Epigenetics: Explaining Male Infertility and Beyond

Tim Jenkins PhD

Associate Professor of Cell Biology and Physiology

MARCH 19 - 23

PCRS 2025

PACIFIC WAVES - EXPLORING SCIENTIFIC FRONTIERS IN AN EVOLVING SOCIETY

INDIAN WELLS, CA

Disclosures

- **Owner/ Co-Owner Founder/ Co-Founder:**
    - Inherent Biosciences/ Wasatch Biolabs

Needs Assessment Statement and Expected Learning Outcomes

- Describe the balance between epigenetics and genetics
- Discuss the mechanistic role of epigenetics
- Summarize Predictive utility vs. mechanistic utility of epigenetics
- Discuss Epigenetics in male fertility
- Discuss Epigenetics in the clinic

The Fallacy: Nature ~~vs.~~ Nurture

The Reality: Nature *AND* Nurture

Extreme views exist

Human Genome Project (2003)

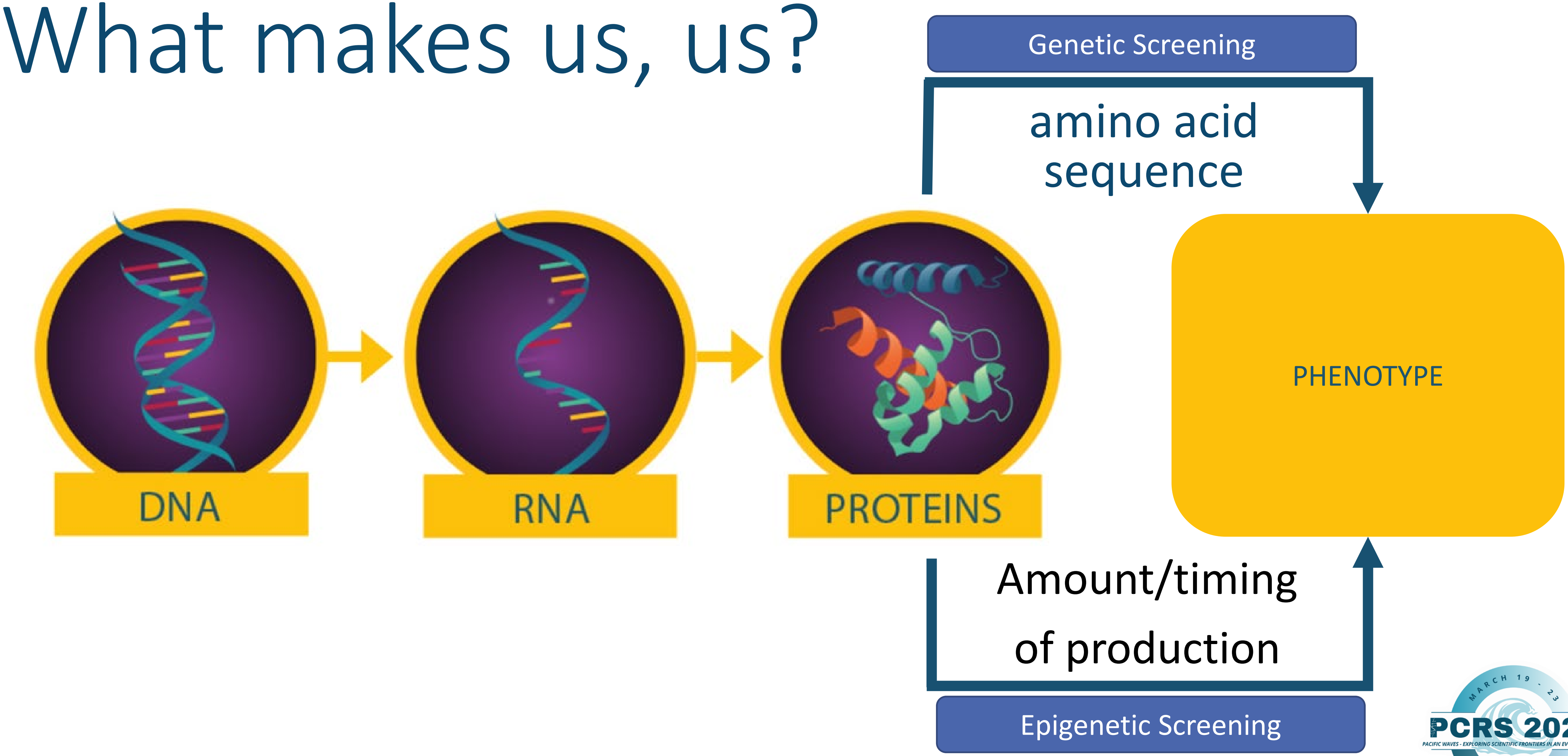
“…revolutionize the diagnosis, prevention and treatment of most, if not all, human diseases.” – Bill Clinton

“you will see a complete transformation in therapeutic medicine.” – Francis Collins

Underlying premise:

If we understand the genome, we’ll understand all phenotypes and pathologies

What makes us, us?



