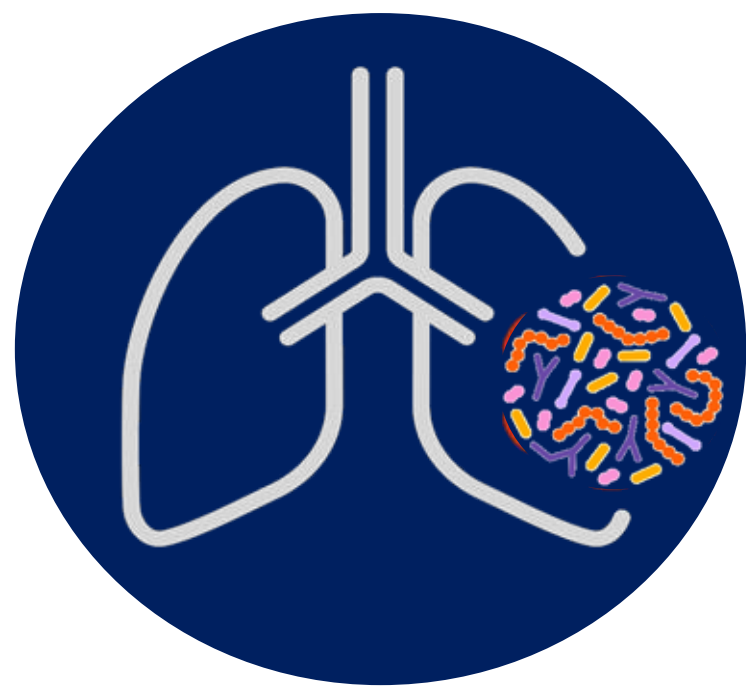




P2.226: The oral microbiome demonstrates potential as a biomarker for primary lung malignancy

AEB McLean^{a,b,c} | WA Cooper^{a,d} | SC Kao^{a,e} | EMT Lau^{a,b} | KKH Wong^a | DJ Barnes^a | X Jiang^f | HCH Yim^f | E El-Omar^f | MRJ Kohonen-Corish^{c,f}
^aFaculty of Medicine and Health Sciences, The University of Sydney, Camperdown, NSW, Australia; ^bRespiratory and Sleep Medicine, Sydney Local Health District, Royal Prince Alfred Hospital, Camperdown, NSW; ^cWoolcock Institute of Medical Research, Macquarie University, NSW; ^dTissue Pathology and Diagnostic Oncology, NSW Health Pathology, Royal Prince Alfred Hospital, Camperdown, NSW; ^eDepartment of Medical Oncology, Chris O'Brien Lifecare, Camperdown, NSW; ^fMicrobiome Research Centre, School of Clinical Medicine, Faculty of Medicine & Health, UNSW, Kogarah, NSW
Correspondence: anna.mclean@health.nsw.gov.au



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INTRODUCTION

- The diagnosis of lung cancer is not always straightforward as tissue can be difficult to obtain and even when biopsies are performed, small tissue samples can lead to inconclusive diagnoses.
- Implementation of lung cancer screening programs has also led to an increased number of intermediate risk pulmonary nodules, for which the decision to biopsy or monitor is often difficult.
- A non-invasive biomarker to stratify malignancy risk could aid clinical decision-making in these scenarios.
- Colonisation of the airways with dysbiotic oral taxa is thought to play an important role in lung cancer pathogenesis¹.
- We hypothesised that a microbial signature from the oral microbiome could therefore act as a non-invasive biomarker of primary lung malignancy.

