# PPMI EPIGENETICS

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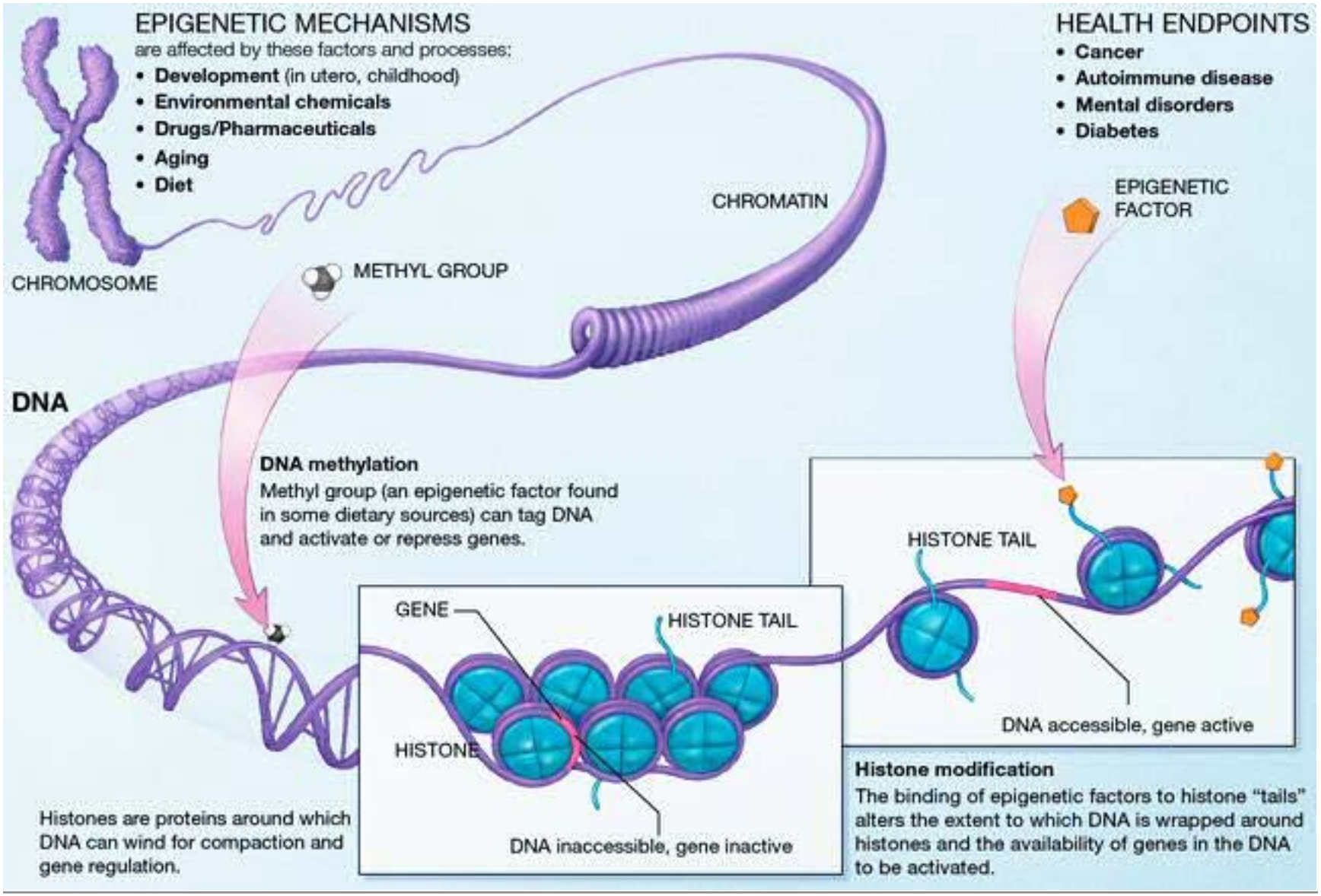
# EPIGENETIC DATA

