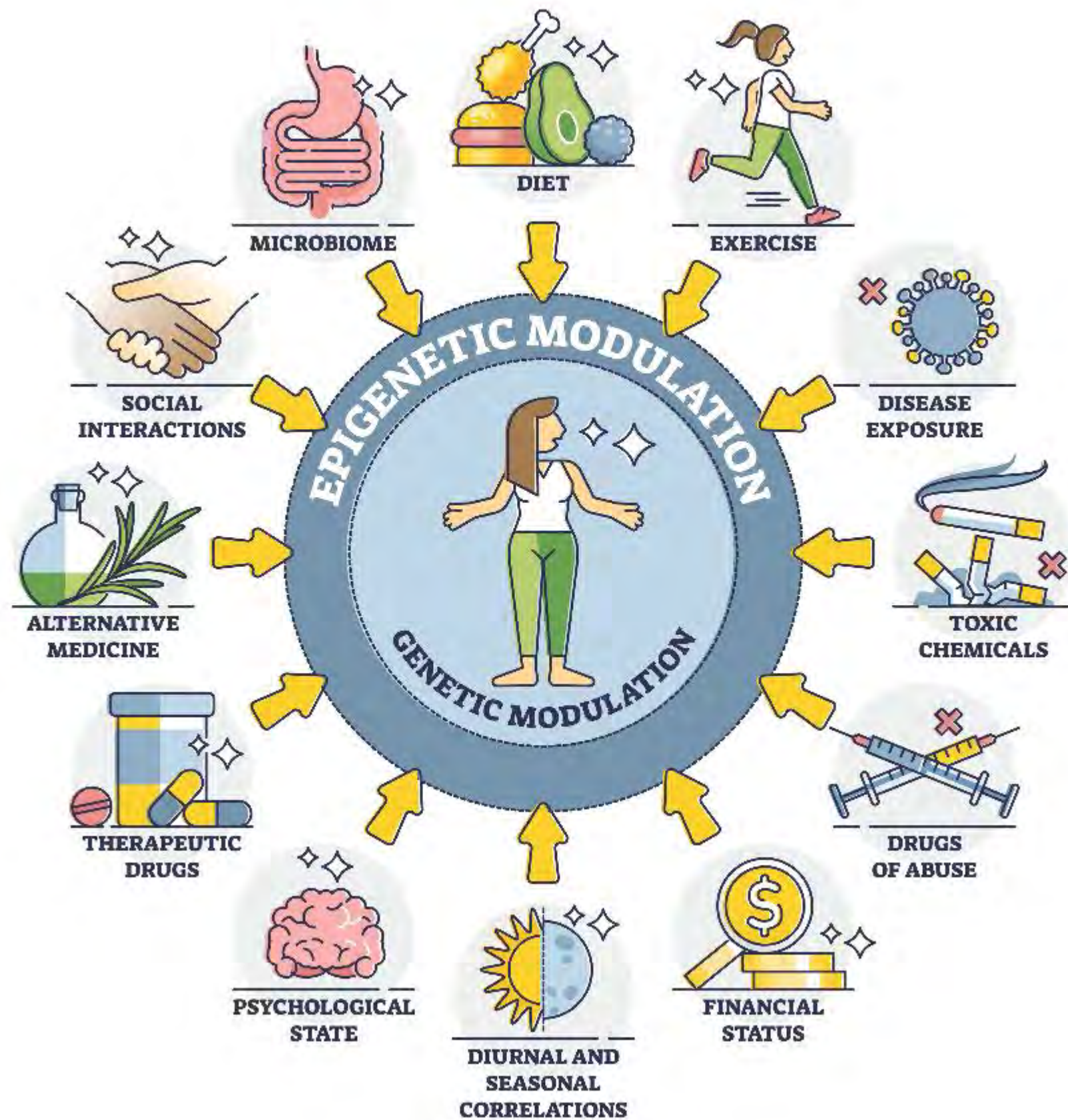
Epigenetics in Normal Development



Epigenetics play an important role in our normal development, turning stem cells into a variety of cells that we need to live, such as:

- Bone cells
- Blood cells
- Nerve cells
- Muscle cells
- Immune cells

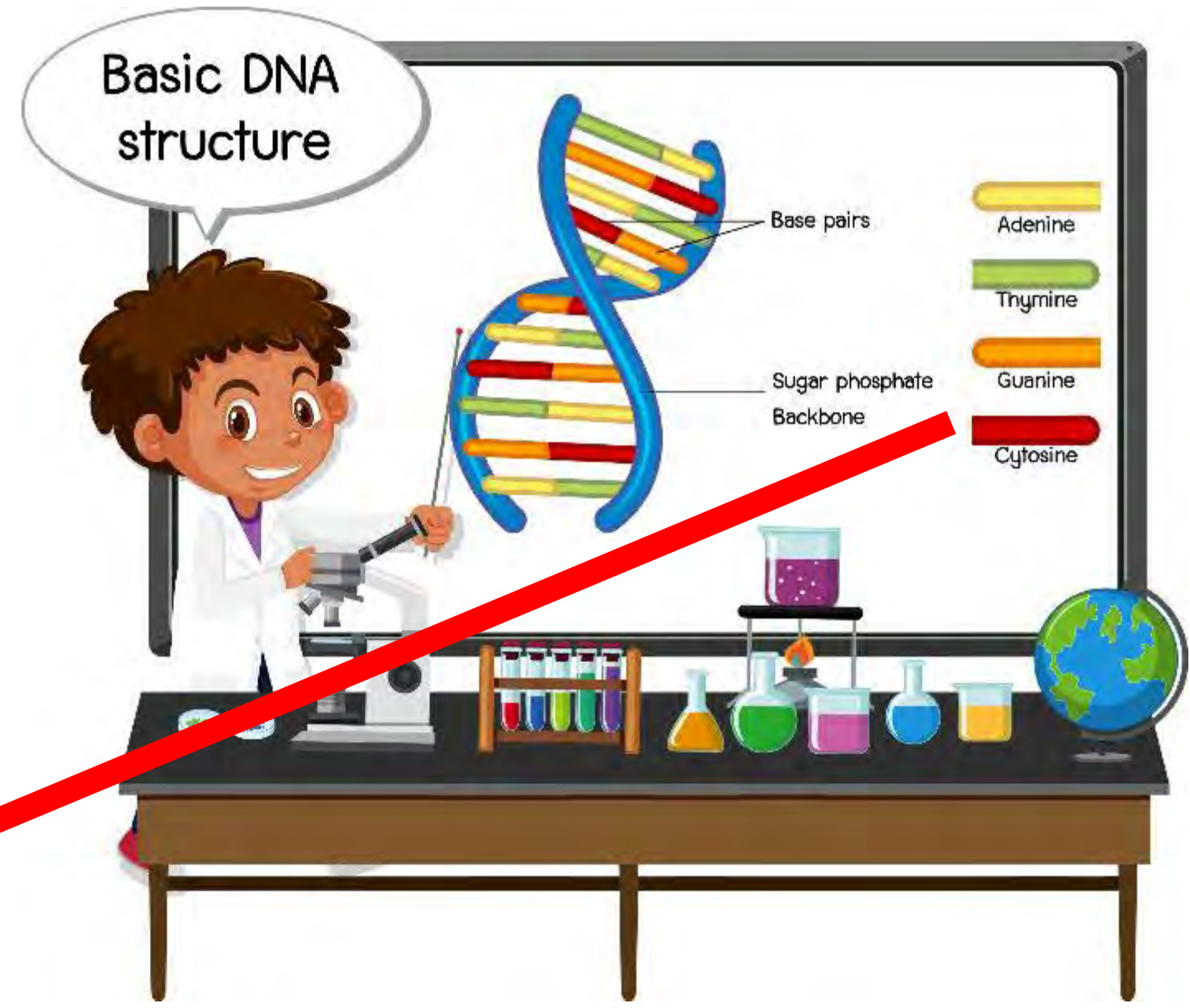
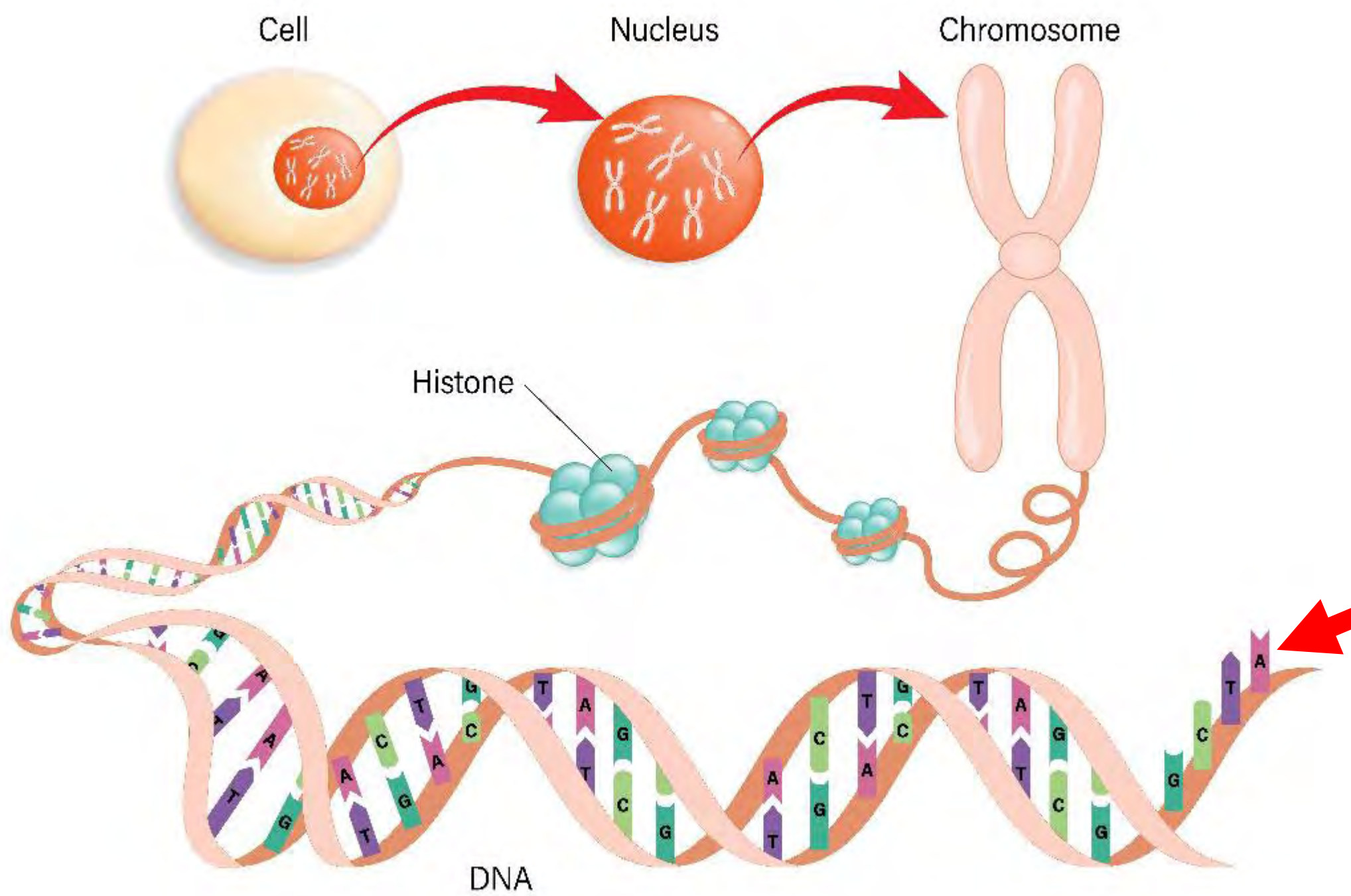
Environmental & Lifestyle Impact