METHODS

- Patients attending our tertiary referral centre with suspected or confirmed primary lung cancer from June 2021 to December 2023 were consecutively recruited to the study.
- Clinicopathological and demographic data as well as information on previous antibiotic and proton pump inhibitor use were collected.
- Oral swabs were performed on 140 participants prior to the diagnostic procedure or the commencement of treatment.
- Whole genome metagenomic sequencing was successfully performed in 138 patients. Of these, 34 (25%) were ultimately diagnosed with a benign condition, 92 (67%) with a primary lung malignancy (NSCLC and SCLC), and 12 (8%) with a non-primary lung malignancy.
- The association of the oral microbiome with primary lung cancer compared to benign lung disease was then investigated to the species level.
- To identify the optimal oral microbial biomarkers for primary lung cancer, species-level taxa were ranked using a composite differential abundance-based scoring pipeline.

DISCUSSION AND CONCLUSION

- The oral microbiome composition is distinct in patients with benign compared to malignant lung disease.
- Unlike previous studies, we demonstrated alpha diversity to be increased in malignancy, driven by increased species richness despite reduced evenness.
- This may be explained by our predominantly Caucasian cohort or the use of metagenomic sequencing in our study which is more sensitive for low abundance species. Almost all research to date has been performed in Asian populations using 16S rRNA sequencing.
- We demonstrated that a panel of microbial species could be selected based on differential abundance and used to discriminate benign vs malignant lung disease. This panel score remained strongly associated with malignancy on multivariable adjustment.
- A non-invasive test able to differentiate or predict likely benign from malignant disease has significant clinical potential in multiple contexts such as improving malignant risk assessment in a lung cancer screening program or as a prognostic tool in patients too unwell to undergo invasive procedures.
- Further studies are needed to validate these findings in larger independent cohorts. However, our study provides impetus for further investigation and development of non-invasive microbiome-based biomarkers.

REFERENCES & ACKNOWLEDGEMENTS

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RESULTS

Table 1. Comparison of patient characteristics between primary lung cancer and benign conditions.

Characteristic	Benign N = 34	Primary lung cancer N = 92	P-value
Age			0.77
median [Q1,Q3]	72.0 [64.2, 81.0]	71.5 [66.0, 77.2]	
Sex			0.759
Male	24 (70.6%)	59 (64.1%)	
Female	10 (29.4%)	33 (35.9%)	
Smoking status			0.0682
Current-smoker	2 (5.9%)	11 (12.1%)	
Ex-smoker	17 (50.0%)	59 (64.8%)	
non-smoker	15 (44.1%)	21 (23.1%)	
Ethnicity			0.649
Asian	6 (17.6%)	22 (24.2%)	
Caucasian	28 (82.4%)	67 (73.6%)	
Other	0 (0.0%)	2 (2.2%)	
Antibiotics within 3 months	21 (61.8%)	37 (41.1%)	0.0637
PPI within 3 months	7 (20.6%)	30 (32.6%)	0.274

*P value calculated using chi-squared or Fisher's exact test as appropriate. "Within 3 months" refers to the period up to and including the date of oral sampling.

