

Epigenetics as a Biomarker in Environmental Health

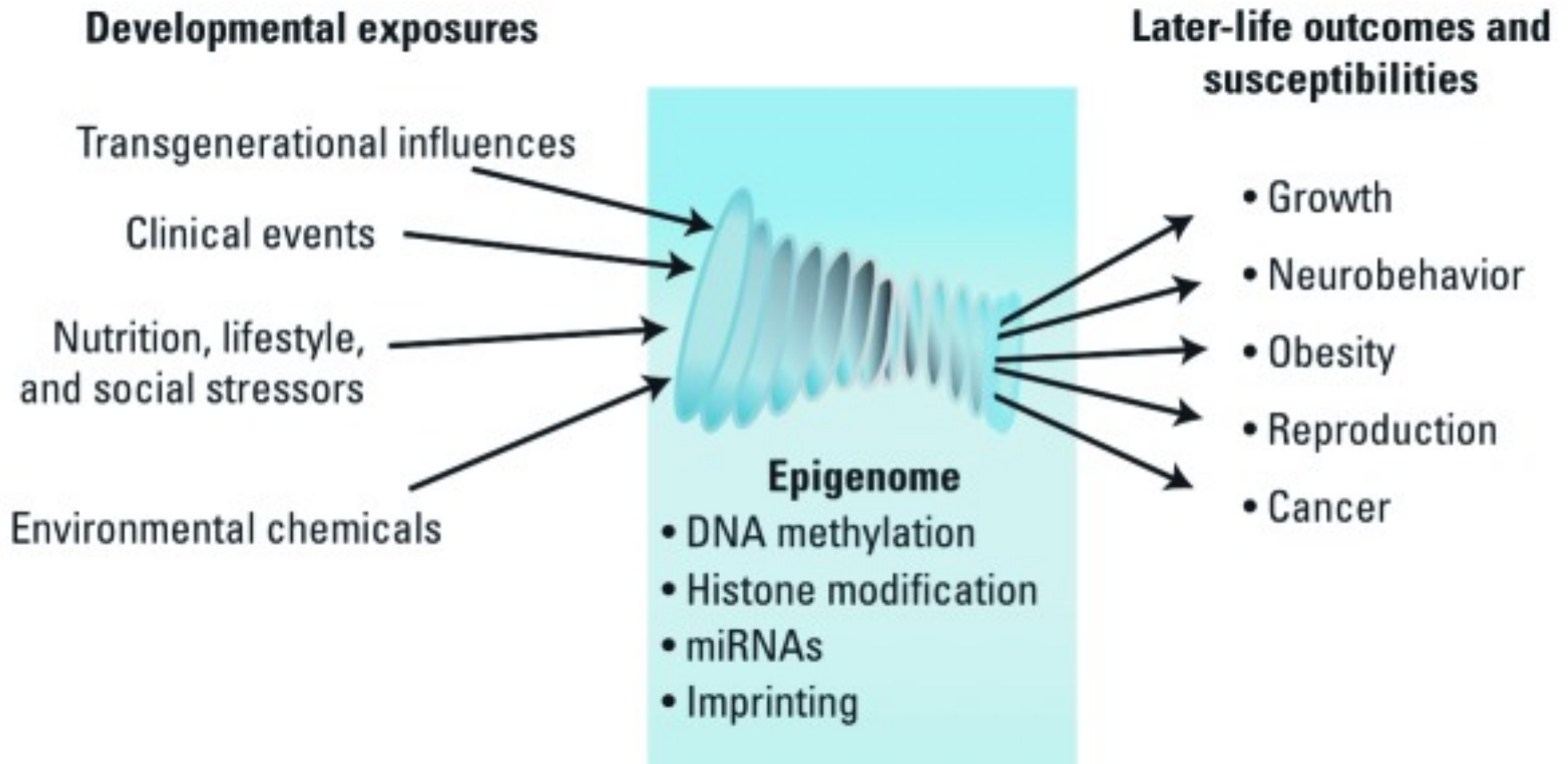
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