Epigenetic modulation

- Alters the phenotype but not the genotype of an organism
 - Can be good or bad
-
- Can negatively occur from many different things, such as:
 - Smoking
 - Diet
 - Drugs of Abuse
 - Lack of Exercise
 - Stress
 - Disease exposure

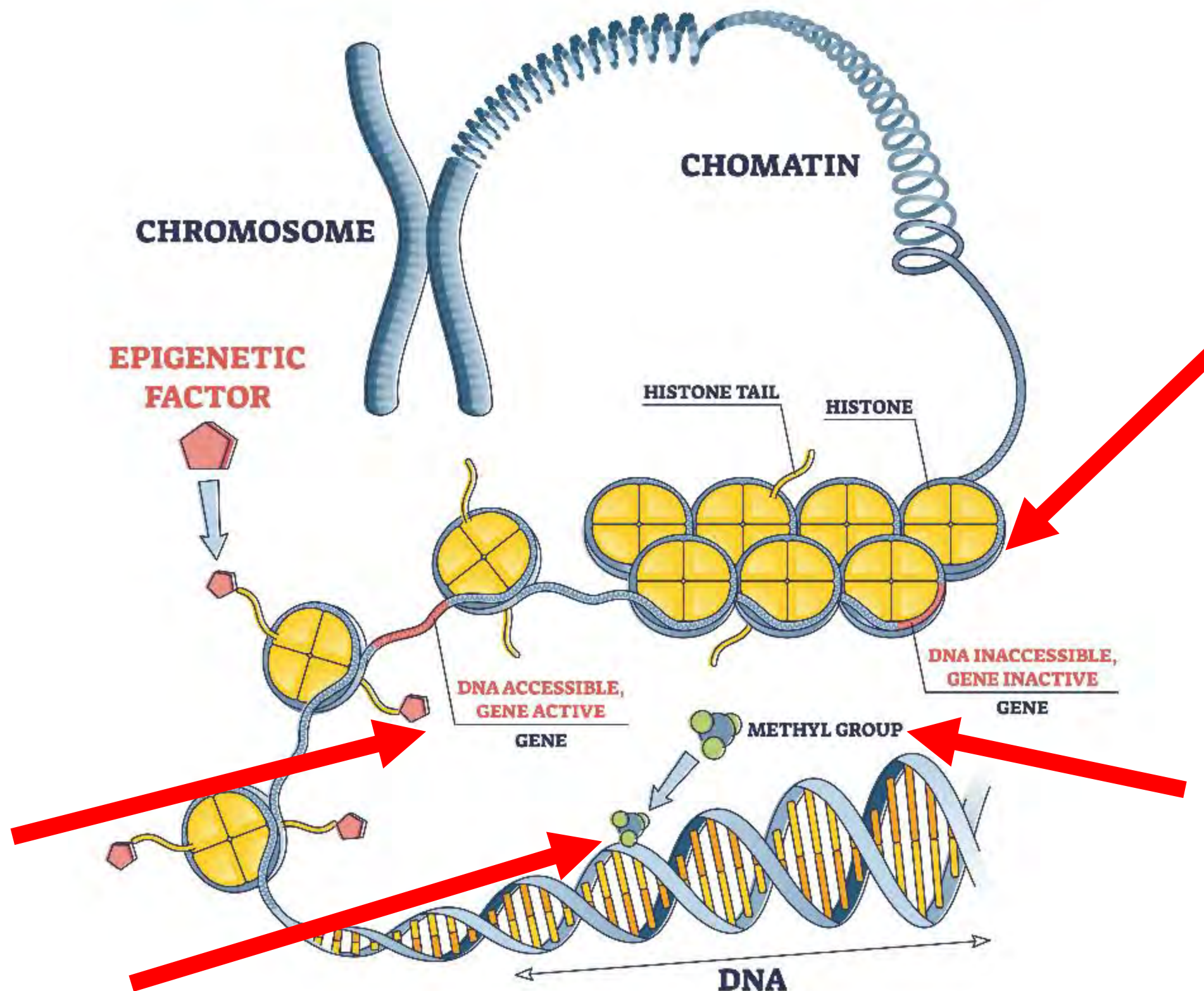
DNA & How Epigenetic Changes Occur



The Science of DNA Methylation



EPIGENETIC MECHANISMS



Types of Epigenetic Modification

- DNA Methylation
 - Methyl group is added, turning a gene off (GOOD!)
 - Demethylation: A methyl group is removed, turning a gene on (BAD!)
- Histone Modification
 - DNA wraps around histones (proteins)
 - Tightly packed: Gene is “off”
 - Loosely packed: Gene is “on”

**The degree of methylation is measured at key sites in the epigenome.



What About Smoking?

