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Epigenetic Age Acceleration as a Marker of Cystic Fibrosis

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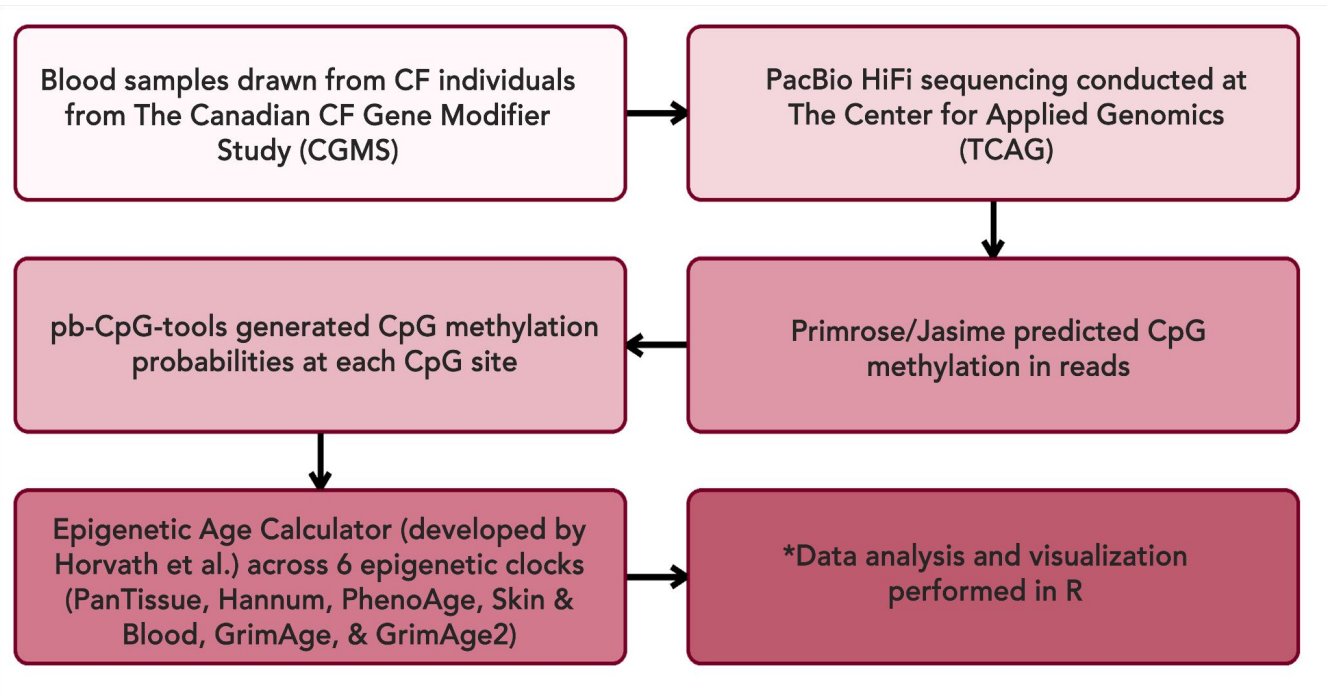
INTRODUCTIONS

Epigenetic age is an estimate of biological age derived from DNA methylation patterns and can be calculated using different epigenetic clocks. The difference between epigenetic age and chronological age is referred to as **epigenetic age acceleration (EAA)**. **Cystic fibrosis (CF)** is a progressive, multisystem genetic disorder caused by pathogenic variants in the *CFTR* gene.

OBJECTIVES

Our study investigates whether **EAA** is associated with **CF severity**.

METHODOLOGY



Our analysis was performed using **R version 4.4.2**. We employed a range of statistical and bioinformatics approaches. The statistical significance of the difference between epigenetic and chronological ages was determined using **paired t-test**. To evaluate the associations between **EAA** and **CF severity**, we utilized **linear regression**, adjusting for relevant covariates.

RESULTS

We calculated epigenetic age **205 European individuals with CF** using 6 different epigenetic clocks. Four of these methods, **PanTissue**, **Hannum**, **GrimAge**, and **GrimAge2**, all demonstrated positive EAA. However, **PhenoAge** and **Skin & Blood** yielded implausibly low estimates, indicating limitations of these methods. Similarly, Hannum did not perform well in children <10 years and often yielded estimates below 0 (Table 1, Figure 1).