Epigenetics is the study of heritable changes in gene function that do not involve changes in the DNA sequence


EPIGENETIC MECHANISMS
are affected by these factors and processes:
• Development (in utero, childhood)
• Environmental chemicals
• Drugs/Pharmaceuticals
• Aging
• Diet
HEALTH ENDPOINTS
• Cancer
• Autoimmune disease
• Mental disorders
• Diabetes
CHROMOSOME
CHROMATIN
METHYL GROUP
EPIGENETIC FACTOR
DNA
DNA methylation
Methyl group (an epigenetic factor found in some dietary sources) can tag DNA and activate or repress genes.
GENE
HISTONE TAIL
HISTONE
DNA inaccessible, gene inactive
HISTONE TAIL
DNA accessible, gene active
Histones are proteins around which DNA can wind for compaction and gene regulation.
Histone modification
The binding of epigenetic factors to histone "tails" alters the extent to which DNA is wrapped around histones and the availability of genes in the DNA to be activated.

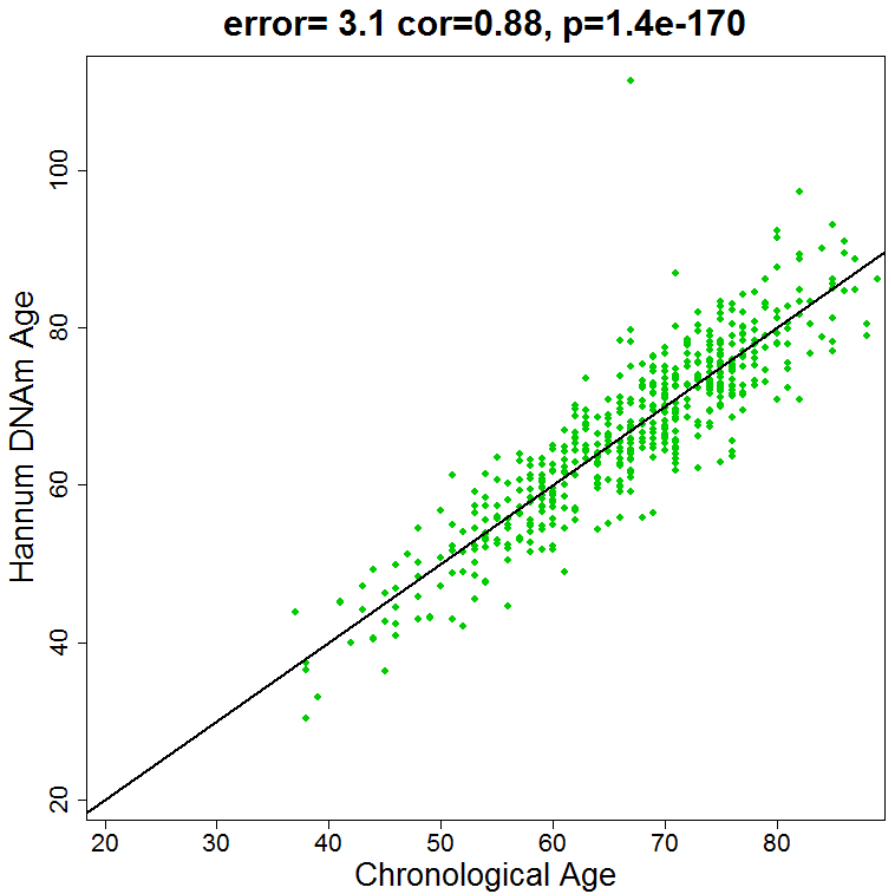
# EPIGENETIC DATA

- Methylation EPIC array interrogates >850,000 methylation sites per sample at single-nucleotide resolution.
- Coverage includes 99% of RefSeq genes,
- Average of 17 CpG sites per gene region across the promoter, 5'UTR, first exon, gene body, and 3'UTR,
- Covers 96% of CpG islands, with additional coverage in island shores.
- Further content includes FANTOM5 and ENCODE enhancers, CpG sites outside of CpG islands