Photo by [Panos Sakalakis](#) on [Unsplash](#)



The Effect of Smoking on the Epigenome



- Smoking has a **profound** effect on the epigenome.
- At the nominal level, over 1/4th of the variable epigenome in white blood cells (WBCs) is affected by smoking.
- From a methylation perspective, it may be the single **worst** thing you can do.

Received: 9 December 2016 | Accepted: 9 June 2017
DOI: 10.1002/ajmg.b.32565

RESEARCH ARTICLE

WILEY  **Neuropsychiatric Genetics**

Genetically contextual effects of smoking on genome wide DNA methylation

Meeshanthini V. Dogan^{1,2}  | Steven R. H. Beach³  | Robert A. Philibert^{1,2,4}

Dogan *et al.* *BMC Genomics* 2014, **15**:151
<http://www.biomedcentral.com/1471-2164/15/151>

 BMC Genomics

RESEARCH ARTICLE

Open Access

The effect of smoking on DNA methylation of peripheral blood mononuclear cells from African American women

Meeshanthini V Dogan^{1,2}, Bridget Shields¹, Carolyn Cutrona³, Long Gao², Frederick X Gibbons⁴, Ronald Simons⁵, Martha Monick⁶, Gene H Brody⁷, Kai Tan^{2,6}, Steven RH Beach⁷ and Robert A Philibert^{1*}

Epigenetic Research With Smoking



Good Science Starts With Reproducible Findings

“...one of the strongest and most consistently replicated epigenetic relationships...”

“There is nothing else comparable with the remarkable AHRR–smoking relationship in the rest of the SUD epigenetics literature”

Gelernter & Polimanti,
Nature Reviews 2021

RAPID PUBLICATION

AMERICAN JOURNAL OF
medical genetics
Neuropsychiatric Genetics

Coordinated Changes in AHRR Methylation in Lymphoblasts and Pulmonary Macrophages From Smokers

Martha M. Monick,¹ Steven R.H. Beach,³ Jeff Plume,^{2,3} Rory Sears,¹ Meg Gerrard,⁴ Gene H. Brody,¹ and Robert A. Philibert^{2,3,5*}

¹Department of Medicine, The University of Iowa, Iowa City, Iowa

²Neuroscience and Genetics Programs, The University of Iowa, Iowa City, Iowa

³The University of Georgia, Athens, Georgia

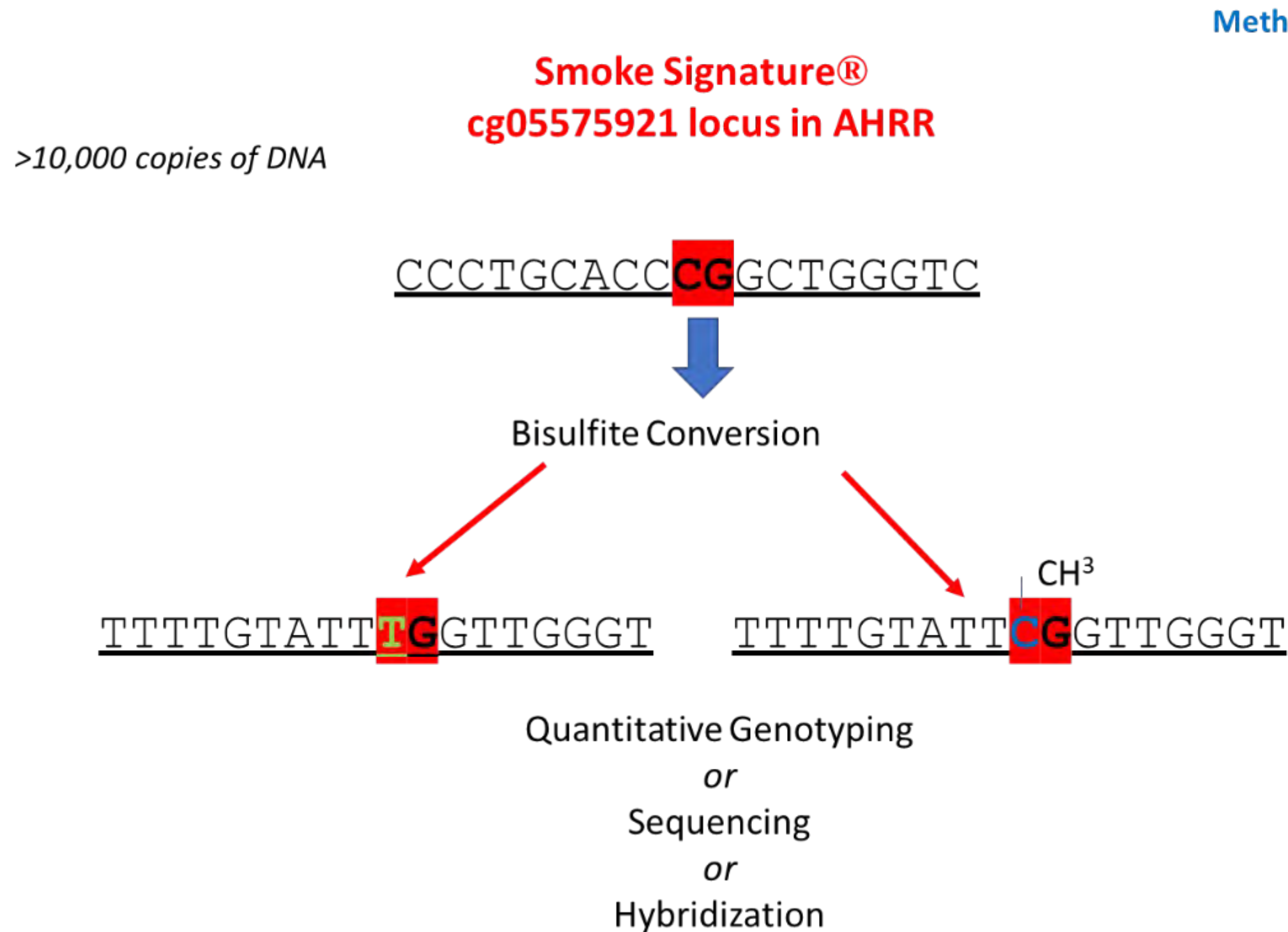
⁴Department of Psychiatry, Dartmouth Medical School, Lebanon, New Hampshire

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Received 14 July 2011; Accepted 21 December 2011

