



A Universal Oral Microbiome-Based Signature for Periodontitis

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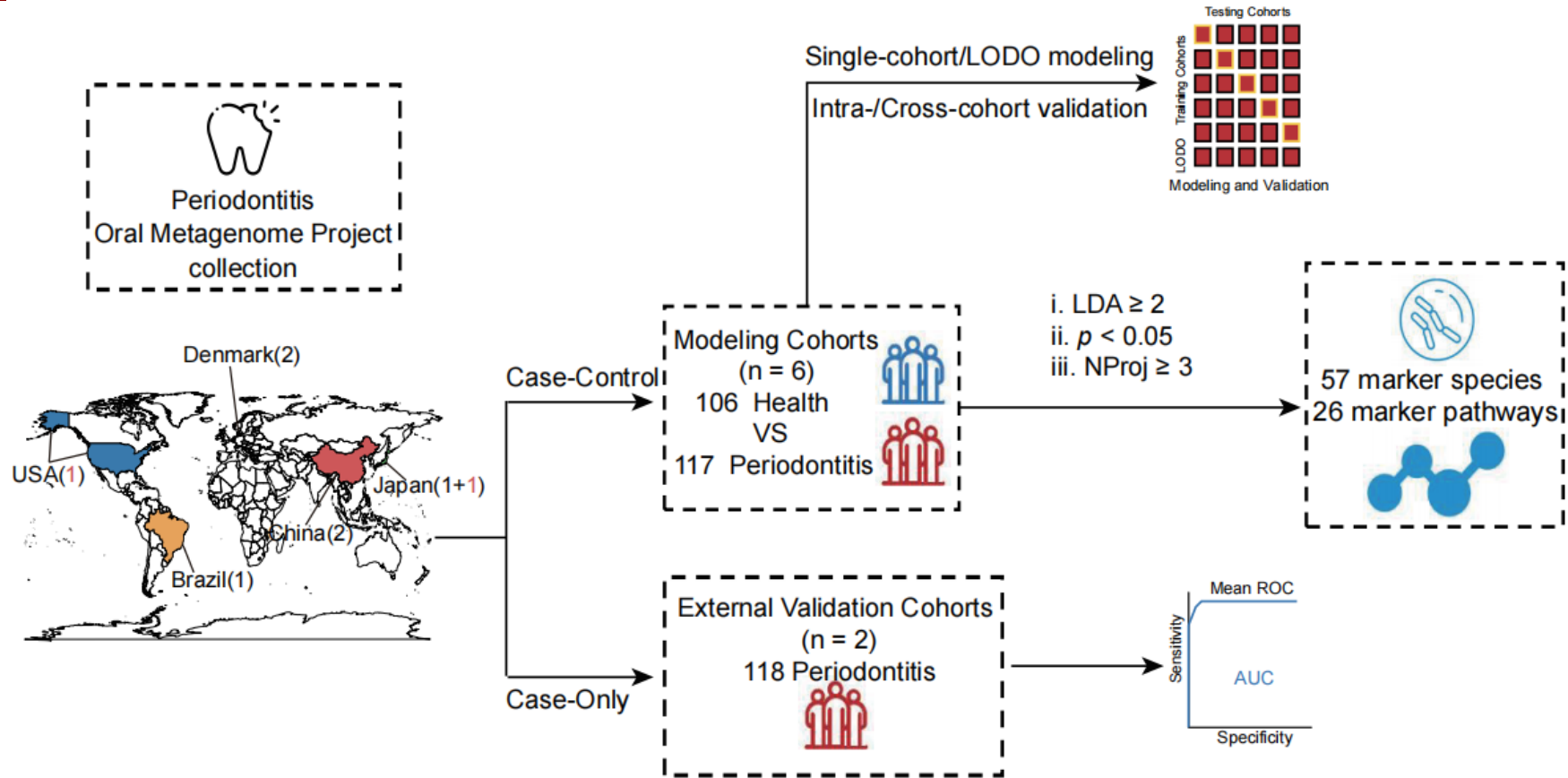