Table 1: Epigenetic age vs. chronological age in 205 European individuals with CF

Epigenetic Clock	Mean	SD	Min	Max	Mean Difference*	P
PanTissue	25	18	1	82	6	3.93E-10
Hannum	28	19	-31	92	9	<2.2E-16
PhenoAge	2	23	-69	69	-17	<2.2E-16
Skin & Blood	10	10	-1	50	-9	<2.2E-16
GrimAge	23	13	-2	71	4	<2.2E-16
GrimAge2	31	14	2	80	12	<2.2E-16
Chronological Age	19	13	1	56	-	-

* Mean of epigenetic age - Mean of chronological age

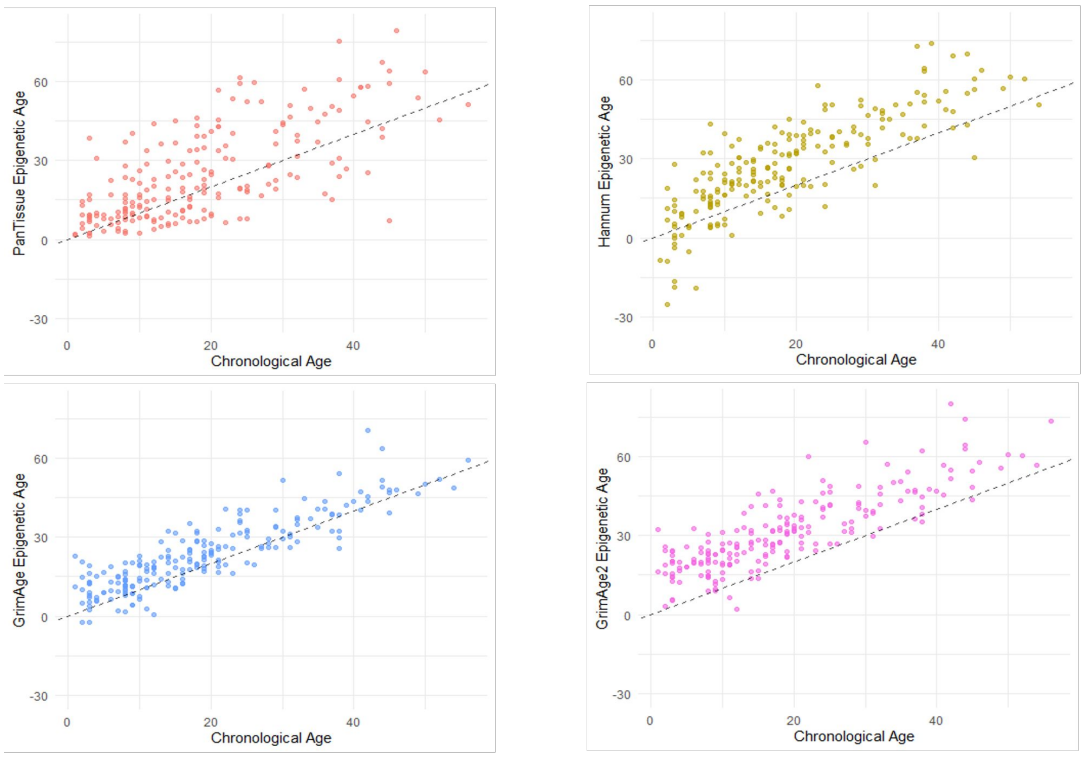


Figure 1: PanTissue, Hannum, GrimAge, and GrimAge2 Epigenetic Age vs. Chronological Age

RESULTS CONT.

- **Lung Function**

Association between **EAA** and **lung function** was assessed using Saknorm, an age-, height-, and sex-adjusted FEV_1 measure in CF. Positive EAA for GrimAge and GrimAge2 trended with lower Saknorm, though not statistically significant (Table 2, Figure 2).

Table 2: Association between Epigenetic Age Acceleration and SaKnorm

Epigenetic Clock	B (SE)	P
PanTissue	0.003 (0.004)	0.51
GrimAge	-0.001 (0.009)	0.28
GrimAge2	-0.002 (0.008)	0.79

