ASCO 2020
Abstract # e15583

Validation of an exome and transcriptome based diagnostic platform enabling clinical cancer therapy selection and emerging composite biomarkers for immunotherapy.

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Background: While immunotherapy has become a pillar of cancer treatment, diagnostic biomarkers that consistently predict patient response to these therapies have remained elusive. There is an increasing need for the development of integrative, composite biomarkers that can model the complex biology driving response and/or resistance to immunotherapy more effectively than existing single-analyte approaches. However, the majority of current cancer diagnostic panels, with their focus on a small set of genes, provide limited ability to support these emerging advanced biomarkers.

Methods: To address these limitations, we developed and validated NeXT Dx, a comprehensive enhanced exome and transcriptome based diagnostic platform designed to simultaneously characterize tumor and immune genomics from a single limited FFPE sample. To achieve higher accuracy and sensitivity for an exome scale diagnostic platform, we developed an augmented exome assay that improves uniformity of coverage across all ~20,000 genes, including boosted coverage of 248 clinically-relevant cancer genes. We validated this assay using genomic DNA and RNA extracted from tumor-derived cell-lines, constructs, clinical FFPE samples, and proficiency testing samples. The assay utilizes > = 25ng of co-extracted DNA and RNA which were sequenced using Illumina NovaSeq instruments at our CAP-accredited, CLIA-certified laboratory. Additional assay enhancements for HLA, immune repertoire, and oncoviruses were designed to further optimize the platform for immunotherapy biomarker discovery applications.

Results: Validation of NeXT Dx demonstrated a performance of 99.5% sensitivity and 99.8% positive predictive value (PPV) for SNVs with > = 5% AF; 98.7% sensitivity and 97.4% PPV for indels with > = 10% AF; 97.2% sensitivity and 94.6% PPV for CNAs in samples with > = 30% tumor content; 94.9% sensitivity and 94.9% PPV for fusions; and a 2.1% error rate for MSI classification. TMB was calculated using gold-standard whole exome data from SNVs and indels. Typical median coverage depth was > 1,000X for 248 clinically-relevant genes, ~300X for the remaining (whole exome) footprint.

Conclusions: With NeXT Dx, we demonstrate a exome/transcriptome scale diagnostic platform that can detect current clinical biomarkers with high sensitivity as well as support emerging, advanced biomarkers that integrate across both tumor and immune features.

J Clin Oncol 38: 2020 (suppl; abstr e15583)