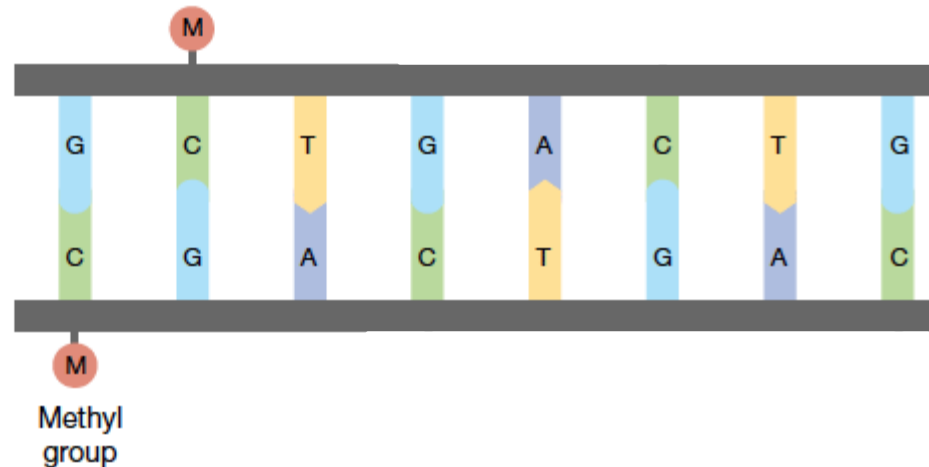
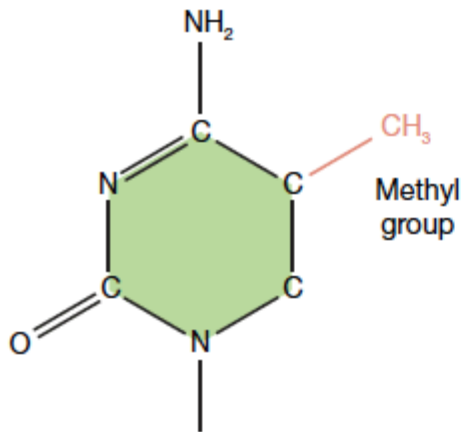
Icahn School of Medicine at Mount Sinai

