An End-To-End Precision Medicine Approach for Matching Cancer Patients to Clinical Trials

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INTRODUCTION
Precise matching of a patient’s tumor genomic profile with appropriate targeted agents is the goal of precision medicine, and the salutary benefits of these targeted therapies upon survival has been well documented in the literature. Using a 413+ cancer-related actionable gene, NGS sequencing panel, KEW CancerPlex®, we analyzed a variety of solid tumors to identify mutations associated with predicted response to approved and investigational targeted therapy agents.

METHODS
Tumor profiling was conducted in a CAPQUA-certified laboratory, licensed by MA and 48 other states (KEW Group Inc.). DNA was extracted from FFPE tissue sections, slides, cell blocks, from FNA or effusions, or cell pellets, followed by hybrid-capture next-gen sequencing. Rapid sequencing runs were employed to generate near-100x depth, and mutational analysis was performed using the KEW Clinical Genomics Analytical pipeline. The coding regions and portions of the introns of 413+ genes were sequenced. The assay simultaneously surveyed multiple classes of genomic abnormalities including single nucleotide substitutions (SNP), small insertions/deletions (indels), copy number alterations (CNV), and translocations.

Variant characterization and annotation were conducted for a MAP cut-off of 10%. Genotype-based personalized molecular modeling was performed to characterize tumors, and response to FDA-approved drugs was predicted. Matches were identified by screening 260,000 clinical trials, including approximately sixty thousand active or recruiting studies.

TECHNICAL PERFORMANCE - CancerPlex® v3
Analytic sensitivity for SNP calls is 98.9%-100% at 95% confidence interval, specificity is 99.99%, for indels sensitivity is 99.8%-100% at 95% confidence interval and specificity is 99.99%. Analytic sensitivity for translocations of the ALK, RET, and ROS1 genes is 100% for tumor purity as low as 10%.

Testing and reporting turnaround time of 7-10 days.

CancerPlex Test requires only a small portion of the biopsy (40 micron section or equivalency), and it can technically be performed with a very low amount of input DNA. The CancerPlex requirement of tissue is determined by biological considerations to obtain a representative sampling of the tumor.

RESULTS
200 cases, representing a variety of tumor types were analyzed using CancerPlex® v2 Assay. Tumors averaged 6.65 somatic variants (range: 1-18), of which 2.48 variants (range: 0-9) were deemed clinically actionable (93%). Tumor-specific resistance markers were identified for FDA-approved therapies (mean: 1.2; range: 0-5) and clinical trials (mean: 7.98 range: 0-24).

Additional 50 randomly selected clinical cases were characterized using the upgraded CancerPlex® v3 Assay that provides about 2-fold deeper sequence coverage (50x) for the same gene panel. Overall, fifty seven alterations were found actionable, those alterations are assigned to 47 cases (94%). None of the samples failed to yield a report.

Clinical Trials available – PRI-724
Mislaid by smaller gene panel

Clinical Trials – Foretinib
Mislaid by smaller gene panel

ACTIONABILITY
Our study shows that the actionability rate is not significantly affected by an increase of sequencing coverage. The major reason is the arbitrary cut-off of 10% MAF. The actionability rate could be improved if one were to consider including clinical alterations assigned to only a subset of the entire tumor cell population.

Another factor impacting actionability may be the gene panel size. Published validation studies show that hot-spot analysis (small panels of ~100 cancer genes) misses up to 20% of clinically important mutations in some tumors (Dhillon et al., 2014). To test this further, we took a subset of CancerPlex genes to match the content of a previously published smaller panel of 315 genes (Frampton et al., 2015), and compared the actionability. The larger panel provided critically important additional mutations (see figures).

FDA approved therapy available – Trametinib
CancerPlex matches all functional domains of proteins involved in “druggable” pathways – indirect targets, which substantially increases the screening power for clinical actionability. Out of 47, 3 cases (6.4%) would be mislaid by smaller, 315 genes, gene panel.

CONCLUSION
Larger NGS panel size increases the likelihood of identifying clinically actionable findings, including FDA-approved therapies missed by NGS panels with fewer genes.