- Assayed 537 Baseline subjects

# EPIGENETIC DATA

- Accurate methods exist to predict chronological age from DNA methylation
- Does this reflect ‘biologic aging’ – and is it conceivable that this is disrupted in age-related diseases



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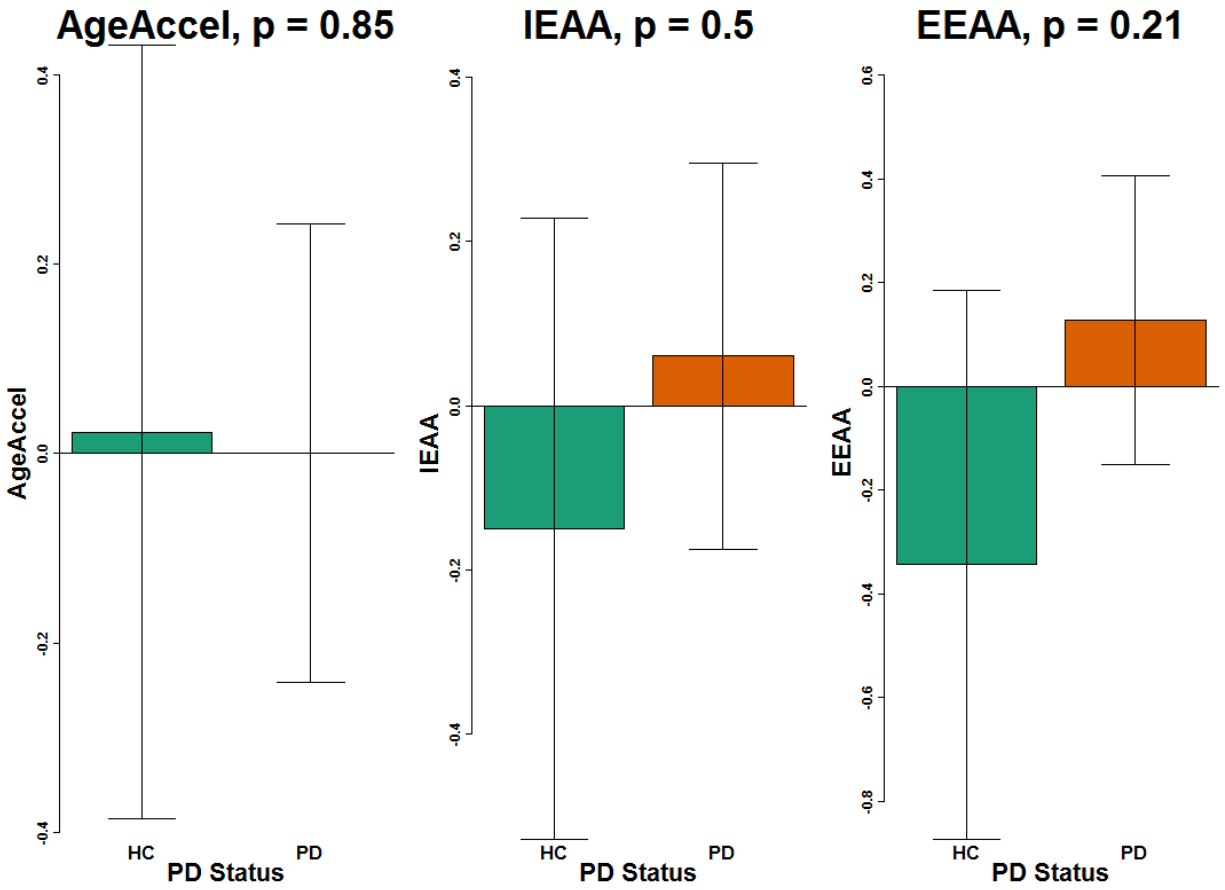