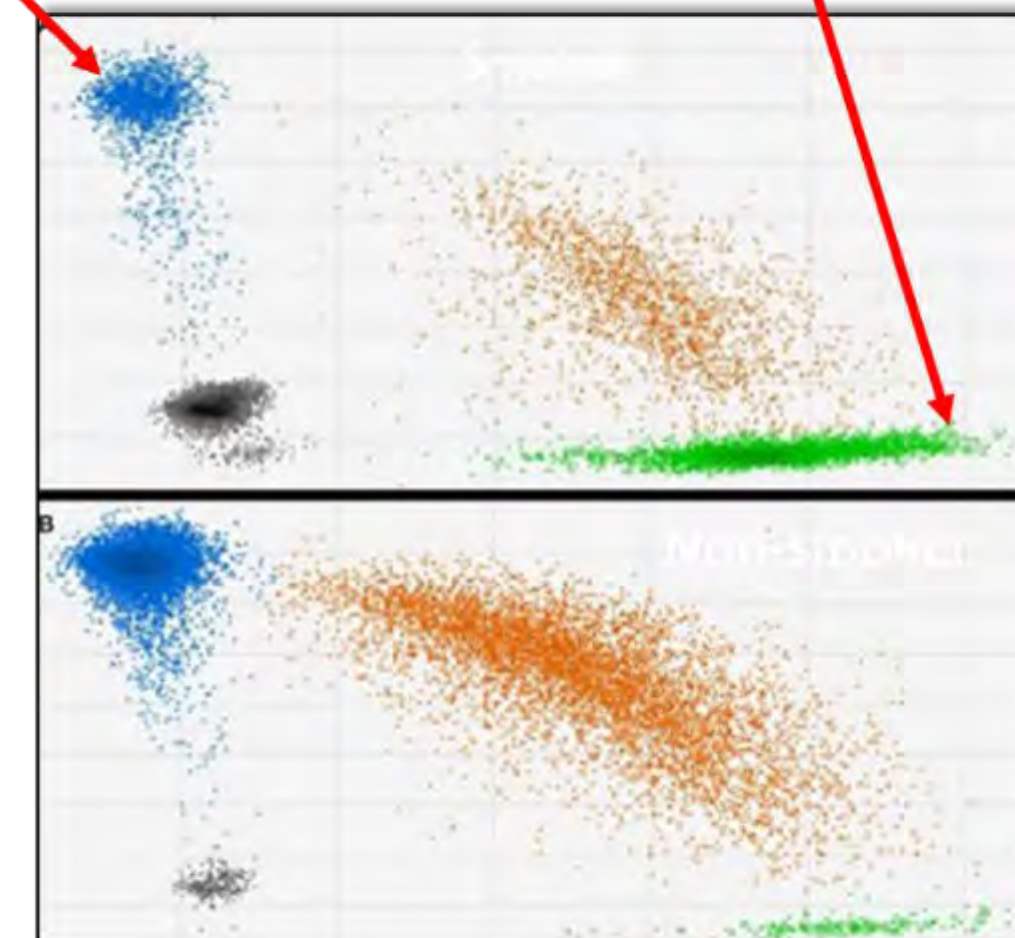


Determining Smoking-Related Methylation Status



Methylated or "C's"

Unmethylated or "T's"



Philibert et al., 2018

Epigenetic Research With Smoking

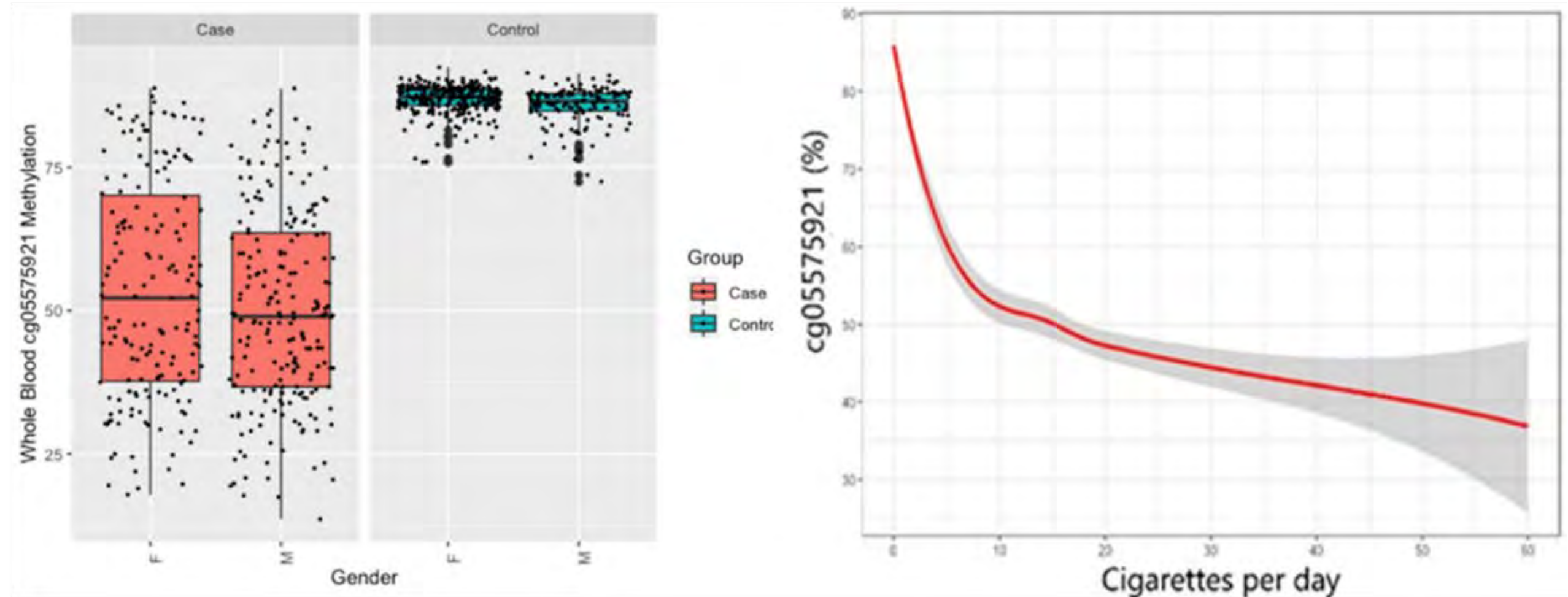


MSdPCR Cg05575921 (Smoke Signature©)

A Powerful Predictor of
Smoking Status in Saliva
and Blood DNA

AUC in blood and saliva
DNA are 0.984 and 0.945,
respectively.
N=844

This is the most
heavily replicated
finding in
epigenetics.



Dawes et al., 2021



Associations of cg05575921 methylation

Medical Conditions

- Mortality
- Alcohol use disorder
- Coronary heart disease
- Lung cancer
- Emphysema
- Stroke
- PTSD
- ADHD

Medically-Related Traits

- Educational achievement
- Accelerated epigenetic aging
- Impaired immune cell response
- Low infant birth weight
- ADHD in offspring
- Frailty
- Impaired cognition
- Poverty

DNA Methylation as a Predictor of Lung Cancer

CANCER EPIDEMIOLOGY, BIOMARKERS & PREVENTION | RESEARCH ARTICLE

AHRR (cg05575921) Methylation Safely Improves Specificity of Lung Cancer Screening Eligibility Criteria: A Cohort Study

Katja Kemp Jacobsen¹, Peter Schnohr², Gorm Boje Jensen², and Stig E. Bojesen^{2,3}

EPIGENETICS
<https://doi.org/10.1080/15592294.2022.2108082>

RESEARCH PAPER

Using Cg05575921 methylation to predict lung cancer risk: a potentially bias-free precision epigenetics approach

Rob Philibert^{a,b,c}, Kelsey Dawes^{a,b}, Joanna Moody^b, Richard Hoffman^d, Jessica Sieren^{c,e,f}, and Jeffrey Long^{b,f}