Epigenetics in perinatal programming



DNA methylation

- 5-methylcytosine residues; usually found in CpG dinucleotides
- Often associated (negatively) with gene expression
- Well studied



Beyond candidate gene approaches: Epigenome-wide platforms



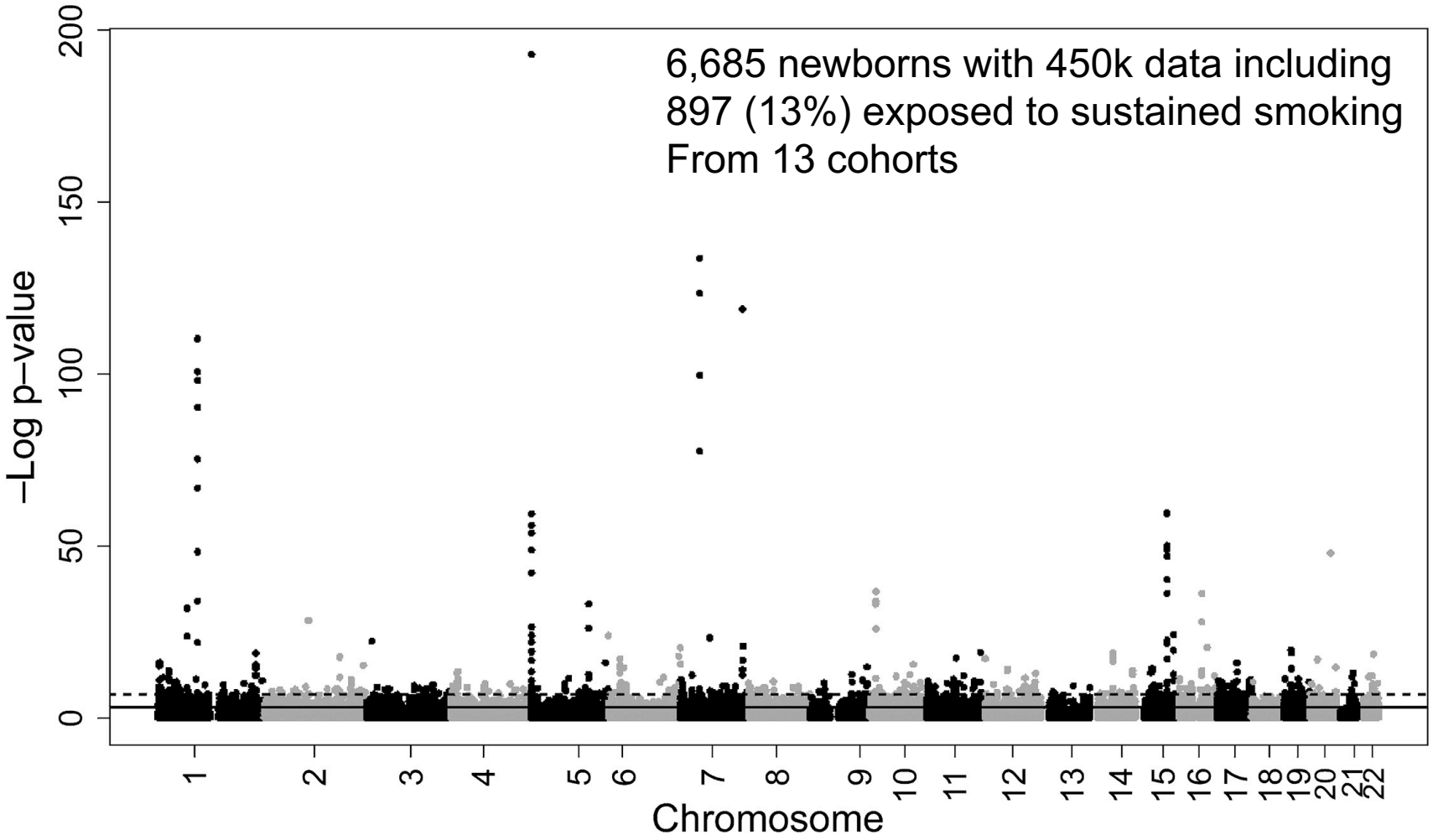
High Density Microarrays

Illumina 450k and 850k



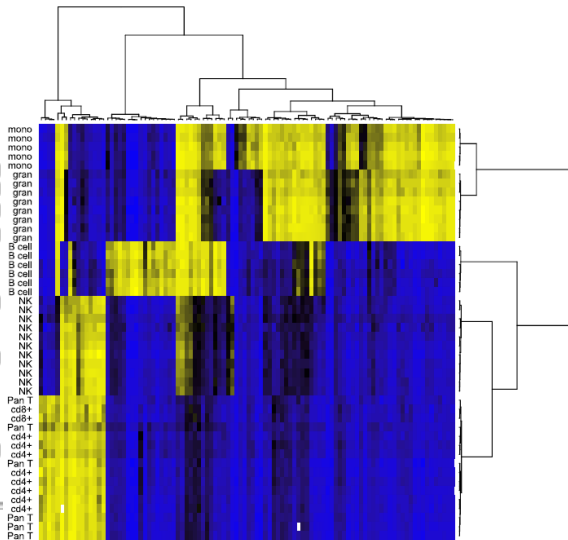
Cost-effective - measures
hundreds of thousands of
pre-specified sites

Early exposures leave a fingerprint on the epigenome: results from a meta-analysis of prenatal maternal smoking and cord blood methylation



