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Quantifying the Functional Gap in Alkaptonuria Through Machine Learning and Clinical Data Integration

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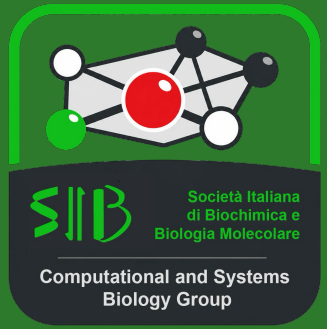
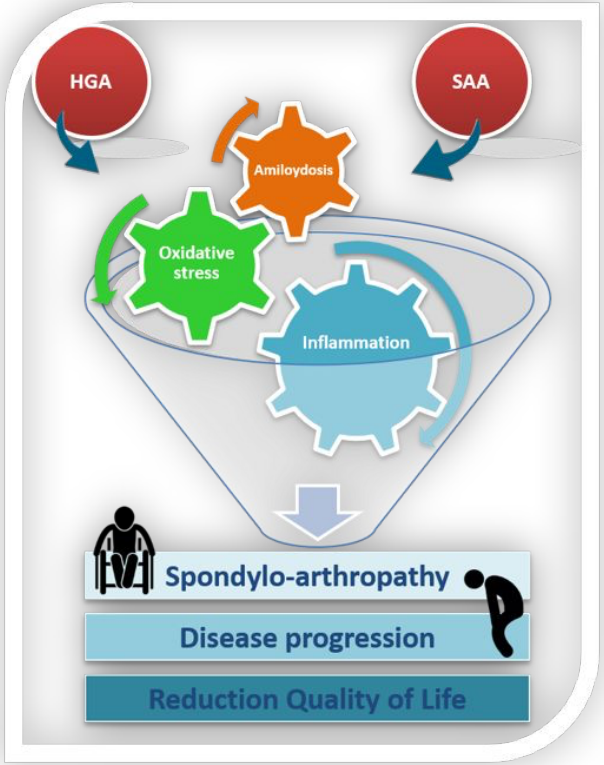


Alkaptonuria

- Ultra-rare autosomal recessive disease
- Mutation in the **HGD** gene, which encodes the enzyme **HGD** (*homogentisate 1,2-dioxygenase*)
- Multisystemic disorder: amyloidosis, cardiovascular complications, chronic inflammation, oxidative stress.



AKU Database

Home Patients About us Admin Logout (admin)

228 PATIENTS

80 ITALY

ApreciseKUre

148 OTHER

Demographic info	Life style	Mutations
Patient code, Gender, Birth year, Country	BMI, Comorbidities, Surgery, Treatment	Variants in the two alleles of the HGD gene, described at three levels: molecular, structural, and functional.

Plasma analysis and Urine analysis	Oxidative stress, inflammation, and tissue damage
Metabolic profile of the disease	Inflammatory and degenerative component of AKU

The clinical problem

General disability in everyday activities

HAQ-DI

Health Assessment Questionnaire - Disability Index

Knee pain, symptoms, daily living, sport and QoL

KOOS

Knee injury and Osteoarthritis Outcome Score

AKU-specific severity, including spinal and joint pain

AKUSSI

Translate multiple functional measures into a single, clinically intuitive metric: the functional age gap.

1 Map HAQ-DI

Assign each patient to the closest normative age category for HAQ-DI.

→

2 Map KOOS

Repeat the mapping for the five KOOS subscales and average them.

→

3 Compute functional age

Average HAQ-derived and KOOS-derived age estimates.

→

4 Compute the gap

Functional age gap = functional age − chronological age.

Statistical Analysis

134 AKU patients

Clinical + biochemical + functional data

Compute the functional age gap

1 Functional vs biological age

Functional age exceeded chronological age in the vast majority of the cohort.