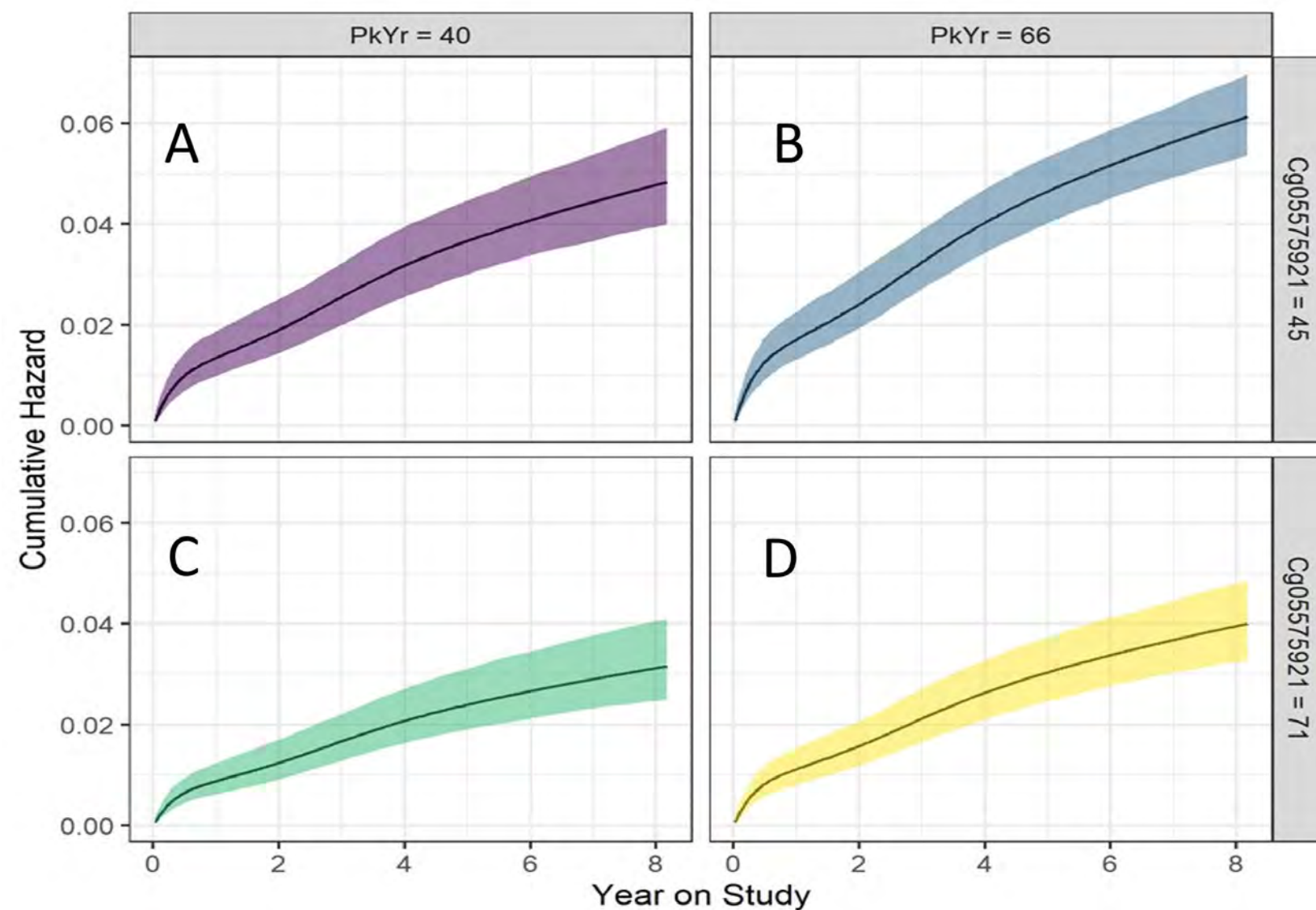
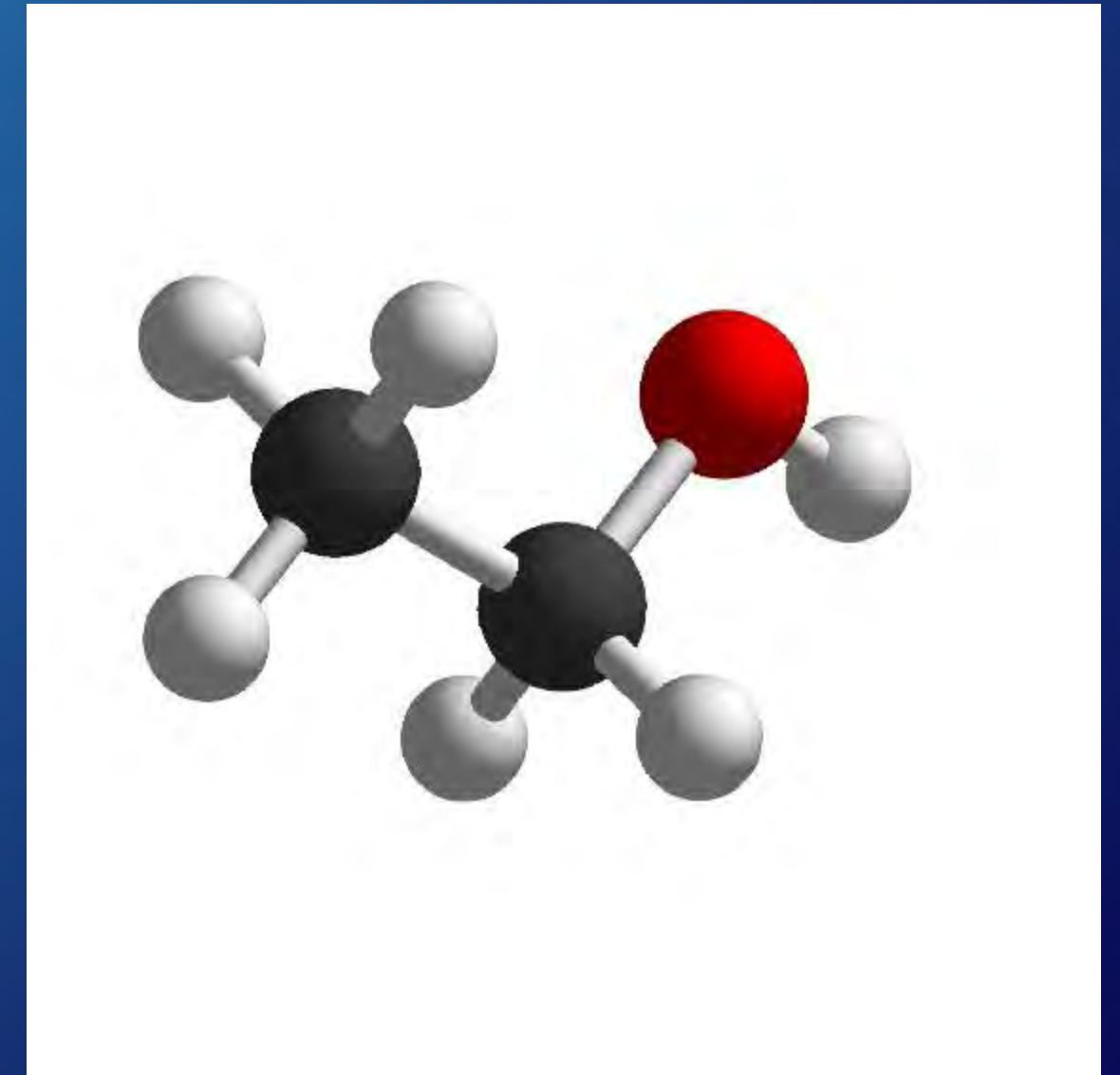


Figure 1. An illustration of the cumulative hazard (95% confidence ribbons) as a function of pack years consumption (PY), and Cg05575921 for four possible 61 yr old subjects. Values for the latter two are set at the 25th and 75th percentiles, and age is set to the mean of the sample. Panel B represents someone at 75th percentile for both PY and smoking intensity, while Panel C represents someone at the 25th percentile for PY and smoking intensity. **From Philibert et al., 2022**

What About Alcohol?





The Effect of Alcohol on the Methylome

- Low amounts of alcohol intake have no discernable effects of DNA methylation.
- However, heavy alcohol consumption (HAC) has profound effects on genome-wide DNA methylation.
- In 2014, Dr. Philibert's group produced the first epigenome-wide study of HAC.





JOURNAL OF INSURANCE MEDICINE
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J Insur Med 2019;48:1-13

LABORATORY TESTING

A Four Marker Digital PCR Toolkit for Detecting Heavy Alcohol Consumption and the Effectiveness of Its Treatment

Robert Philibert, MD, PhD^{1,2}; Shelly Miller¹; Amanda Noel¹; Kelsey Daves²;
Emma Paptworth²; Donald W. Black, MD²; Steven R. H. Beach, PhD³; Jeffrey D. Long,
PhD^{2,4}; James A. Mills, MS²; Meeshanthini Dogan, PhD¹