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Background



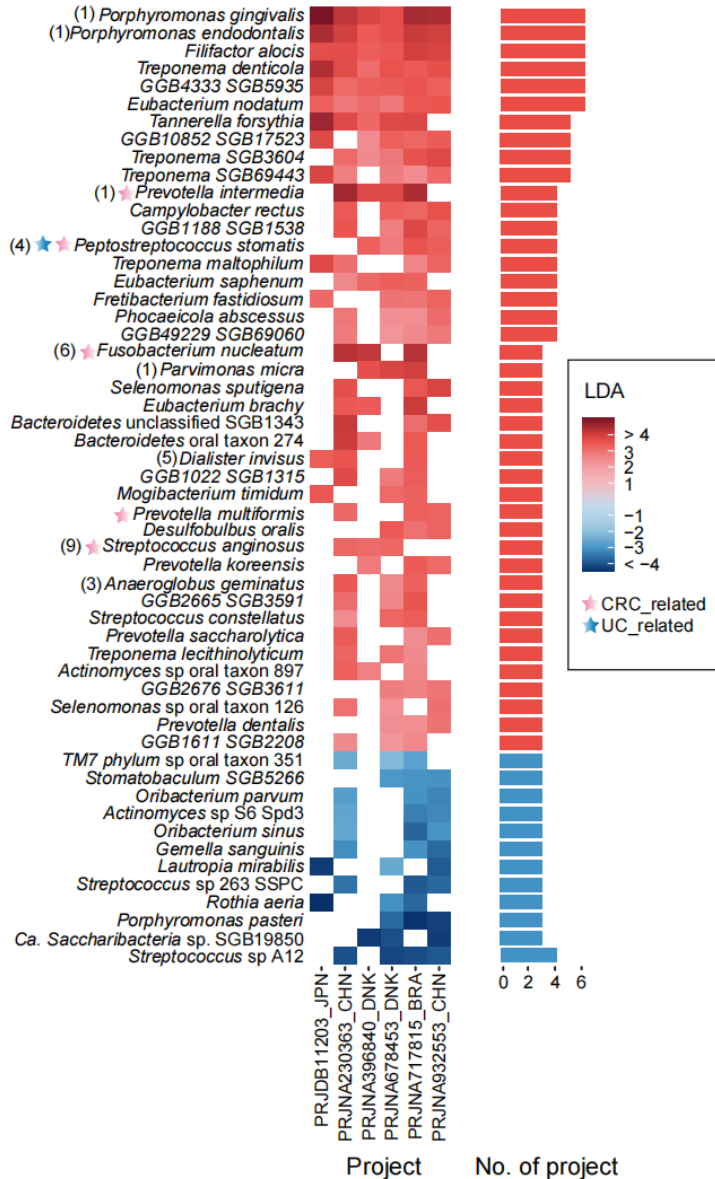
- Periodontitis is a crucial global public oral health concern and increases risks of systemic diseases.
- Earlier studies developed machine learning models from periodontitis patients' oral microbiomes using 16S sequencing, but suffered from low taxonomic resolution, limited datasets, and a lack of wider representation of the global population.



Results

◆ Identification of cross-cohort species biomarkers for periodontitis

(B)