# DISEASE PREDICTION/BIOMARKER

- Machine learning approach similar to what we've done with genetics
- Can we take lots of factors (each DNA methylation site), find the ones that are correlated with disease (which will be tiny) and use them in combination to construct a significant predictor

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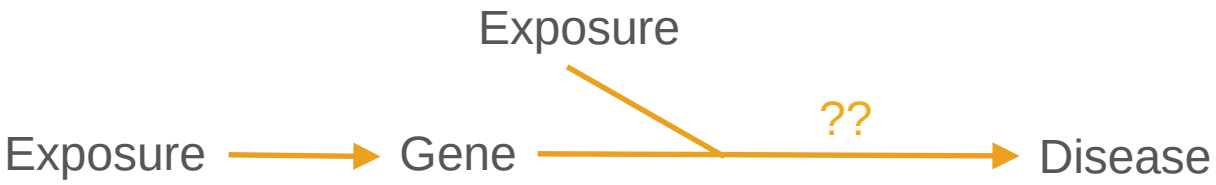
- So far, No.
- These do not function well as a predictor; however, there are the following caveats – relatively small n, no replication, and no longitudinal data

# DISEASE BIOLOGY

- So how can we use these “as is”
- First – we haven’t given up on the prediction – ML takes time, tuning, and resources – still ongoing
- Second – integrating with other biologics may be informative as a biomarker, but clearly complex
- Disease Biology – we are using these to provide confidence and information to biology



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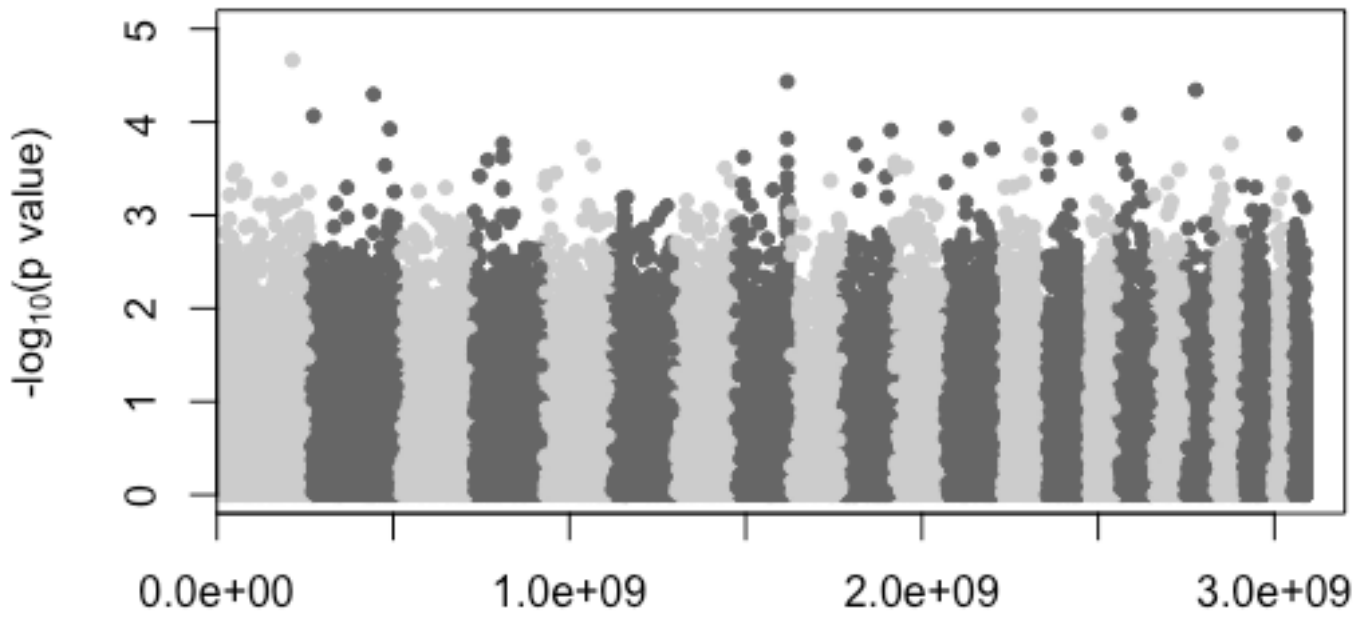

