

Precision Medicine/Health

Predicting survival in patients with neuroendocrine prostate cancer*

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OBJECTIVES/GOALS: The impact of genetic alterations on survival in patients with neuroendocrine prostate cancer (NEPC) is unclear. This study assessed how genetic alterations and tumor mutational burden (TMB) affect overall survival (OS) in patients with NEPC treated at Mayo Clinic. **METHODS/STUDY POPULATION:** Demographic, clinicopathologic, and genomic data from patients with NEPC treated at Mayo Clinic (2015–2025) were abstracted from electronic medical records. Patients had consented to research and received at least one cycle of therapy. Descriptive statistics summarized patient characteristics, and survival was estimated with Kaplan–Meier analysis. OS was compared by disease type (de novo vs treatment-emergent NEPC), TMB (high vs low), and RB1, TP53, and PTEN alteration status. **RESULTS/ANTICIPATED RESULTS:** Among 66 patients in the study, the average age at NEPC diagnosis was 67.5 years. There were no significant differences between the age at diagnosis of de novo and treatment emergent NEPC (t-NEPC). t-NEPC made up 77.3% of the cohort. Median follow-up was 46.5 months (IQR 28–120). The most common alteration was TP53. RB1 alterations were associated with significantly shorter OS compared to patients without RB1 alterations (mOS Not Reached (NR) vs 13.8 months; $p = 0.0056$). Similarly, patients with high TMB had worse overall survival (mOS NR vs 14.9 months; $p = 0.077$). We did not observe worse OS in patients with alterations in TP53 or PTEN. RB1 alteration and high TMB were the strongest predictors of worse survival. **DISCUSSION/SIGNIFICANCE OF IMPACT:** RB1 alterations and high TMB predict poor survival in patients with NEPC, highlighting potential biomarkers for risk stratification. TP53 and PTEN did not significantly affect OS. Early genomic profiling and targeted management of actionable alterations such as BRCA and ATM may improve survival and inform future translational studies.

High-risk peripheral blood immune dysregulation signature is elevated in obesity and is reduced by lifestyle interventions

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OBJECTIVES/GOALS: The Human Immune Dysregulation Evaluation Framework (Hi-DEF) quantifies myeloid dysregulation

in infectious and non-infectious illness using peripheral blood gene expression (Moore, Nat Med). We evaluated immune dysregulation in obesity and quantified the changes in dysregulation due to lifestyle and medical interventions. **METHODS/STUDY POPULATION:** We assessed the association of obesity with myeloid dysregulation in the Framingham Cohort using linear regression. In two additional datasets (GSE66175, GSE19790), we assessed the effect of dietary interventions and bariatric surgery on myeloid dysregulation using paired Wilcoxon rank sum test pre- and post- intervention and Pearson's correlation. **RESULTS/ANTICIPATED RESULTS:** In the Framingham cohort ($n=5321$), myeloid dysregulation score was associated with BMI ($p=2.2e-6$) after correcting for age and sex. Patients assigned to diet/exercise experienced significant reductions in myeloid score after 3 months ($n=63$, $p=1.2e-7$), which was not seen in controls ($n=63$, $p=0.29$). Change in myeloid score was significantly correlated with change in weight loss ($r=0.32$, $p=0.006$). This reduction in myeloid dysregulation was also seen post-bariatric surgery ($n=11$, $p=0.0001$). **DISCUSSION/SIGNIFICANCE OF IMPACT:** Patients with obesity have significantly higher myeloid dysregulation compared to healthy subjects, which is modifiable with lifestyle and medical interventions. These results suggest that we may be able to quantify and monitor immune dysregulation from obesity which may place these patients at risk for worse outcomes.

Serum bile acid and gut microbiome composition in heterogeneous individuals

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OBJECTIVES/GOALS: Colorectal cancer risk varies across populations. Bile acid (BA) composition and the gut microbiome can impact CRC risk, but their differences across populations is poorly understood. We characterized serum BA and gut microbiome profiles in non-Hispanic Black and White Americans and examined associations with diet and social determinants of health. **METHODS/STUDY POPULATION:** To characterize BA composition, participants from the Chicago Multiethnic Prevention and Surveillance Study with a banked serum sample ($n=100$) were selected, with a subset of participants having completed a diet recall survey (ASA24; $n=23$). Sixty-two BA (primary, secondary, and glyco/tauro-conjugated BA) from serum samples were analyzed using liquid chromatography-mass spectrometry. For microbiome profiling, normal colonic biopsy samples from non-cancer participants were obtained from the Digestive Disease Research Core Center's Integrative Clinical and Biospecimens Core (University of Chicago; $n=109$). Following DNA extraction, the mucosally adherent microbial community was assessed by 16S rRNA sequencing. **RESULTS/ANTICIPATED RESULTS:** Of the BA detected in over 80% of the samples, glycochenodeoxycholic acid (GCDCA) and