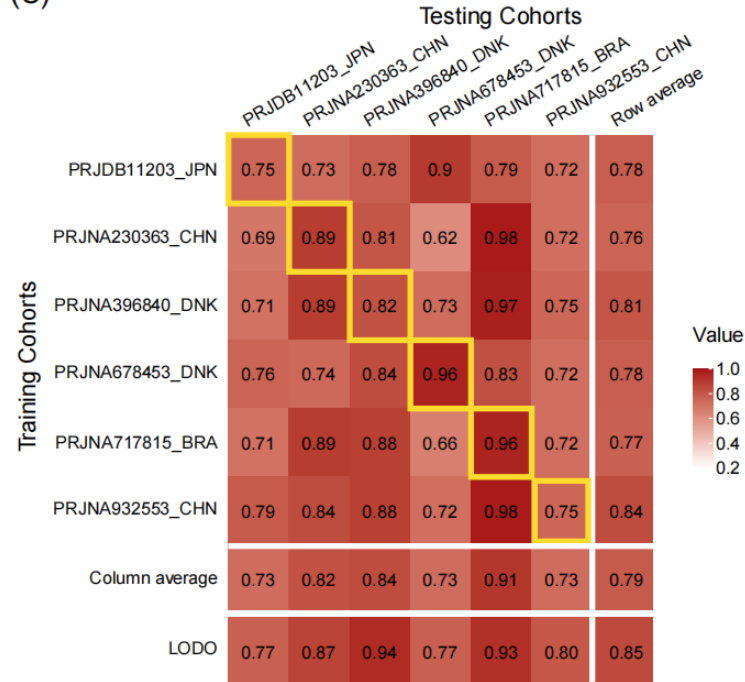
- We identified 54 that showed consistent trends in three and more cohorts, including 42 and 12 disease- and health-enriched ones, respectively.
- The disease-enriched markers included many known periodontitis-associated species, including the “red complex” members (i.e., *P. gingivalis*, *T. forsythia*, and *T. denticola*), and *Porphyromonas endodontalis*, *Filifactor alocis*, and *Eubacterium nodatum*.
- We also identified novel species that have not been widely studied, including *GGB4333 SGB5935* which was enriched in six cohorts, and three novel species present in five cohorts.
- We found that some of these biomarkers were also enriched in the gut microbiome in patients of colorectal cancer (CRC) and Crohn’s Disease (CD).



Results

◆ Taxonomy-based classifiers have high classification performance and cross-cohort generalization ability

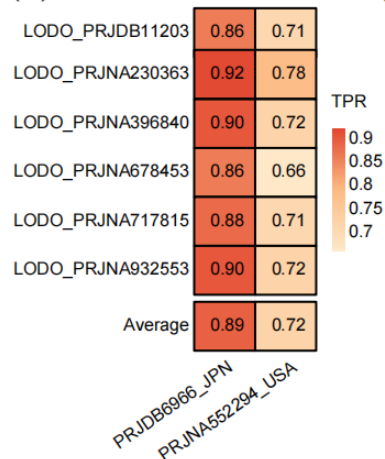
(C)



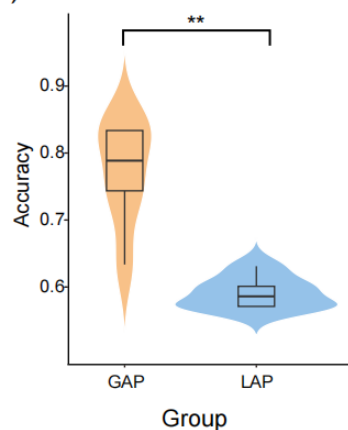
- We used a random forest classifier with oral microbiome data to differentiate cases from controls, achieving an internal AUC of **0.86** and an external AUC of **0.79**. Leave-one-dataset-out analysis improved the external AUC to **0.85**.

- Our LODO classifiers were robust, with TPRs of **89%** and **72%** in two patient cohorts (PRJDB6966 and PRJNA552294).

(D)



(E)