Genetic Screening

amino acid sequence

PHENOTYPE

Amount/timing of production

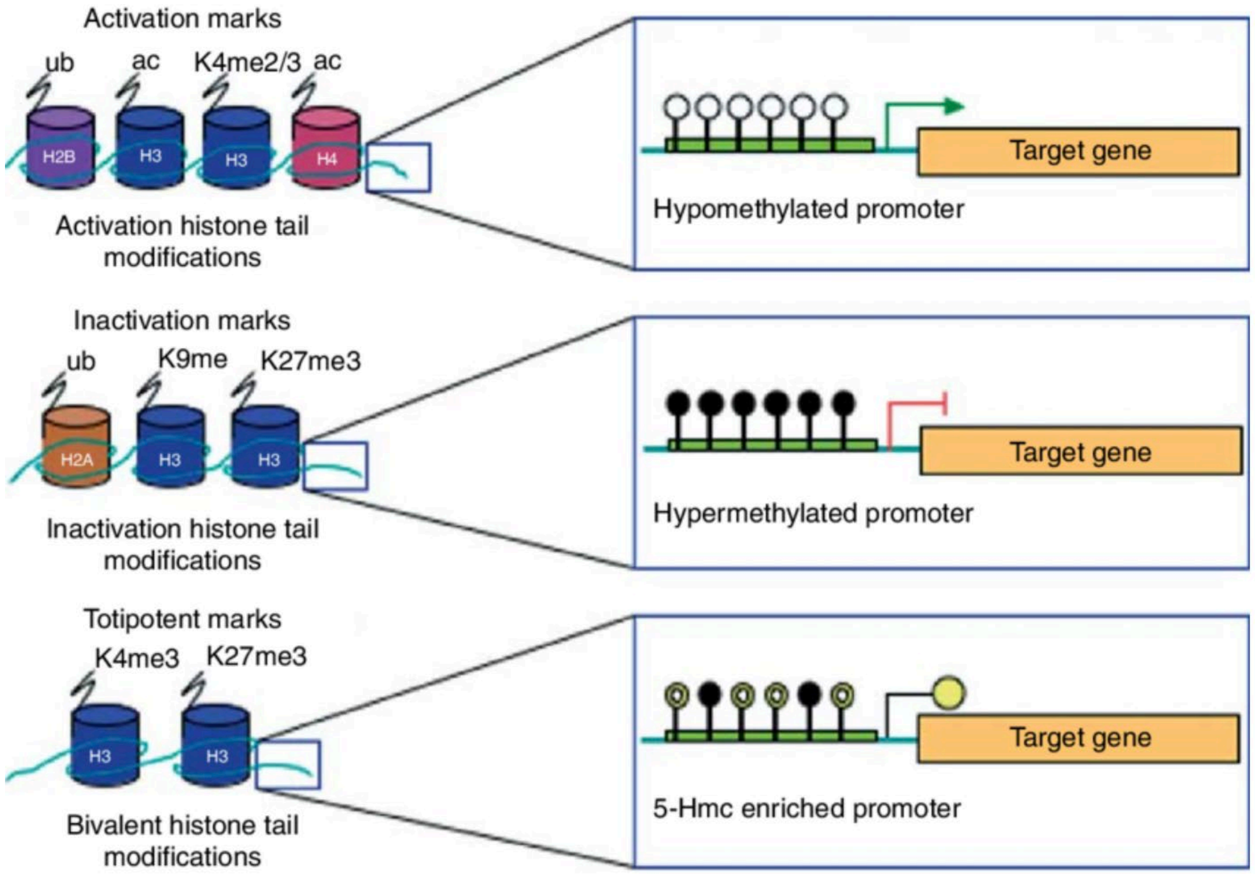
Epigenetic Screening

Needs Assessment Statement and Expected Learning Outcomes

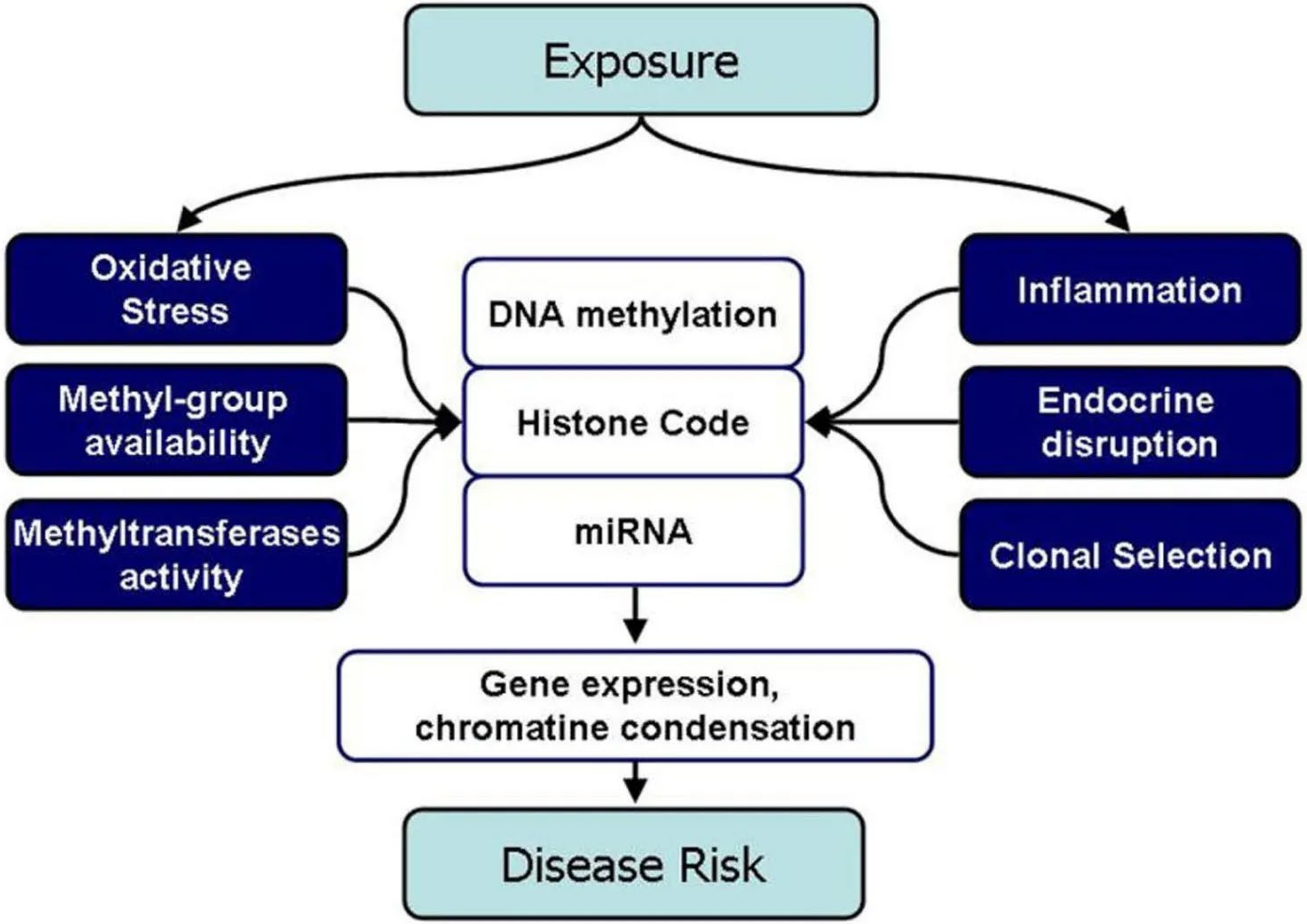
- The balance between epigenetics and genetics
- The mechanistic role of epigenetics
- Predictive utility vs. mechanistic utility of epigenetics
- Epigenetics in male fertility
- Epigenetics in the clinic

Epigenetics and gene regulation

- Histon tail modifications
  - Methylation
  - Acetylation
  - Ubiquitination
- DNA methylation
  - 5-mC and 5-hmC
  - At CpG dinucleotides
- Non-coding RNAs
  - snRNA
  - lncRNA
  - miRNA
  - Etc.



The link between environment and gene regulation



Exposure

Oxidative Stress

Methyl-group availability

Methyltransferases activity

DNA methylation

Histone Code

miRNA

Inflammation

Endocrine disruption

Clonal Selection

Gene expression, chromatine condensation

Disease Risk

Agouti Variable Yellow

Link between environment and phenotype

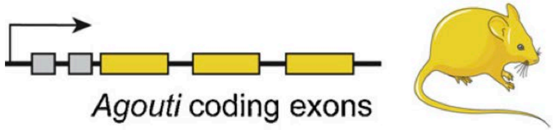
Agouti expression can impact metabolism:

Agouti mice (yellow) are also obese and have type II diabetes

Why difference in methylation?

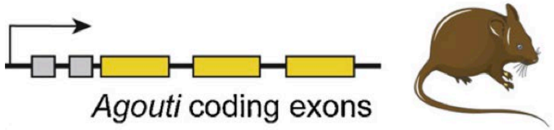
In part…
Mothers diet

Unmethylated promoter



More likely if mother consumed certain environmental toxins: Bisphenol A (BPA)

Methylated promoter



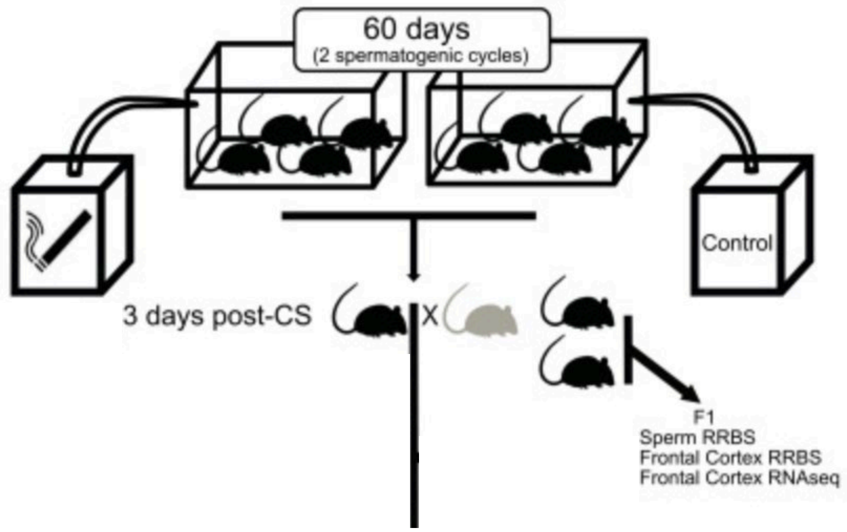
More likely if mother consumed Folate or genistein (soy)