Challenges measuring epigenetic associations in epidemiologic studies

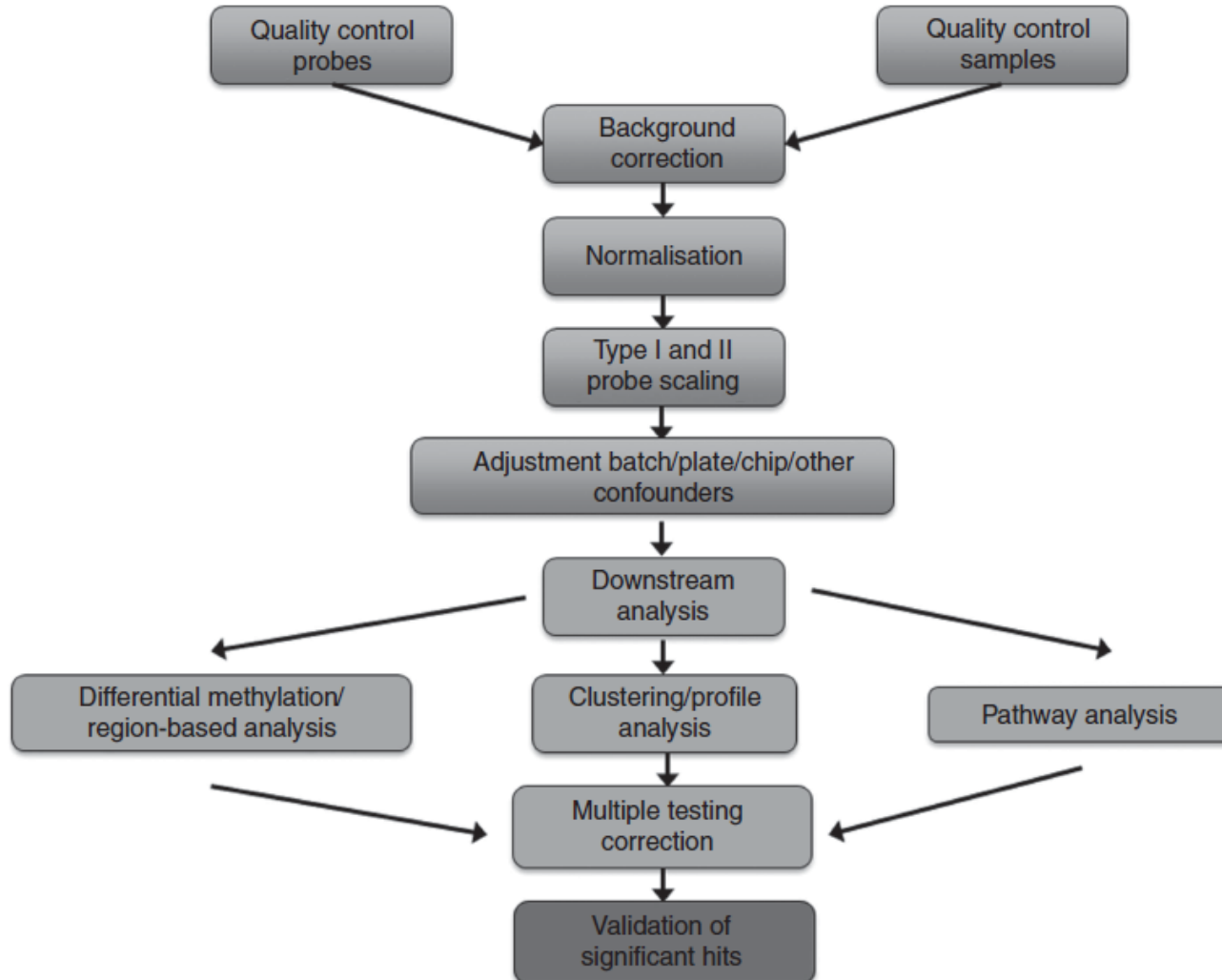
- Biological
 - Target tissues
 - Cell mixture changes
- Analytical
 - Noise
 - Bias



Swimming in data: a new challenge for environmental health

- Need for new diagnostic tools
- Adapt to check assumptions and results

Reliant on multi-step pre-processing pipelines



Quality Control is Essential

Check your dataset carefully!