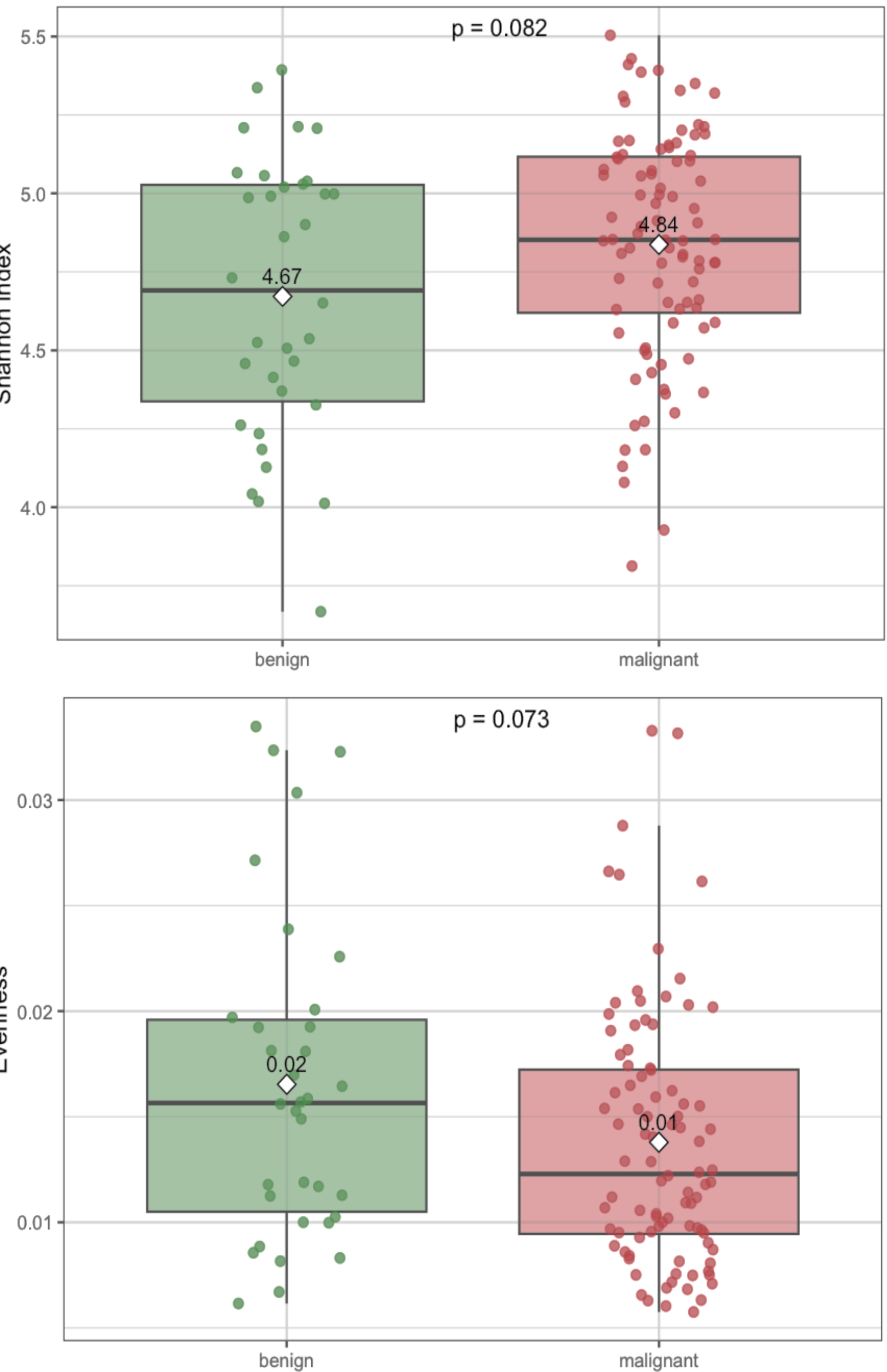


Figure 2. Boxplots demonstrating increased Shannon diversity index (above; $p = 0.08$) but reduced Evenness diversity index (below; $p = 0.07$) with primary lung cancer. Benign refers to non-malignant conditions affecting the lungs, such as infection or inflammation. Primary lung cancer (malignant) refers to NSCLC and SCLC.