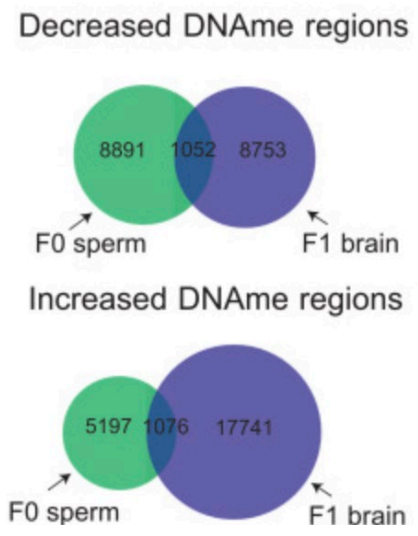
Needs Assessment Statement and Expected Learning Outcomes

- The balance between epigenetics and genetics
- The mechanistic role of epigenetics
- Predictive utility vs. mechanistic utility of epigenetics
- Epigenetics in male fertility
- Epigenetics in the clinic

Typical findings in sperm…

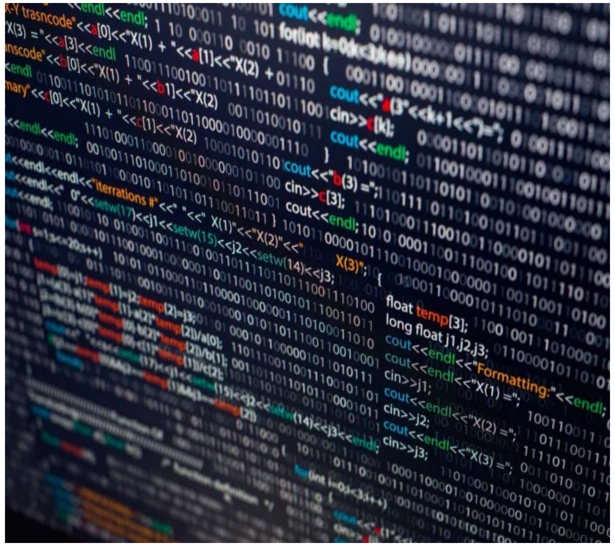
- >2,000 publications: search for *“DNA Methylation Sperm”*
- Differential methylation ≠ differential gene expression in every case
- Can’t check the impact methylation differences directly





Despite our best efforts:

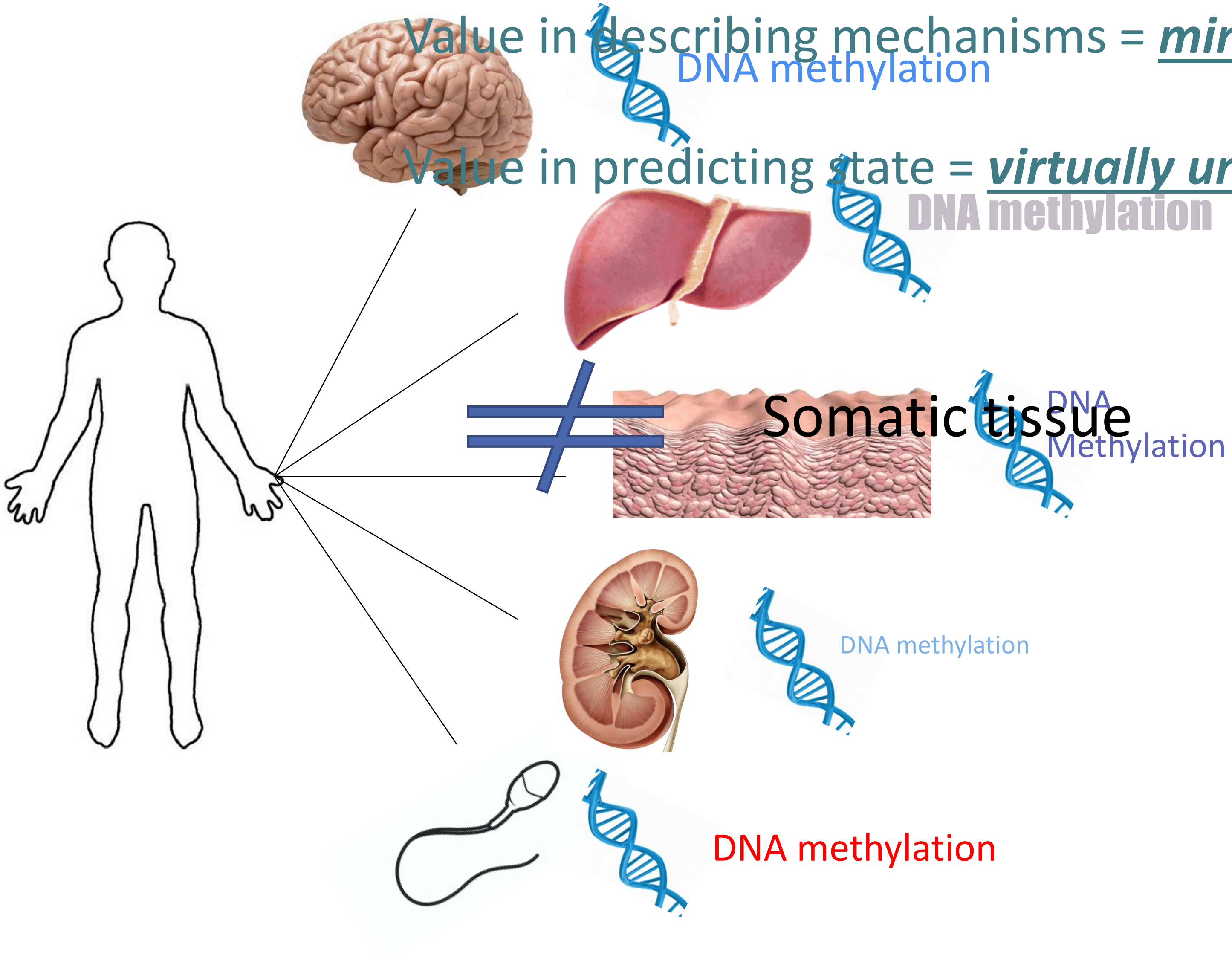
Epigenetic data = Not interpretable

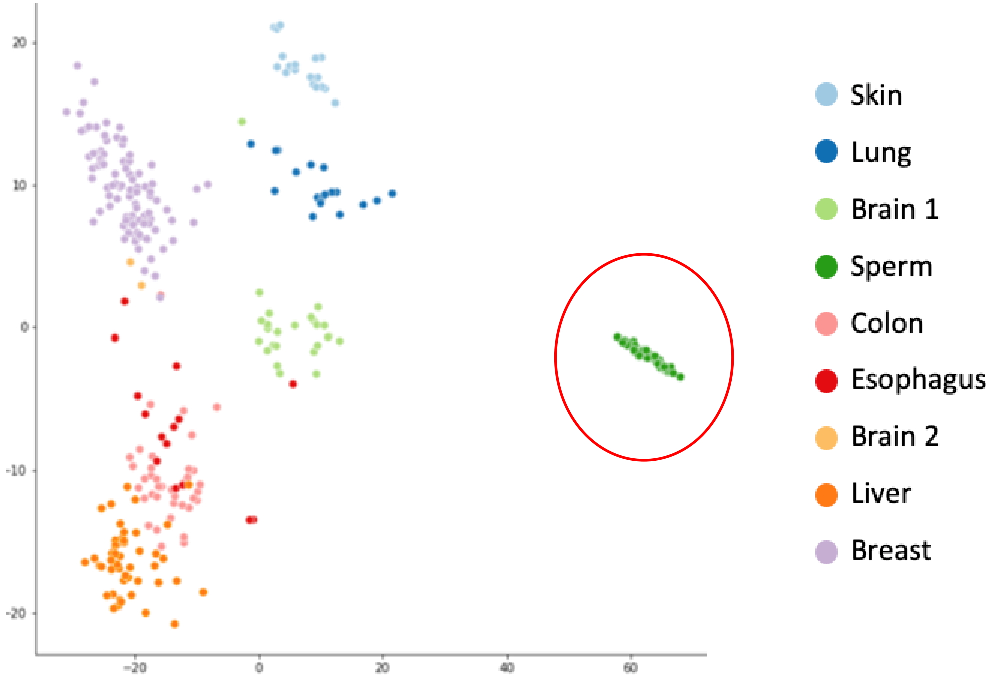


So, what is the value of Epigenetic data?

Value in describing mechanisms = ***minimal***

Value in predicting state = ***virtually unparalleled***

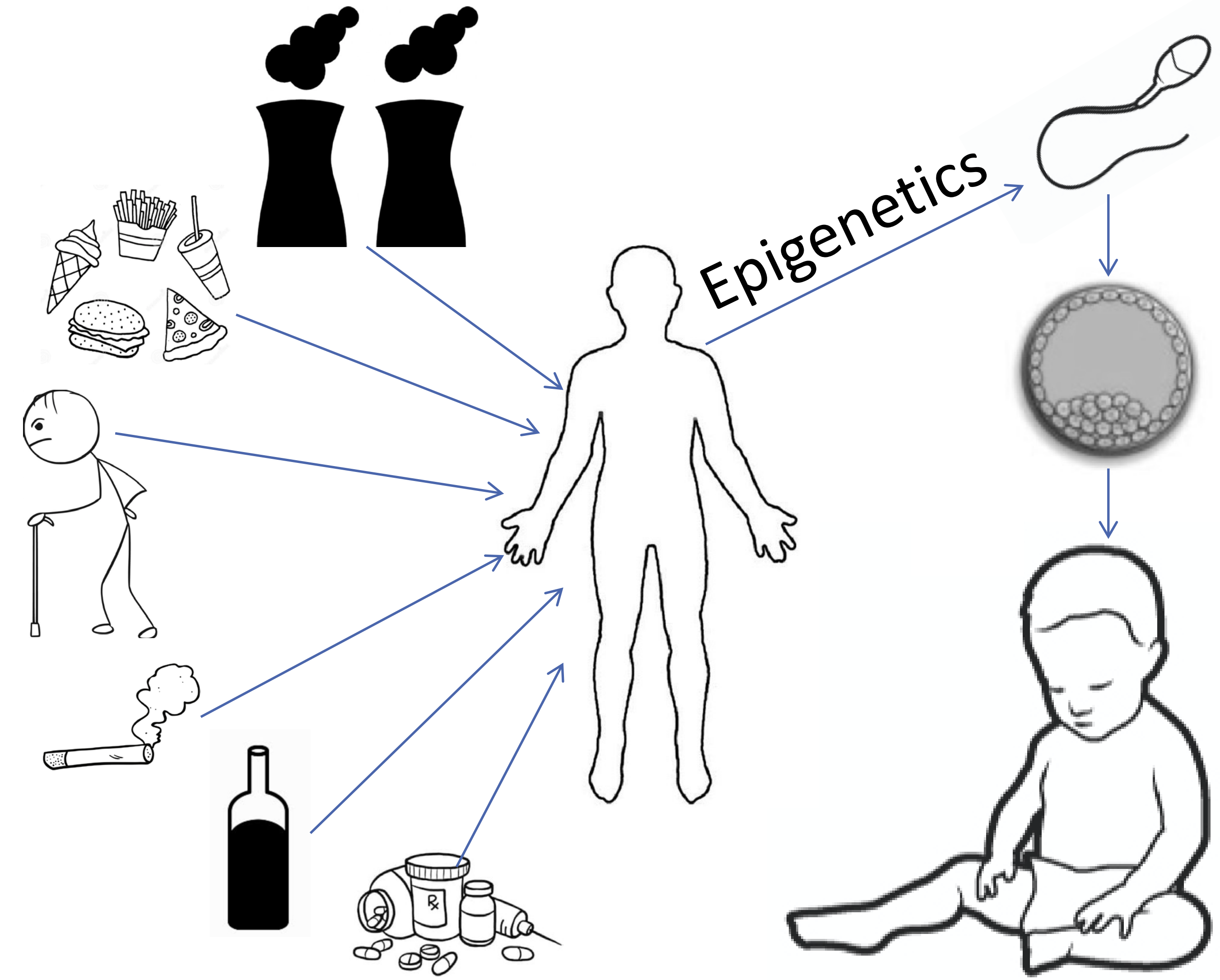


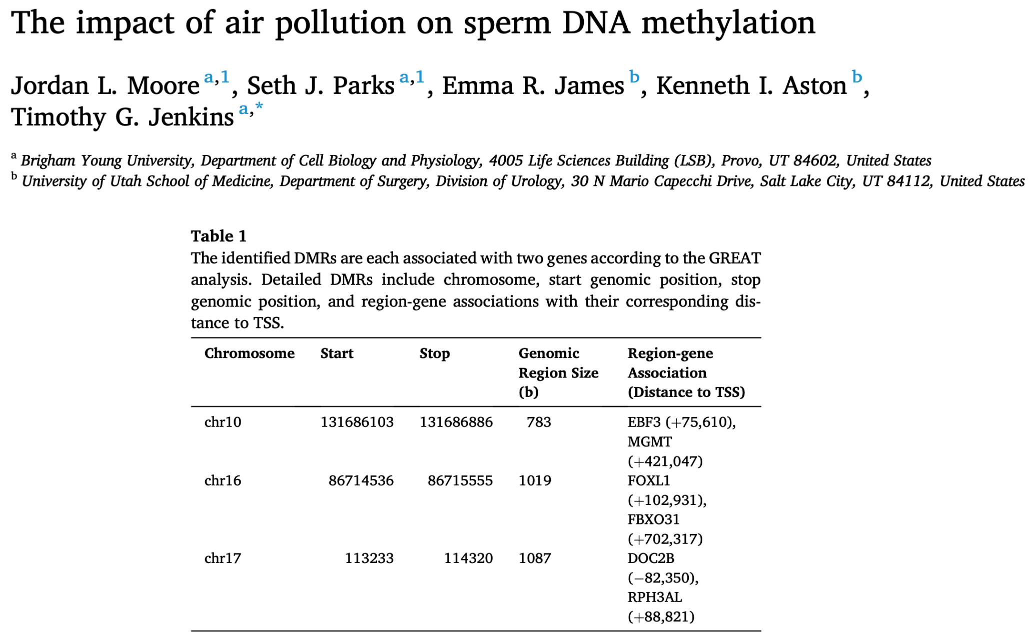


Needs Assessment Statement and Expected Learning Outcomes

- The balance between epigenetics and genetics
- The mechanistic role of epigenetics
- Predictive utility vs. mechanistic utility of epigenetics
- Epigenetics in male fertility
- Epigenetics in the clinic