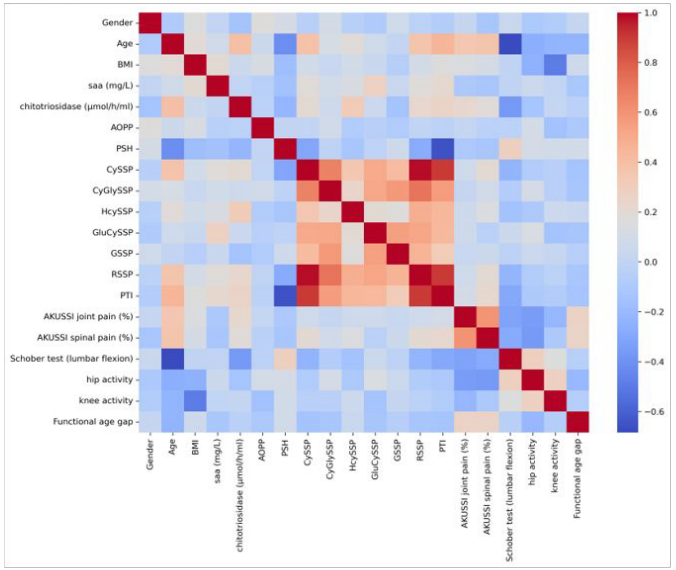
94.8% Patients with a positive functional age gap

15 years Mean difference between functional and chronological age

8–20 years Interquartile range of the functional age gap

Premature functional decline is a predominant feature

2 Correlation analysis



Pearson correlation analysis revealed only weak-to-moderate linear associations with functional age gap.

Functional Age Gap prediction

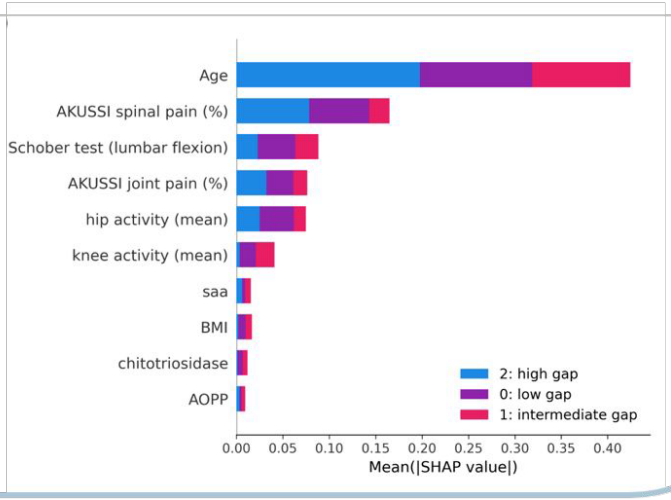
3 Model implementation

The decision-tree classifier outperformed XGBoost, SVM, and KNN in this cohort. Performance is moderate but stable, consistent with an exploratory rare-disease study.

3 classes	0.64 ± 0.08	0.61 ± 0.09
low, intermediate and high functional age gap severity	mean accuracy	macro F1-score

4 Shap analysis

- Pain and mobility-related variables are central drivers of functional impairment.
- Biochemical markers such as SAA, chitotriosidase and AOPP contributed less strongly.
- The model therefore points to a clinically meaningful multivariable structure.



Mean functional age gap: +15 years

94.8% showed a positive gap

Model accuracy: 0.64

Top predictors: age, spinal pain, joint pain, Schober test, hip/knee activity

Potential applications

The functional age gap condenses functional information into a single clinically intuitive descriptor.

Premature decline

Most AKU patients appear functionally older than expected.

Systems-level phenotype

The gap integrates pain, disability and mobility into a single emergent phenotype.

Precision-medicine

It may support patient stratification and identification of unexpectedly severe cases.

Potential applications

A candidate digital endpoint for future treatment-response studies.

Next steps

- Validate the metric in larger, longitudinal cohorts.
- Integrate treatment exposure, imaging and biomechanical parameters.

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