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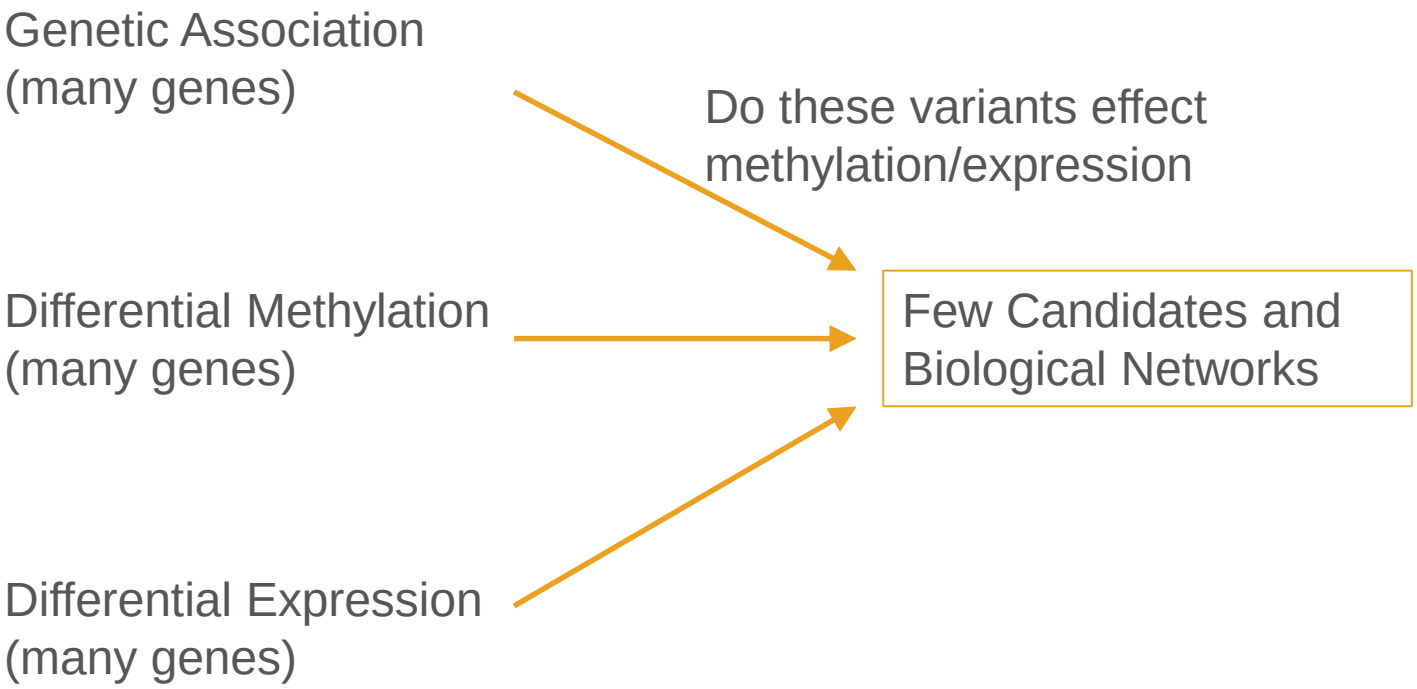

# NEXT STEPS – DNA METHYLATION

1. Further analyses of existing baseline data
2. Incorporation of the longitudinal data
3. Extend the ML approaches for prediction
4. Identify replication cohorts