Environment / Epigenetics and male fertility





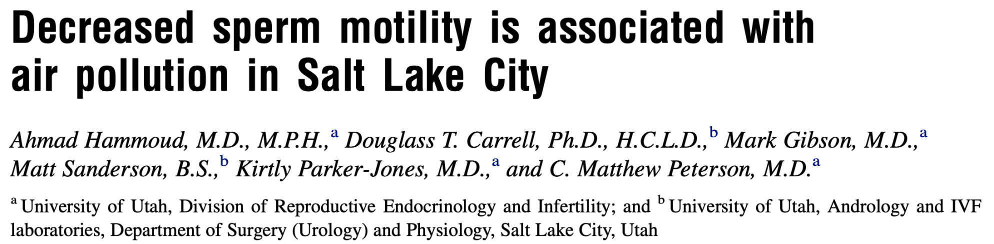
The impact of air pollution on sperm DNA methylation

Jordan L. Moore[a,1], Seth J. Parks[a,1], Emma R. James[b], Kenneth I. Aston[b], Timothy G. Jenkins[a,*]

[a] *Brigham Young University, Department of Cell Biology and Physiology, 4005 Life Sciences Building (LSB), Provo, UT 84602, United States*
[b] *University of Utah School of Medicine, Department of Surgery, Division of Urology, 30 N Mario Capecchi Drive, Salt Lake City, UT 84112, United States*

Table 1
The identified DMRs are each associated with two genes according to the GREAT analysis. Detailed DMRs include chromosome, start genomic position, stop genomic position, and region-gene associations with their corresponding distance to TSS.

Chromosome	Start	Stop	Genomic Region Size (b)	Region-gene Association (Distance to TSS)
chr10	131686103	131686886	783	EBF3 (+75,610), MGMT (+421,047)
chr16	86714536	86715555	1019	FOXL1 (+102,931), FBXO31 (+702,317)
chr17	113233	114320	1087	DOC2B (−82,350), RPH3AL (+88,821)



Decreased sperm motility is associated with air pollution in Salt Lake City

Ahmad Hammoud, M.D., M.P.H.,[a] Douglass T. Carrell, Ph.D., H.C.L.D.,[b] Mark Gibson, M.D.,[a] Matt Sanderson, B.S.,[b] Kirtly Parker-Jones, M.D.,[a] and C. Matthew Peterson, M.D.[a]

[a] University of Utah, Division of Reproductive Endocrinology and Infertility; and [b] University of Utah, Andrology and IVF laboratories, Department of Surgery (Urology) and Physiology, Salt Lake City, Utah

Needs Assessment Statement and Expected Learning Outcomes

- The balance between epigenetics and genetics
- The mechanistic role of epigenetics
- Predictive utility vs. mechanistic utility of epigenetics
- Epigenetics in male fertility
- Epigenetics in the clinic

Future of DNA methylation testing: two flavors

Methylation Risk Scores (MRS)

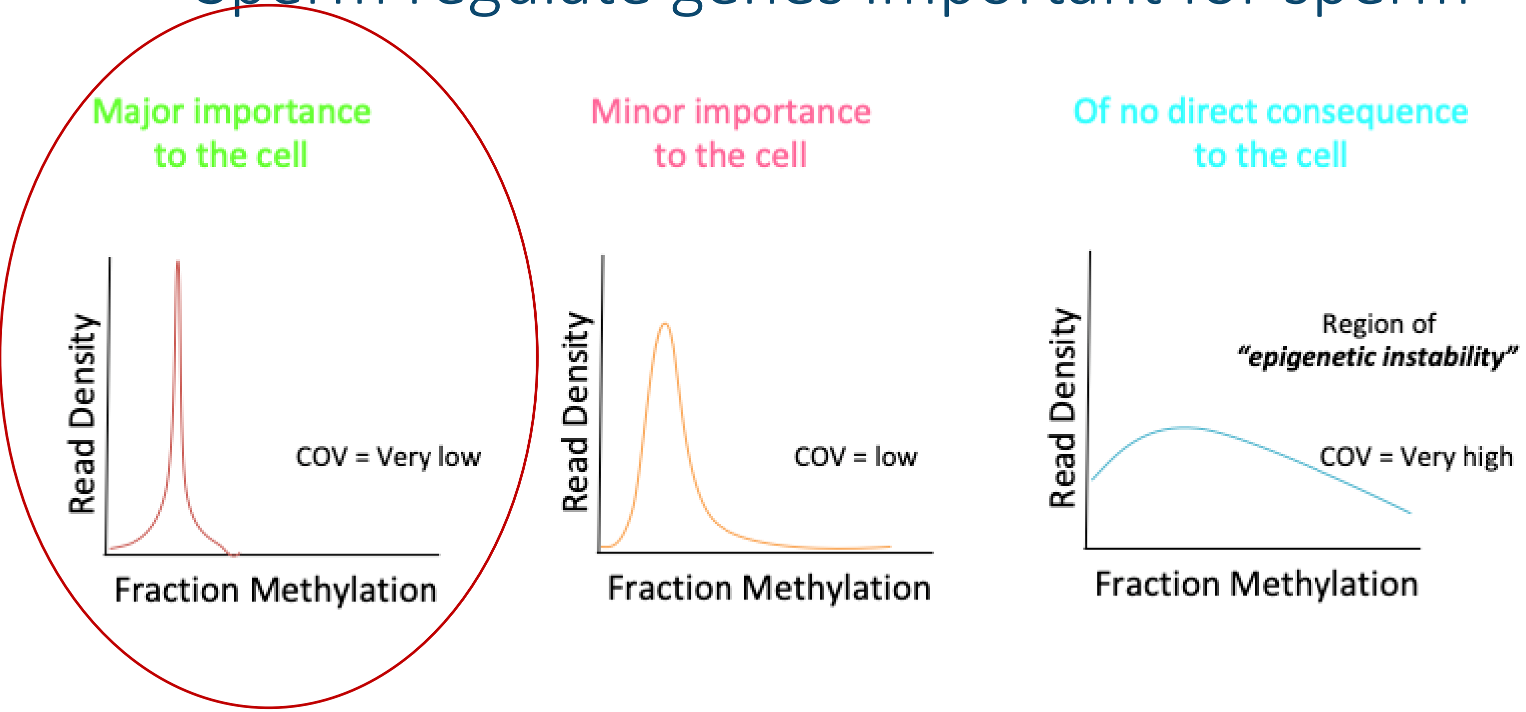
- Based on machine learning
  - Too big for us to interpret
- Cumulative assessment of every tree to understand the forest
- Black box