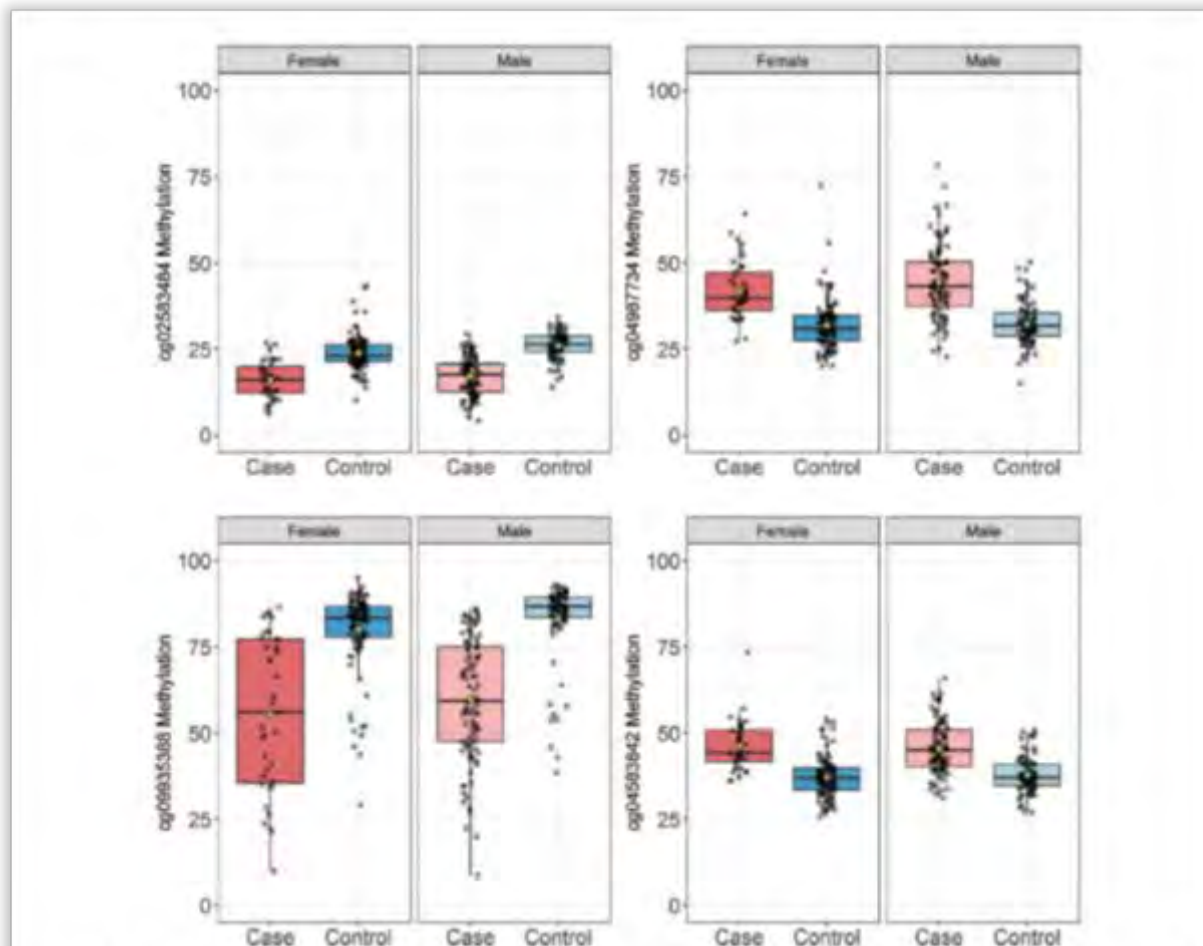


Figure 1. Distribution of the methylation values for each marker for the cases (red) and controls (blue) split by gender. Mean values are indicated by the gold-colored symbol.

Epigenetics can Detect Heavy Alcohol Consumption

Direct Head-to-Head Comparison of CDT to Methylation Alcohol T Score (ATS) Metric

- 182 Clean Controls
- 131 Heavy Drinkers

Receiver Operating Characteristic (ROC) area under the curve (AUC) Analyses

- CDT had an AUC of 0.87 with gender bias present.
- ATS had an AUC of 0.96 with no gender bias.

DNA Methylation Tools for Quantifying Alcohol

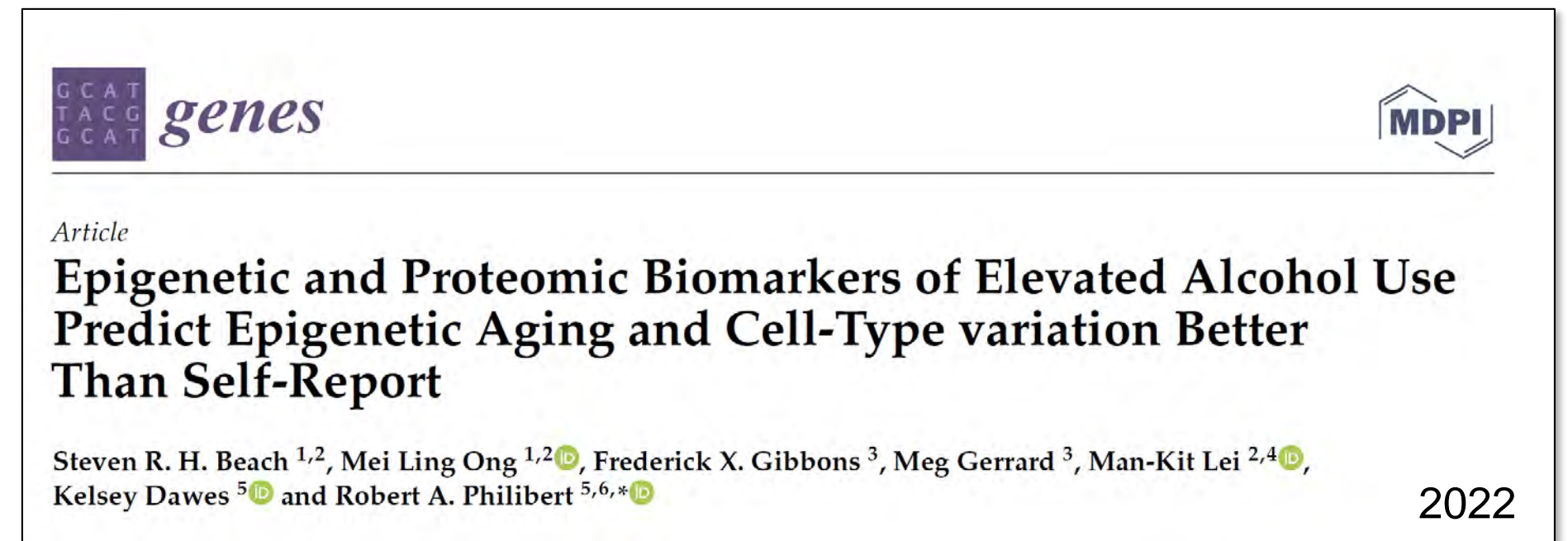
Two methylation tools available for assessing alcohol

Alcohol T Score (2019)

- Metric based on 4 MSdPCR assays
- Validated using CDT, hospital records & BAC
- Commercially available

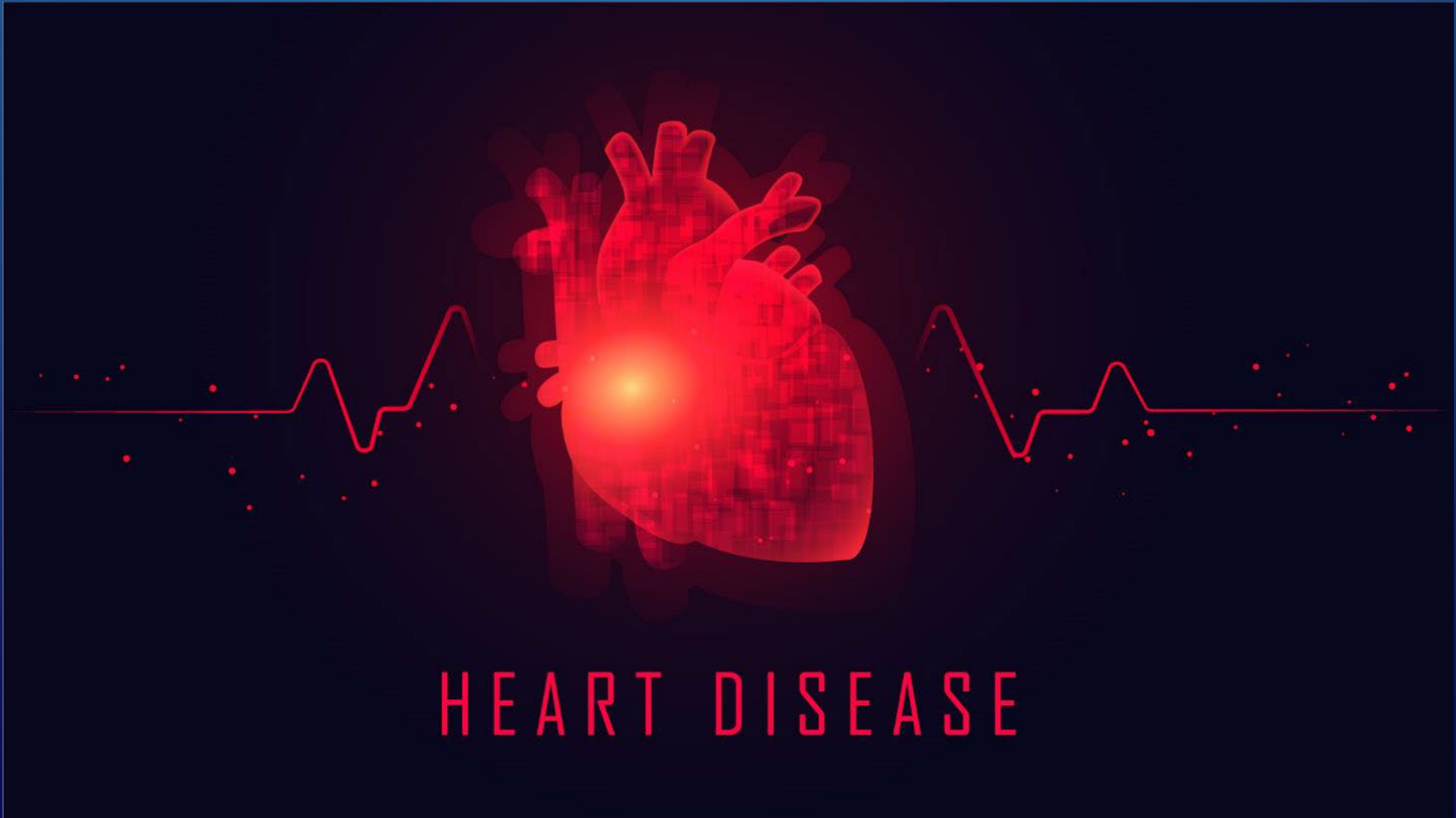
MethylDetectR (2021)