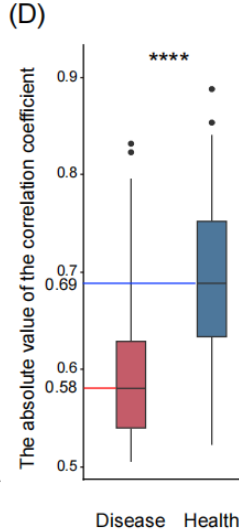
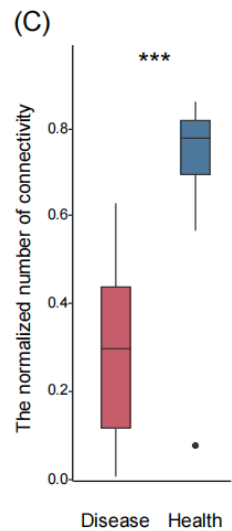
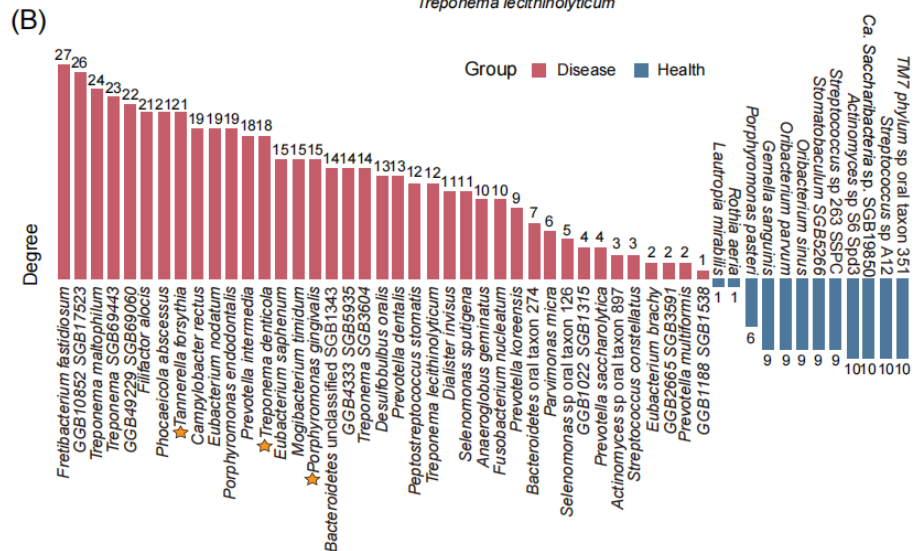
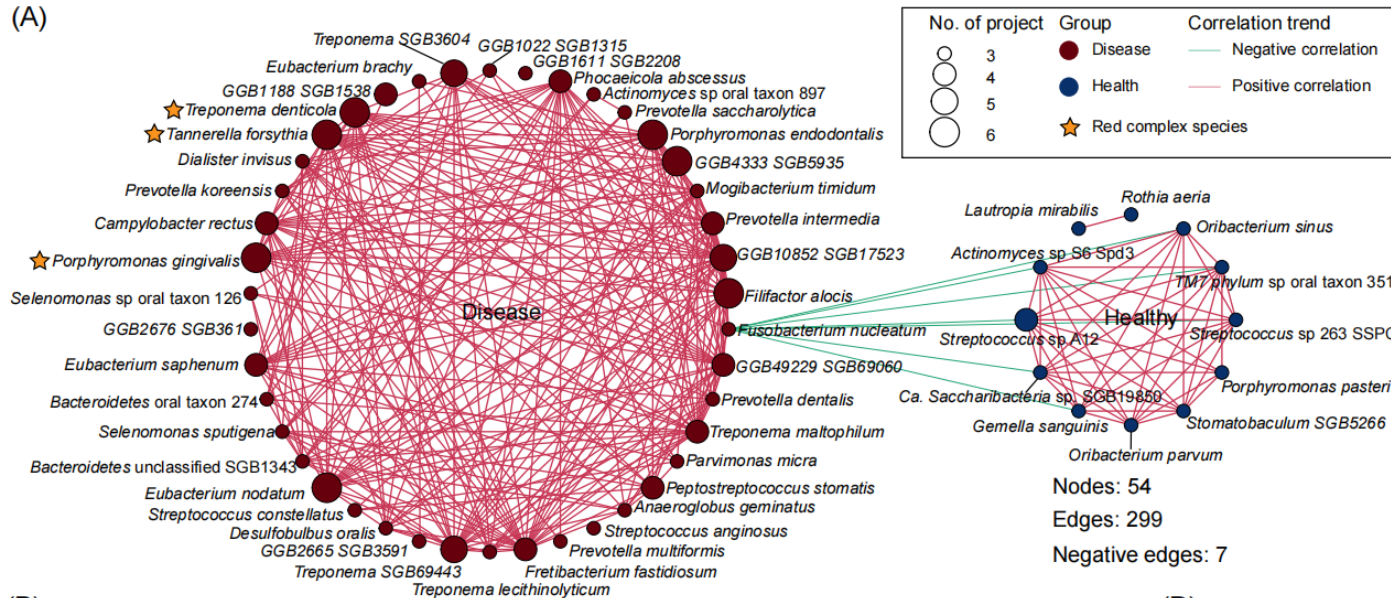


- Grouping patients by disease severity, TPRs were ~**80%** for generalized aggressive periodontitis (GAP) and ~**60%** for localized aggressive periodontitis (LAP), demonstrating high precision and good sensitivity.