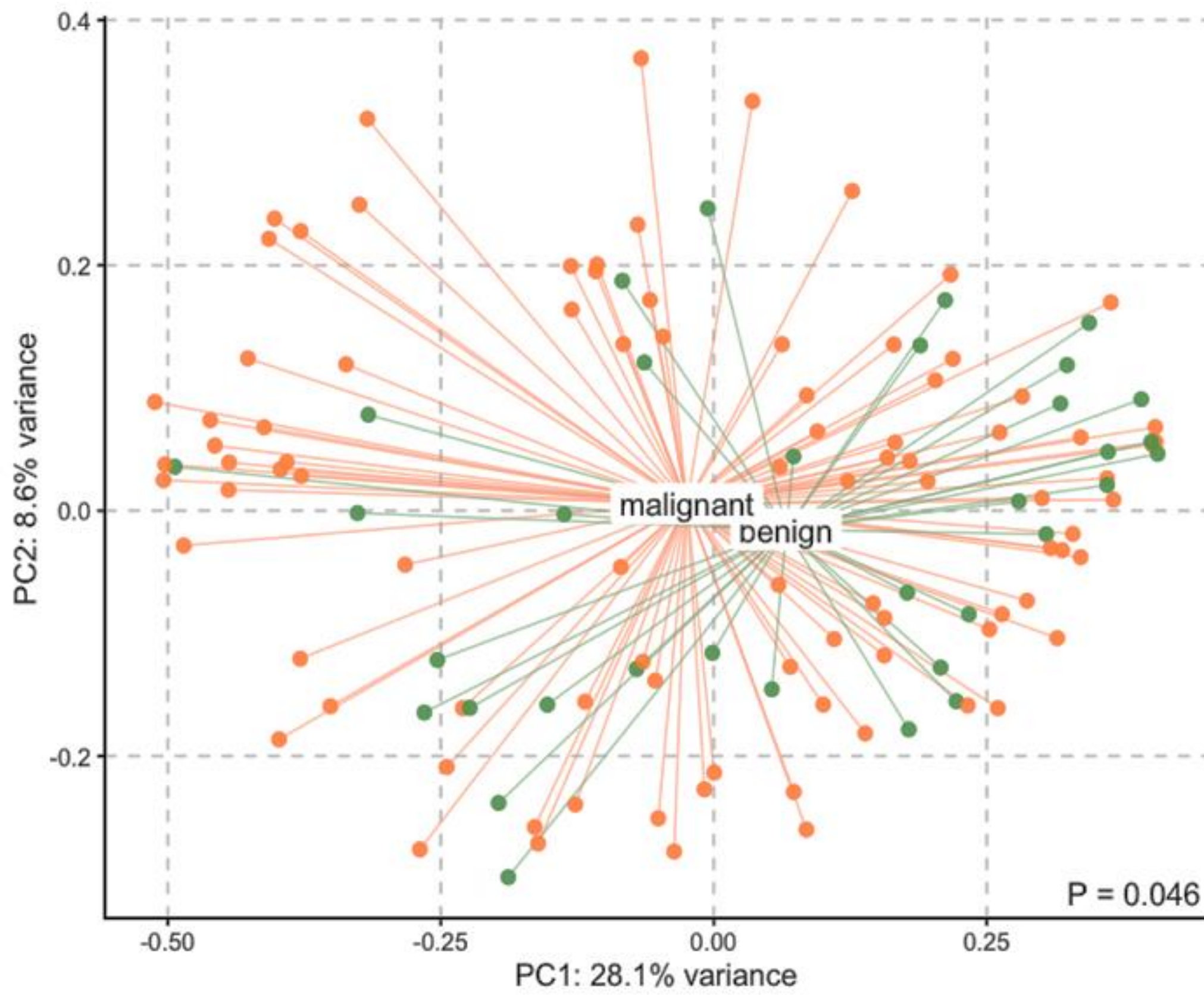


Figure 1. Comparison of oral microbiome composition between primary lung cancer and benign conditions. Principal coordinate analysis based on Bray-Curtis distances demonstrating distinct microbial community structure in participants with primary lung malignancy vs benign disease (PERMANOVA $P = 0.046$)