Tissue of origin assessment

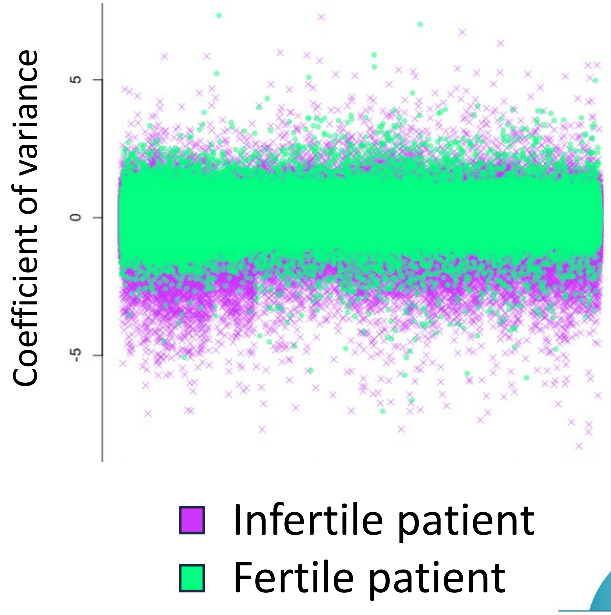
- ID genomic regions whose methylation patterns are predictive of tissue type
- Generation of a ratio
  - Ex. % of unknown DNA that was sperm derived

MRS for IUI fertility success: Sperm Epigenetic Instability

- Sperm regulate genes important for sperm



At genes important to sperm



SpermQT: IUI or straight to IVF?

Multisite Retrospective Analysis, N=544

Result	%Pregnancy	% Live Birth	Avg. IUI Cycles	% Total Motile Count ≥20M
Normal	46.45%	34.08%	2.5	89%
Abnormal	25.49%	17.6%	2.5	80%
All Results	44.49%	32.54%	2.5	87%
P Values	0.004	0.006		

Miller RH, DeVilbiss EA, Brogaard KR, et al. Epigenetic determinants of reproductive potential augment the predictive ability of the semen analysis. F S Sci. 2023;4(4):279-285.

Real World, Multi-site, Analysis N=202

Result	%Pregnancy	Avg. IUI Cycles	% Total Motile Count ≥20M
Normal	22%	2.8	86.8%
Abnormal	0%	2.4	72.2%
All Results	19.3%	2.8	85%
P Values	0.009		

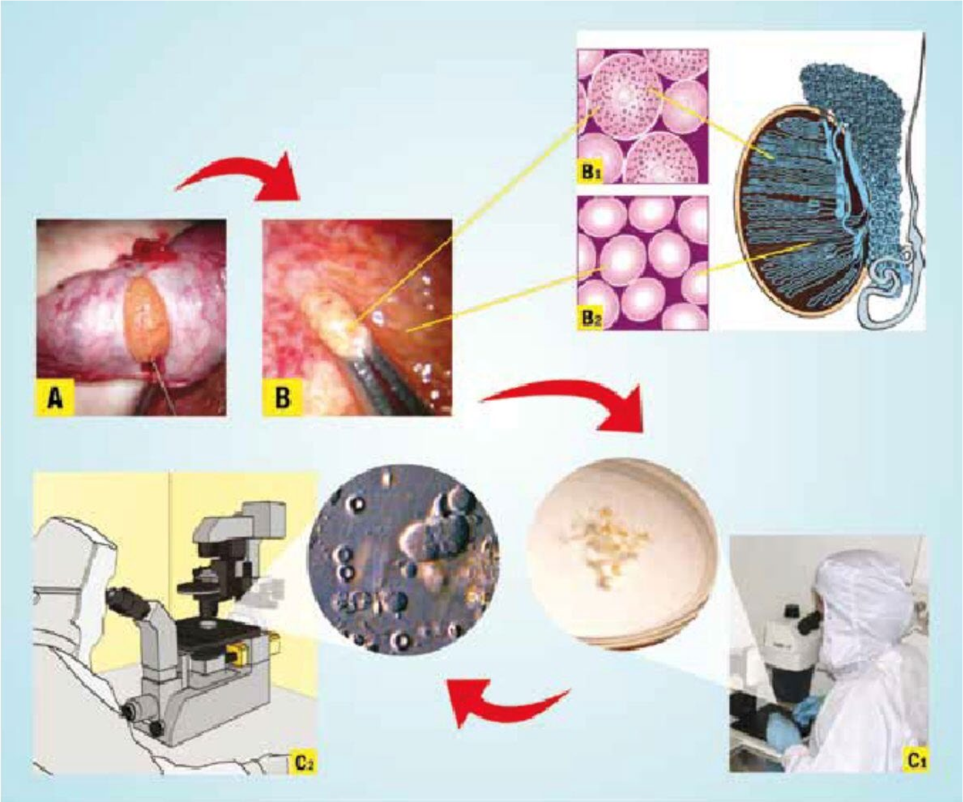
Publication pending

Tissue of origin assessment in NOA patients

Non-obstructive azoospermia

- No sperm in the ejaculate and no known obstruction in the male reproductive tract
- 1% of all men (10-15% of all infertile men)

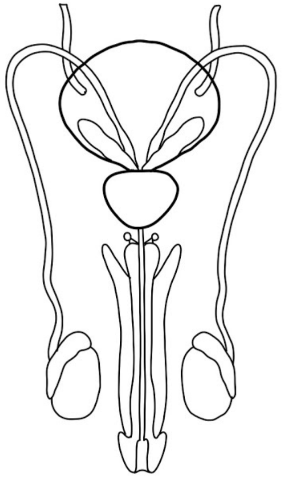
Microsurgical Testicular Sperm Extraction (**microTESE**)



Can DNA methylation help?

≠ Somatic

Sperm
DNA methylation ≠ SOMATIC
DNA METHYLATION



→ Seminal cfDNA

cfDNA in semen sample

Sperm
DNA methylation

Sperm
DNA methylation

SOMATIC
DNA METHYLATION

Sperm
DNA methylation

SOMATIC
DNA METHYLATION

SOMATIC
DNA METHYLATION

Sperm
DNA methylation

Sperm
DNA methylation

Translation to clinical viability

- Long read sequencing (one molecule at a time)
- Simple test: one molecule, two CpGs
- Assessed ~10,000 reads

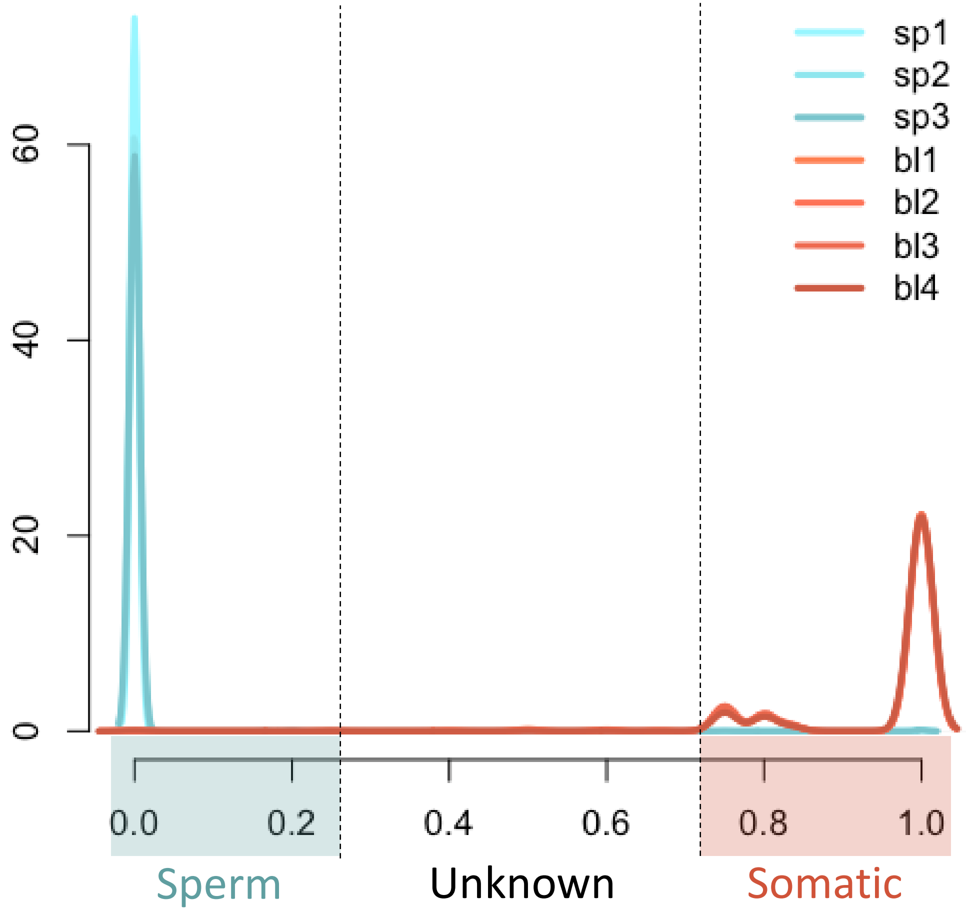
Blood	CpG A	CpG B	Semen sample	Chance of sperm origin
0%	▮	▮	85.1%	100%
0%	▮	▯	7.24%	100%
0.12%	▯	▮	6.87%	99.02%
99.88%	▯	▯	0.79%	0.78%

