Hepatocellular carcinoma (HCC) is treatable if detected early. However, recommended surveillance strategies for at-risk patients exhibit suboptimal sensitivity for early-stage HCC detection. DNA methylation abnormalities are found in HCC and are widely recognized as potential biomarkers of disease. Our research aimed to identify differentially methylated DNA markers (MDMs) in cell-free DNA (cfDNA) that discriminate between HCC cases and HCC-negative controls. These MDMs were evaluated along with serum protein markers; top performing markers were used to develop a novel, blood-based test for HCC detection. We utilized blood samples from an international, multicenter, case-control study (NCT03628651) for marker panel development, algorithm development and test validation. HCC cases were identified per American Association for the Study of Liver Diseases (AASLD) criteria. Controls were at-risk patients with chronic liver disease and classified as HCC-negative by imaging. Following marker selection, the panel was finalized (3 MDMs and 1 protein) and incorporated into an algorithm with patient sex. The final assay demonstrated 72% early-stage HCC sensitivity at 88% specificity in this algorithm development study (136 HCC cases and 404 controls). In a subsequent independent validation cohort (156 HCC cases and 245 controls), the test demonstrated 82% early-stage HCC sensitivity and 87% specificity. Further sub-analyses suggest test performance is consistent across important patient populations. Our research efforts are focused on improving the performance of blood-based detection of early-stage HCC and enhancing early HCC detection for patients undergoing surveillance. These results, and the opportunities and challenges of developing a clinically useful early cancer detection tests, will be discussed.