- Uses genome wide array data to estimate alcohol intake
- Academic
- Calibrated off self report



Only Direct Comparison of the ATS with MethylDetectR

- Neither were correlated with current self-report.
- Both predict CDT levels equally well.
- ATS better predicts immune cell changes.



HEART DISEASE



What About Coronary Heart Disease?

	Performance ¹		Cost ²	Strengths			Weaknesses		
	Sensitivity	Specificity		Invasiveness	Global CHD	Etiological Insight	Radiation	Contrast Dye	Availability
Exercise ECG	0.58	0.62	\$891	None	Yes	No	No	No	Fair
Stress Echo	0.85	0.82	\$1740	Low	Yes	No	No	No	Fair
SPECT Study	0.87	0.7	\$1,404	Moderate	Yes	No	No	No	Moderate
PET	0.83	0.89	\$4637	Moderate	Yes	No	Moderate	Yes	Limited
CMRI	0.88	0.89	\$1432	Moderate	Yes	Yes	No	Yes	Moderate
CCTA	0.97	0.78	\$806	Moderate	No	Yes	Moderate	Yes	Moderate
PrecisionCHD	0.79	0.76	\$850	None	No	Yes	No	No	Mail Order
Angiogram	-	-	\$9438	High	No	Yes	High	Yes	Limited

1. Performance metrics per Morrow and De Lemos, 2022. 2. Cost is the U.S. national average per MD Save website (<https://www.mdsave.com/>).

From Broyles and Philibert, in submission



OPEN ACCESS

Citation: Dogan MV, Grumbach IM, Michaelson JJ, Philibert RA (2018) Integrated genetic and epigenetic prediction of coronary heart disease in the Framingham Heart Study. PLoS ONE 13(1): e0190549. <https://doi.org/10.1371/journal.pone.0190549>

Editor: Tanja Zeller, Universitätsklinikum Hamburg-Eppendorf, GERMANY

Received: October 4, 2017

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Data Availability Statement: The Framingham Heart Study data are available through dbGAP (<https://dbgap.ncbi.nlm.nih.gov>).

RESEARCH ARTICLE

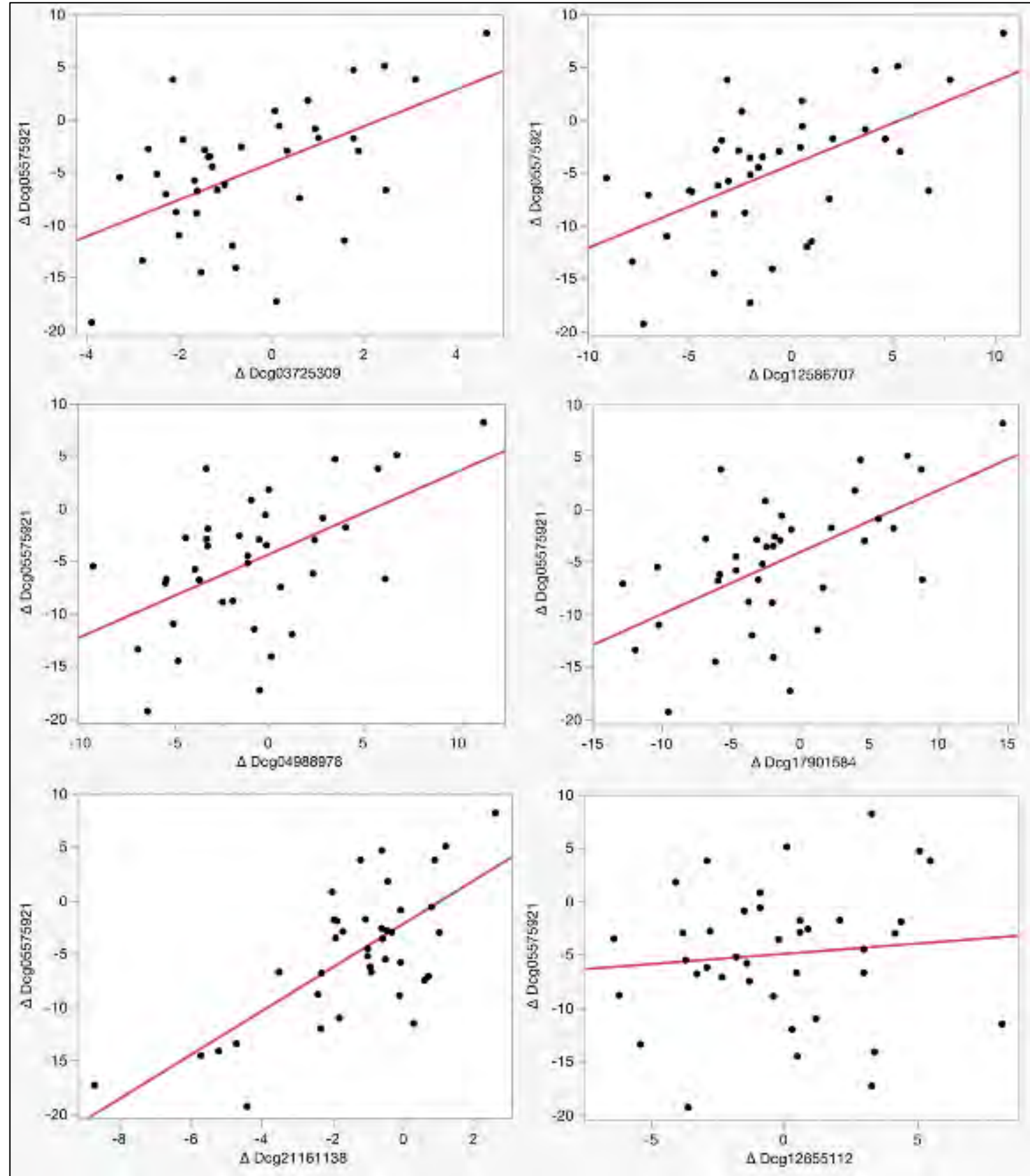
Integrated genetic and epigenetic prediction of coronary heart disease in the Framingham Heart Study

Meeshanthini V. Dogan^{1,2,3}, Isabella M. Grumbach^{4,5}, Jacob J. Michaelson², Robert A. Philibert^{1,2,6*}

1 Department of Biomedical Engineering, University of Iowa, Iowa City, Iowa, United States of America, **2** Department of Psychiatry, University of Iowa, Iowa City, Iowa, United States of America, **3** Cardio Diagnostics LLC, Coralville, Iowa, United States of America, **4** Department of Internal Medicine, University of Iowa, Iowa City, Iowa, United States of America, **5** Iowa City Veterans Affairs Healthcare System, Iowa City, Iowa, United States of America, **6** Behavioral Diagnostics LLC, Coralville, Iowa, United States of America

* robert-philibert@uiowa.edu

Epigenetic Diagnostic Testing for CHD



PrecisionCHD™

The world's first artificial intelligence (AI)-driven integrated epigenetic-genetic diagnostic test for coronary heart disease



Epigenetic changes caused by coronary artery disease are now able to be detected through blood testing.