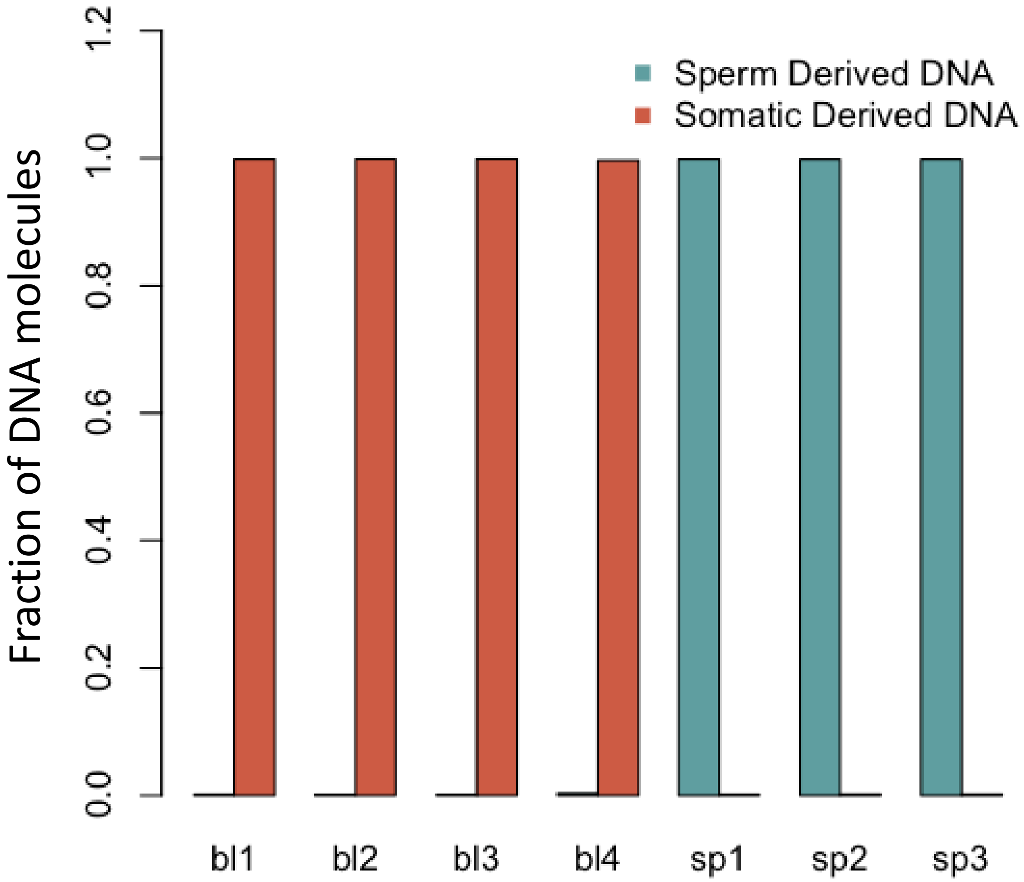
Methylation @ CpGs		
	CpG A	**CpG B**
PPV	100%	99.87%
NPV	92.89%	92.56%
Sensitivity	92.35%	91.97%
Specificity	100%	99.88%