- Look for sample mix-ups, failures, and contamination

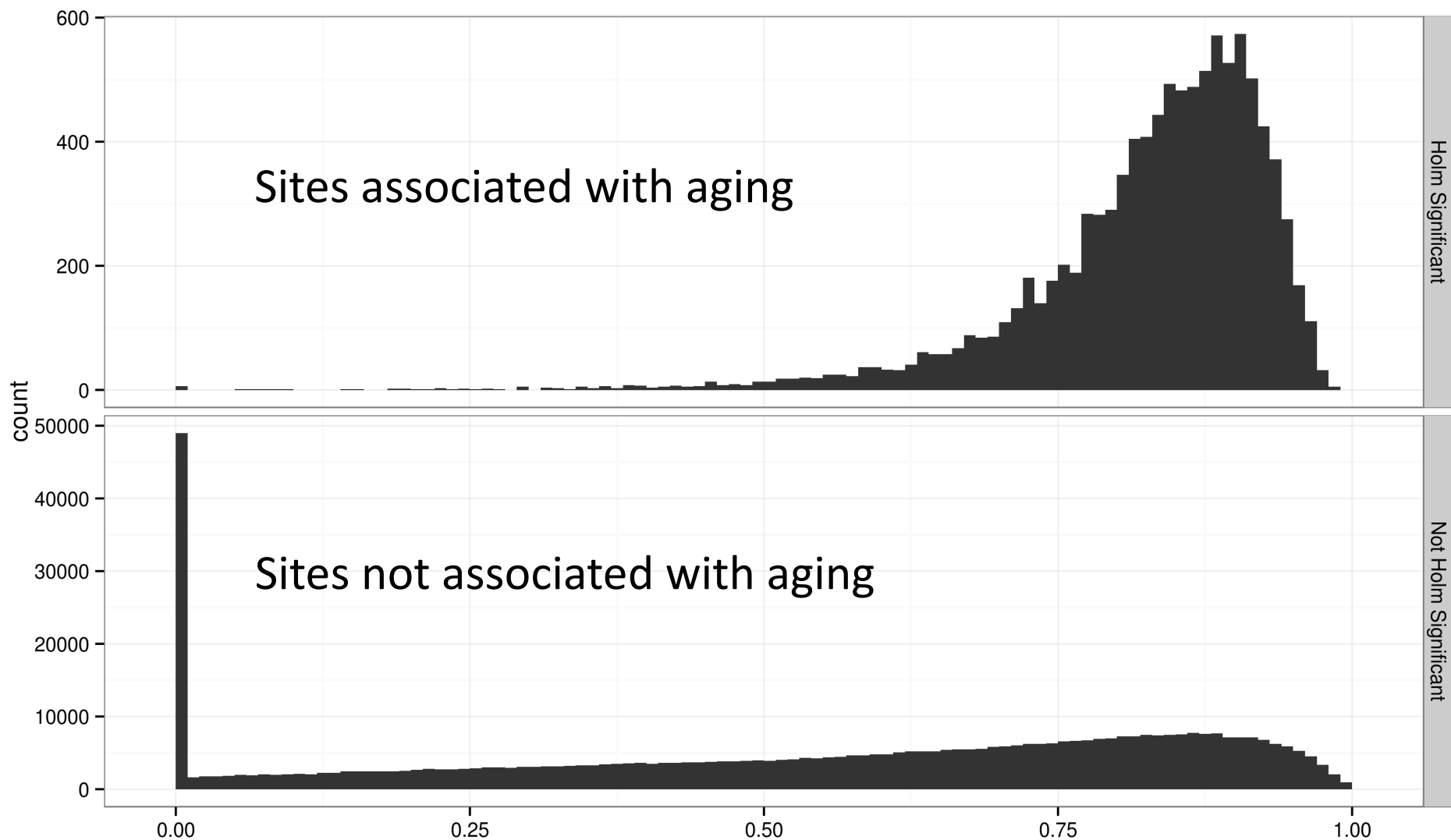
R package *ewastools* on github

- Thoughtful detection p-values (fluorescence signal quality) slashes rate of outliers

Heiss and Just. BioArxiv preprint: <https://doi.org/10.1101/245217>

Even low numbers of misidentified samples or big outliers can have a devastating impact on power and robustness of findings

Technical replicates can give estimate of Signal versus Noise



Intraclass correlation coefficient (ICC) using replicates
EWAS of age in n=675 males from the Normative Aging Study

Improved analytic approaches

Restrict the search:

- Prioritize best measured features
- Prioritize biologically relevant features

Borrow information:

- Pathway analyses
- Regional analyses

Larger sample sizes

Epigenomic Meta-analysis Consortia:

Prenatal And Childhood Epigenetics (PACE)

Felix JF et al. 2017. Cohort profile:
Pregnancy and childhood epigenetics
(PACE) consortium. *Int J Epidemiol*.



PACE

Pregnancy And Childhood Epigenetics

Cohorts for Heart & Aging Research in Genetic Epidemiology (CHARGE)



CHARGE
CONSORTIUM

COHORTS FOR HEART & AGING RESEARCH
IN GENOMIC EPIDEMIOLOGY

Note: correction for multiple comparisons doesn't protect against confounding: high type I error in epigenomic epi



Summary: epigenomics in environmental health

1. Exciting prospects to discover links with early environmental exposures and later outcomes
2. Measurements are standardized; analyses are complicated
3. Need care when $n \ll p$; borrow information using biology and statistics

Thank you!

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