Results

◆ Network analysis reveals predominantly positive interactions among biomarkers of health- or disease-groups



- **Correlation Network Analysis:** A total of **299** interactions were identified among biomarkers using a Spearman Correlation Coefficient (SCC) threshold > 0.5 and $p < 0.05$.

- **Role of Novel Species:** A new species, *GGB10852 SGB17523*, was highlighted for its potential role in periodontitis due to significant interactions with disease-enriched species.

- **Connectivity and Correlation Strength:** Health-biomarkers demonstrated stronger correlations and higher synchronization, suggesting a better adaptation to the oral environment compared to disease-biomarkers.



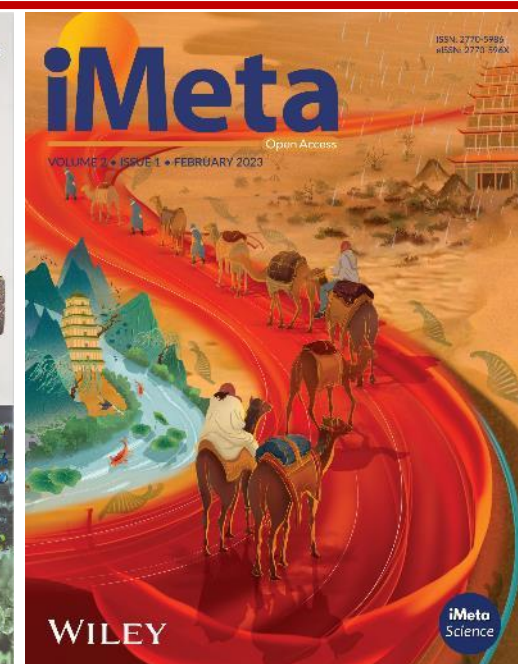
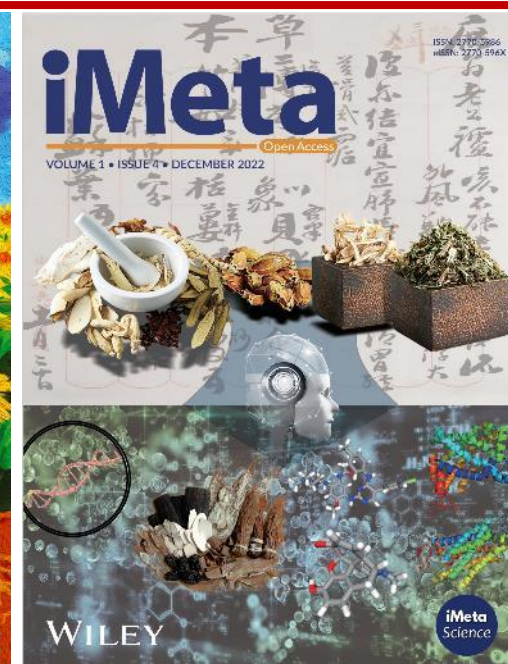
Summary

Identification of cross-cohort biomarkers consistently altered across more than three cohorts, comprising 54 species and 26 metabolic pathways. The taxonomic biomarkers include both known pathogens and novel species.



Development of machine learning models with high accuracy in distinguishing periodontitis from controls, achieving AUCs of 0.86 and 0.85 in within-dataset validation and cross-cohort testing, respectively.


Discovery of predominantly positive correlations among disease- or health-enriched species, highlighting potential synergistic interactions or shared growth requirements. This underscores the need to adopt a holistic approach to improve oral physiological conditions, while favoring the growth of health biomarkers and inhibiting the growth of disease biomarkers.



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