▯ Unmethylated CpG

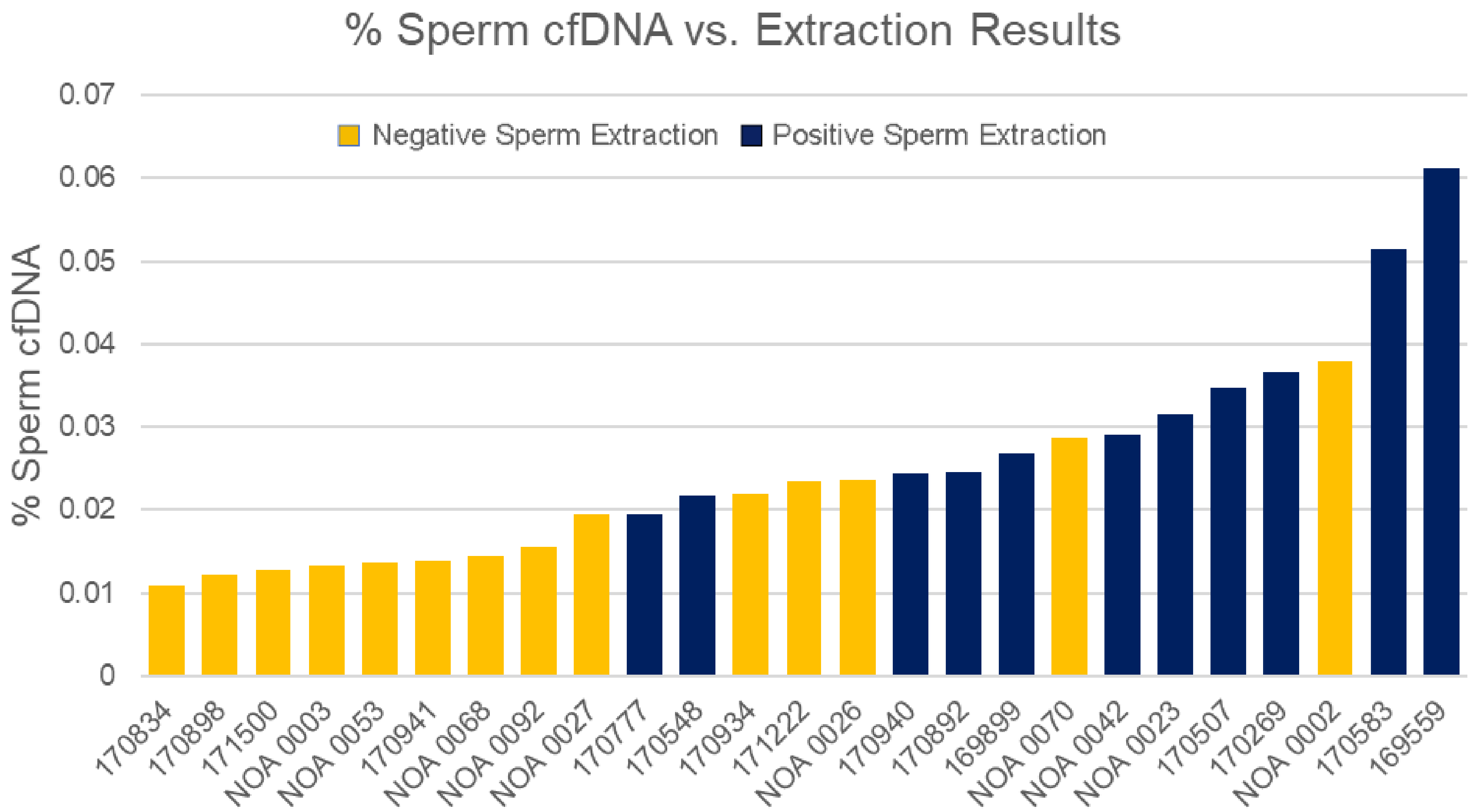
▮ Methylated CpG

Single region of interest: 400bps | 9 CpGs
Blood and sperm assessment



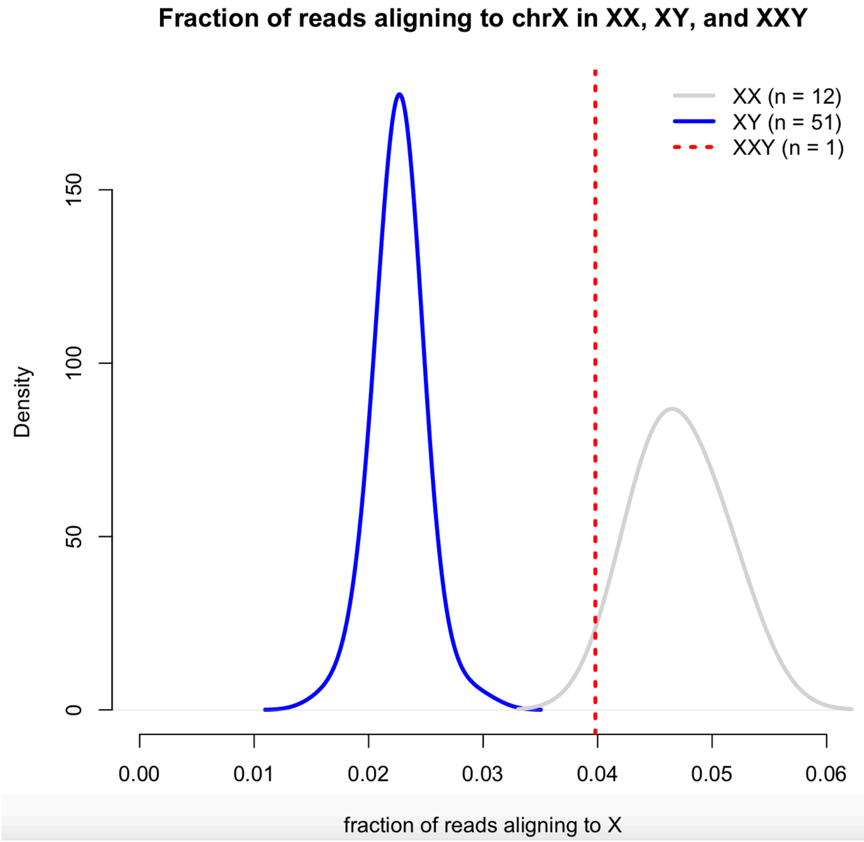


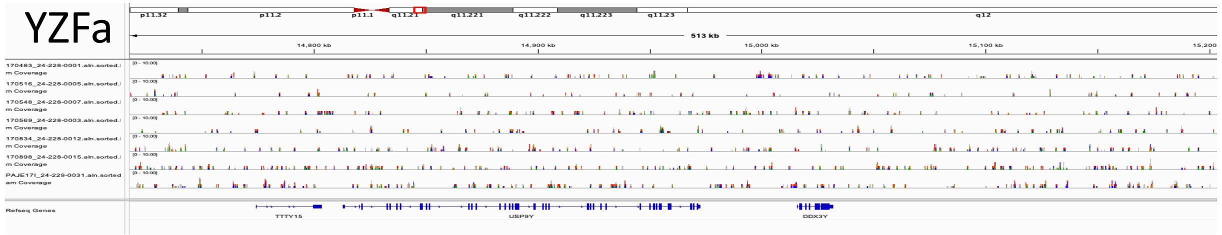
Can we predict biopsy success?

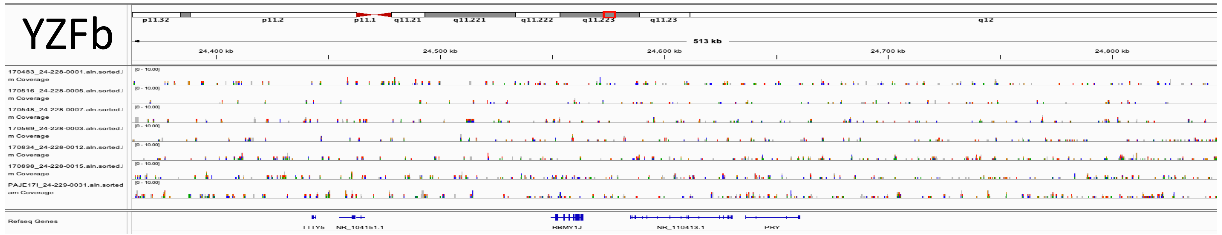


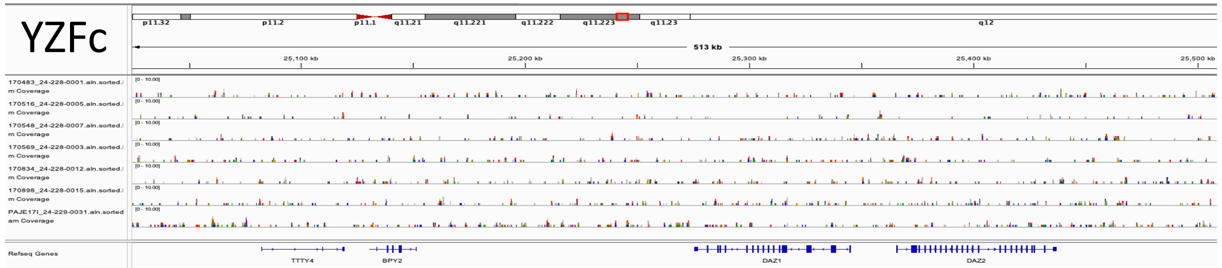
Combining genetics and epigenetics

Sequencing data to screen for XXY. and Y-micro deletions









Why it matters

- Epigenetics bridges the gap between nature and nurture
- Key component to gene regulation that is responsive to the environment
- Epigenetic data will be used in the clinic in the future
- Not ideal for mechanistic studies
- Well-suited for predictive models
- Can be used for the assessment of male infertility and the prediction of ART success

Thank You!

BYU
- Ryan Barney
- Kelaney Stalker
- Carter Norton
- Ryan Miller
- Jonathon Hill

Inherent Biosciences
- Kristin Brogaard
- Andy Olson

Baylor College of Medicine
- Larry Lipshultz
- Jordan Kassab

Funding Sources

NIH
Eunice Kennedy Shriver
National Institute of
Child Health and
Human Development

BYU

Q&A