Neonatal DNA methylation as a predictor of cognitive, language, and motor performance at 24 months adjusted age, among children born very preterm

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Disclosure

Stefan Graw
Has documented no financial relationships to disclose or Conflicts of Interest (COIs) to resolve.

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Unapproved or Off Label
• Disclosures for Stefan Graw

Presenter: Stefan Graw has documented this presentation will not involve discussion of unapproved or off-label, experimental or investigational use.
Epigenetics

Interface between our Environment and Health

DNA Methylation (DNAm)

- Addition of methyl group to cytosine
- Cytosine-phosphate-Guanine (CpG)
- Involved in gene expression regulation


https://en.wikipedia.org/wiki/DNA_methylation
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Epigenome-Wide Association Study

- Genome-wide examination of relationship between epigenetic marks (DNA methylation) and some exposure or phenotype

Epigenetic clocks

- DNAm levels changes with age
- Epigenetic clocks estimate age via DNAm profiles
- Differences between estimated and chronological age are associated with age-related diseases
Goal

Is neonatal DNA methylation (DNAm) predictive of cognitive, language, and/or motor performance at 24 months of age in children that were born very preterm?
Bayley Scales of Infant and Toddler Development-III

- Cognitive
- Language
- Motor
- Composite scores: M = 100, SD = 15, range = 40-160
- Mild impairment: composite scores < 85
• Neonatal Neurobehavioral Outcomes in Very Preterm Infants (NOVI)
• 433 preterm neonates
• DNAm measured from buccal swabs at NICU discharge
• Illumina MethylationEPIC BeadArray
Elastic Net Regression

- Penalized linear regression model
- Regularization and variable selection
- Combines penalties of ridge regression and lasso

\[
\hat{\beta} = \arg \min_{\beta} ||y - X\beta||^2 + \lambda_2 ||\beta||^2 + \lambda_1 ||\beta||_1
\]

- Identify sets of CpGs predictive of composite scores

Leave-one-out cross validation

https://medium.com/100daysofmlcode/day-59-of-100daysofml-542274f360c8
Cognitive Composite Scores

BSID–III Cognitive Composite Scores

RMSE: 14.24
Cor: 0.33 (p = 2.7e–12)
Cognitive Composite Scores

BSID–III Cognitive Composite Scores

- RMSE: 14.24
- Cor: 0.33 (p = 2.7e–12)

Mild Cognitive Impairment (< 85 measured score)

- AUC = 0.68

Graphs showing predicted vs. measured scores and ROC curve for mild cognitive impairment.
Language Composite Scores

BSID–III Language Composite Scores

RMSE: 14.21
Cor: 0.47 (p = 1.5e–25)

Mild Language Impairment (< 85 measured score)

AUC = 0.71
Motor Composite Scores

**BSID-III Motor Composite Scores**

RMSE: 14.05  
Cor: 0.32 (p = 8.3e−12)

**Mild Motor Impairment (< 85 measured score)**

AUC = 0.66
Epigenetic RS and neonatal Factors

Neonatal Factors (NF):
- NICU Network Neurobehavioral Scale (NNNS) profiles
- Gestational age
- Morbidity Score (Bassler)
- Infant’s sex
- Birth weight

AUC across different model

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Summary & Future plans

- Limited ability to predict Bayley composite scores
- Early prediction of impairment at 2 years
- DNAm proximal to birth is informative of potential impairments
- Guidance for what infants should be monitored more closely
- Polyepigenetic risk scores as research tool

- Explore DNAm differences at birth
- Include post-natal information
- Expand work beyond 2-year Bayley scores (up to 7 years)
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