Imagine diagnosing heart disease through a blood test & not a stress test!

Philibert et al., 2023

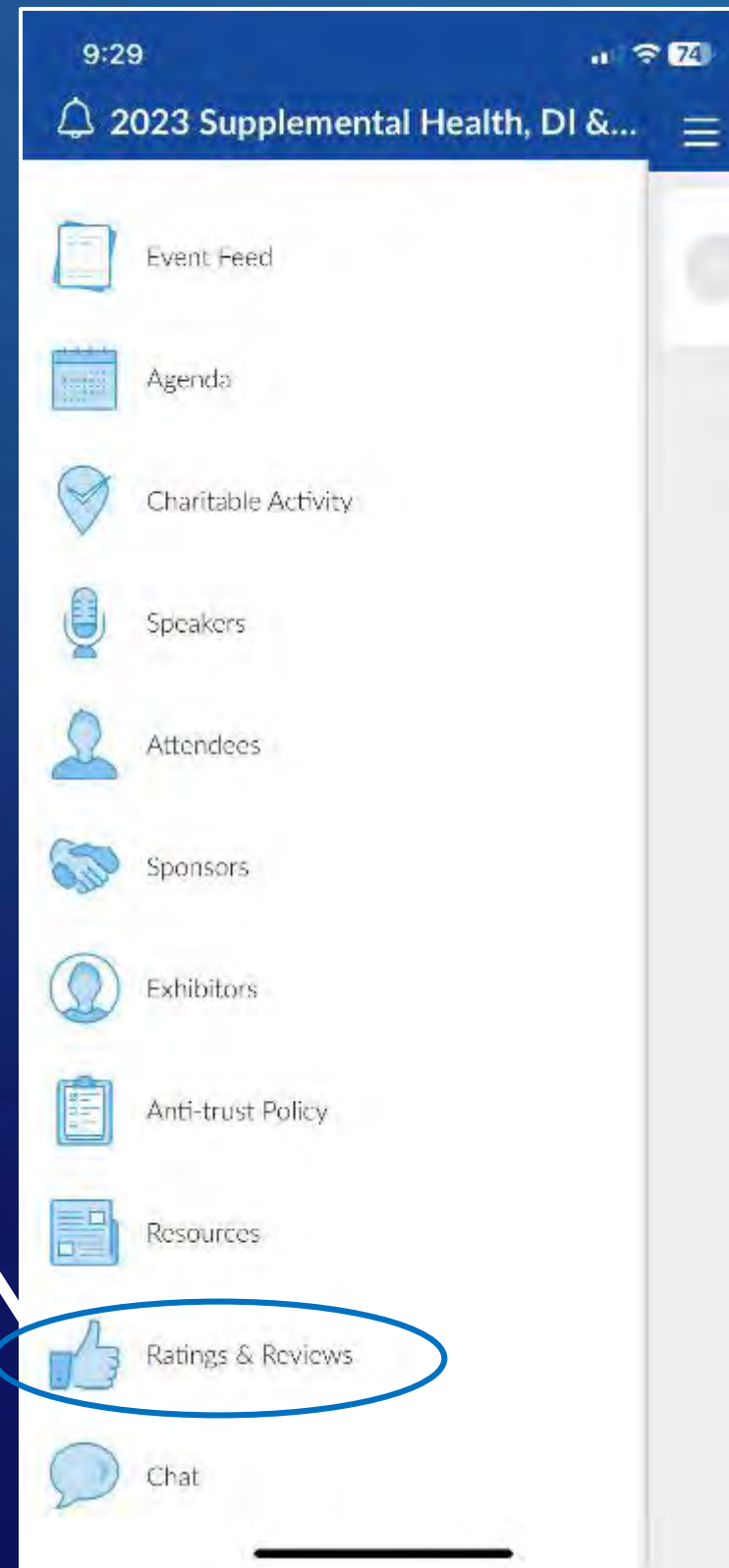


Summary

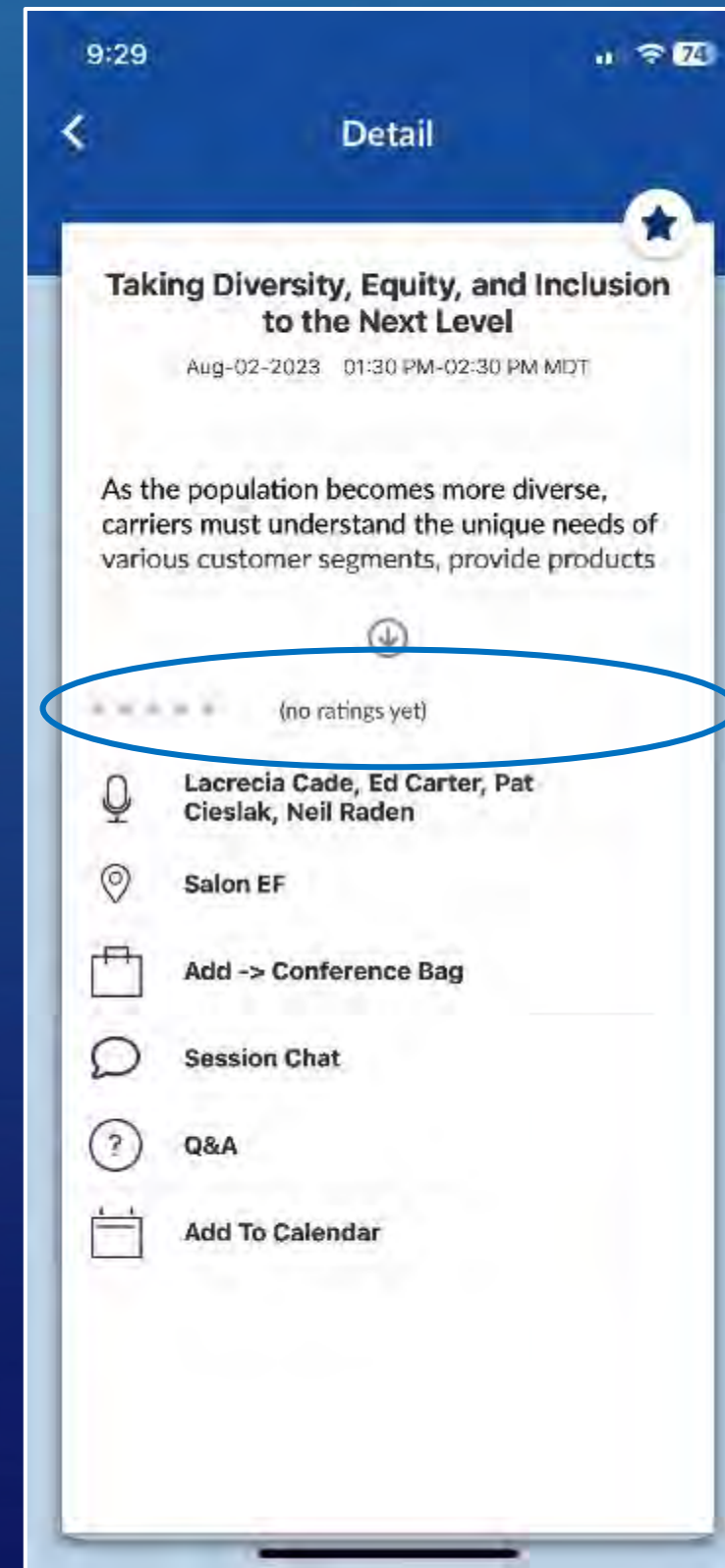
- The science of epigenetics will change both clinical medicine & insurance medicine as we know it.
- Epigenetic changes are part of our normal development but also assist in detection of increased morbidity & mortality risk.
- Lifestyle behaviors such as cigarette smoking & excess alcohol intake cause deleterious epigenetic changes, which lead to diseases that negatively impact morbidity.
- New methods of epigenetic testing use blood to detect coronary heart disease.

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 (no ratings yet)

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