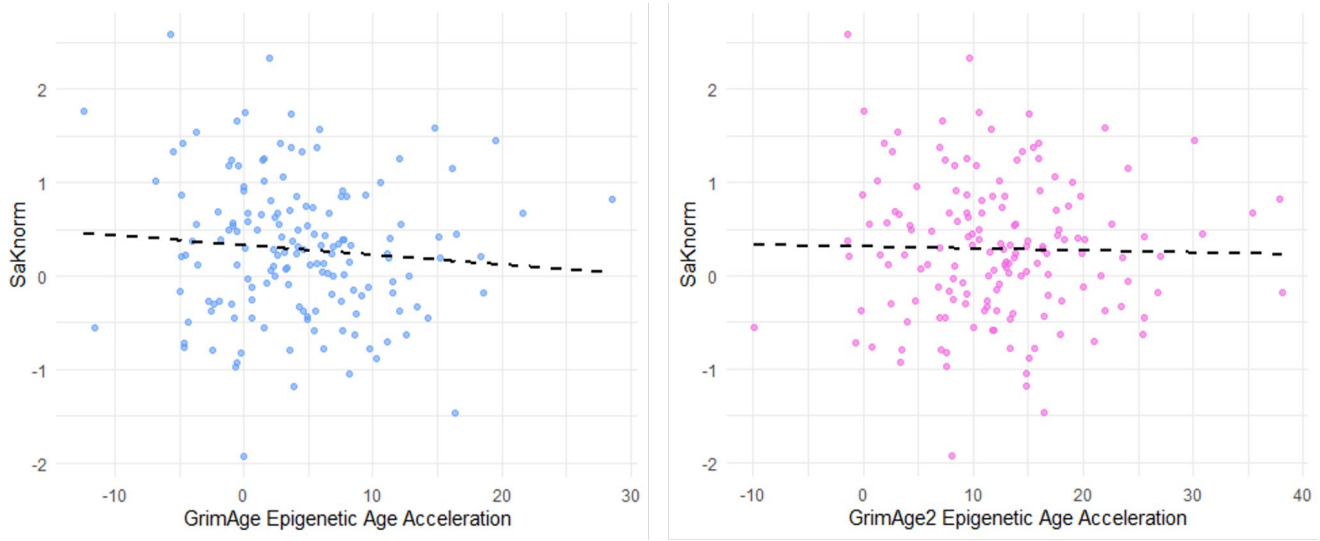


Figure 2: GrimeAge and GrimAge2 Epigenetic Age Acceleration vs. SaKnorm

- ***CFTR* Genotype**

Association between **EAA** and ***CFTR* genotype** severity score (range: 1-5; higher = more severe genotypes) showed no significant differences, though GrimAge2 trended higher EAA with greater severity. Most individuals (92%) had scores of 3 or 4 (Table 3, Figure 3).

Table 2: Association between Epigenetic Age Acceleration and *CFTR* Genotype Severity Score

Epigenetic Clock	B (SE)	P
PanTissue	-1.67 (2.23)	0.46
GrimAge	1.56 (1.09)	0.15
GrimAge2	2.18 (1.31)	0.10

RESULTS CONT.

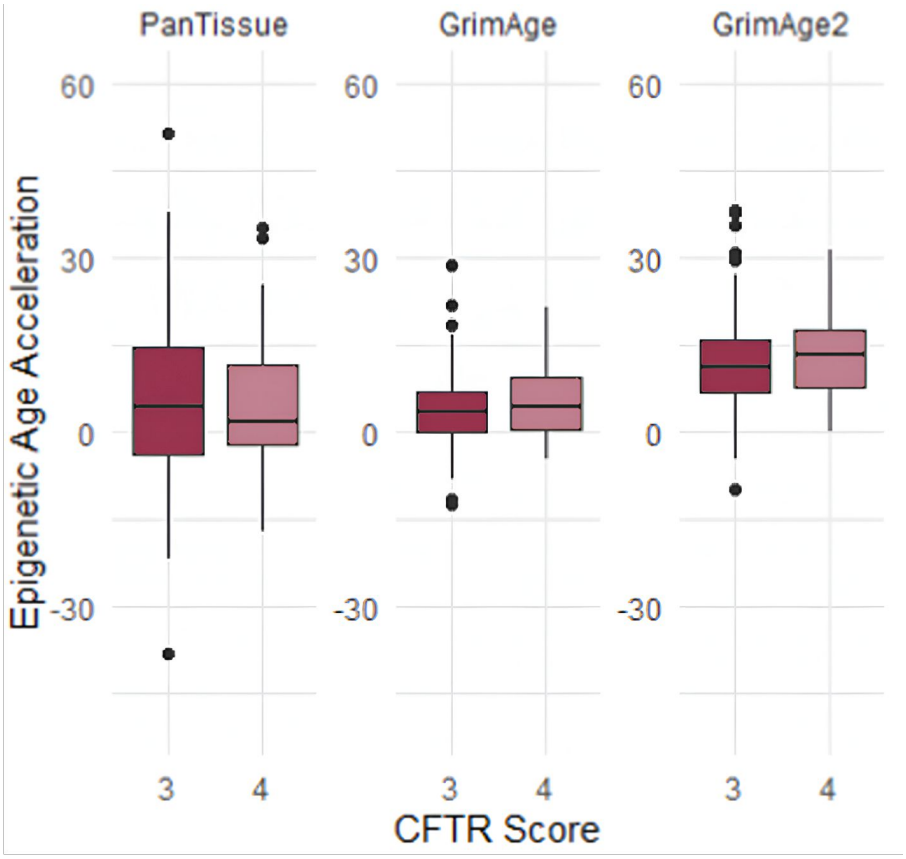


Figure 3: Epigenetic Age Acceleration by CFTR Genotype Severity Score for PanTissue, GrimAge and GrimAge2

CONCLUSION & FUTURE WORK

Our findings indicate that epigenetic age is elevated in individuals with CF when measured by several epigenetic clocks. Although trends suggested higher EAA with poorer lung function and more severe CFTR genotype, these associations were not statistically significant probably due to small sample size. We are planning to increase whether EAA can serve as a biomarker for CF severity. We will also investigate association of EAA with CF severity in other organs.