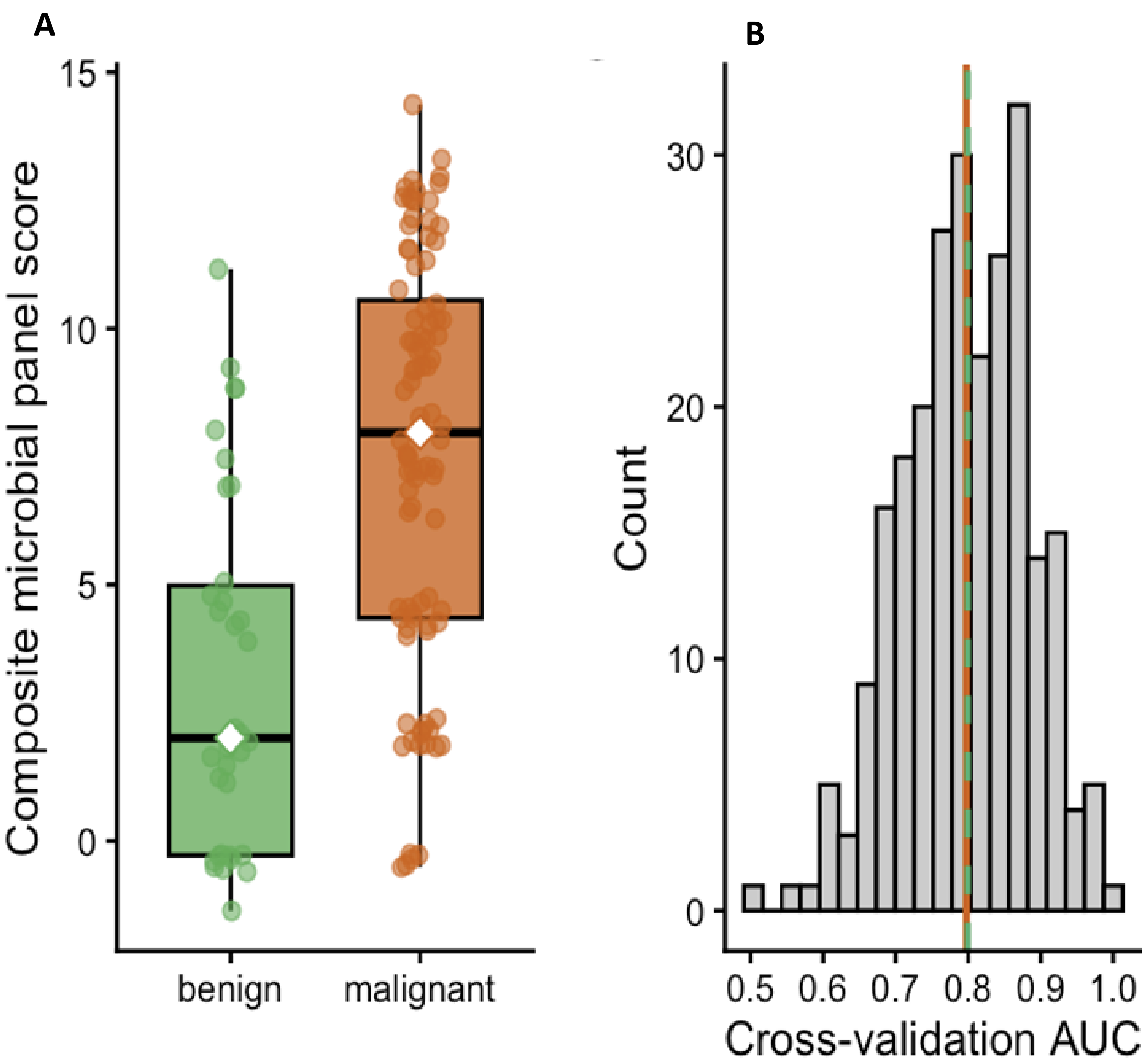


Figure 3. Performance of oral microbiome biomarker panel for primary lung cancer. **A** Bar plot of microbial panel scores across outcome groups demonstrating substantial separation between benign and malignant samples (median Cohen's $d = -1.13$). Malignant samples were associated with higher panel scores. **B** Distribution of cross-validation AUC values from repeated stratified resampling with vertical lines indicating mean (red) and median (green) AUC. Mean cross-validated AUC = 0.80 (0.62–0.90). The panel score remained strongly associated with malignancy following multivariable adjustment for smoking status, antibiotic use, PPI use and age (OR 1.33 (1.17–1.54); $p < 0.01$).