Abstract# 11185: Comparative analysis of actionable gene reporting in targeted panels versus comprehensive NGS testing for solid tumor samples.

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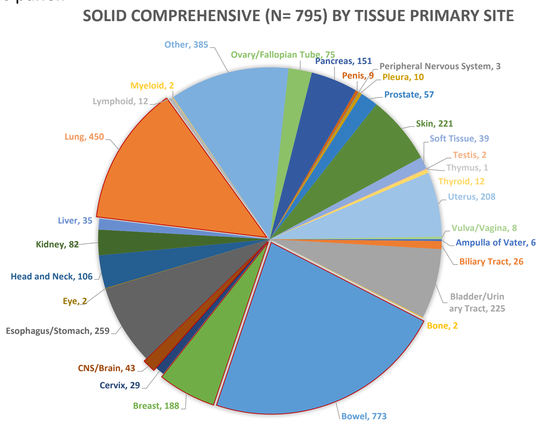
Background:

The landscape of actionable genes significantly influences clinical decisions in cancer diagnosis, prognosis, and treatment planning. In a clinical context, the selection of NGS panels hinges on striking a balance among informative data, insurance coverage, and the preferences of patients and healthcare providers. Molecular pathology reference laboratories commonly employ large-scale next-generation sequencing (NGS) testing, curating smaller, disease-specific targeted panels. This study investigates the prevalence of unreported actionable genes in real-world clinical samples subjected to disease-specific panels.

Methods:

We analyzed SNV/InDel DNA variants in 795 clinical solid tumor samples using the Illumina TSO 500 platform for comprehensive NGS panel testing of 517 genes. Comprehensive NGS panel-tested samples were intersected with disease-specific targeted NGS panels for breast (54 genes), brain (62 genes), colorectal (36 genes), and lung (44 genes). An artificial filter was applied to align targeted panels with patient disease. Variants were classified based on pathogenicity, and benign variants were filtered out. Detected variants were assessed for actionable mutations as defined by the FDA recognized OncoKB actionable gene database criteria. Additionally, 1484 lung patient samples tested with a lung-specific targeted panel were de-identified and unmasked to the comprehensive NGS tumor profiling to investigate the prevalence of actionable alteration beyond those covered by the disease-specific panel.



A. Figure 1:Distribution of samples tested with a Comprehensive gene panel across 30 primary tumor sites from which only pathogenic and likely pathogenic variants were analyzed in the study.

Comprehensive testing captures each patient's full actionable profile

- Well-curated, disease-specific panels are well-suited for traditional clinical biomarker testing
- Comprehensive testing increases the chance of identifying markers for clinical trials, especially for stage III/IV and therapy-resistant cancers.

Keywords: Clinically actionable, tumor agnostic, Real World Data, NGS comprehensive testing

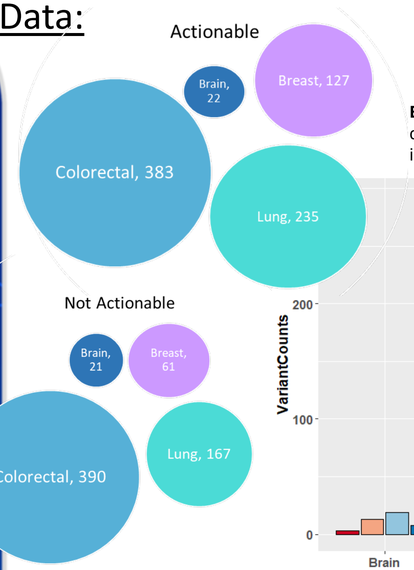
Future Direction of Research:

An aggregate understanding of actionable tumor profiles requires the analysis of all available modalities for Comprehensive genomic profiling, including, at minimum, copy number variants, fusions, tumor mutation burden, and microsatellite instability.

Results:

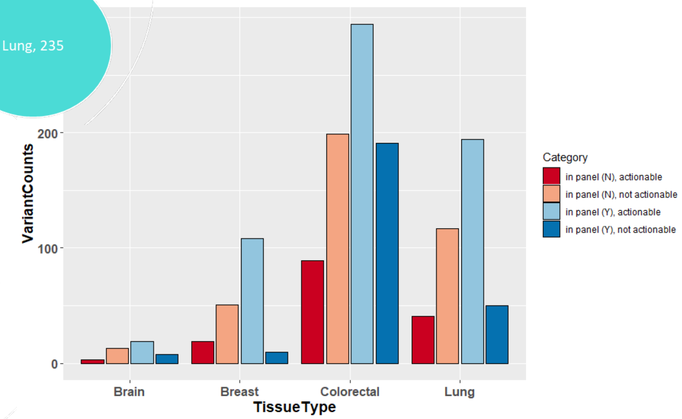
The study revealed that 3.2% of breast, 0% of brain, 66.2% of colorectal, and 2.7% of lung samples had additional actionable mutations undisclosed by the targeted panels. The number of actionable genes beyond those included in the targeted panels were 14 for breast, 2 for brain, 25 for lung, and 41 for colorectal cancer. This underscores the importance of comprehensive testing to fully capture each patient tumor's actionable mutation profile.

Data:

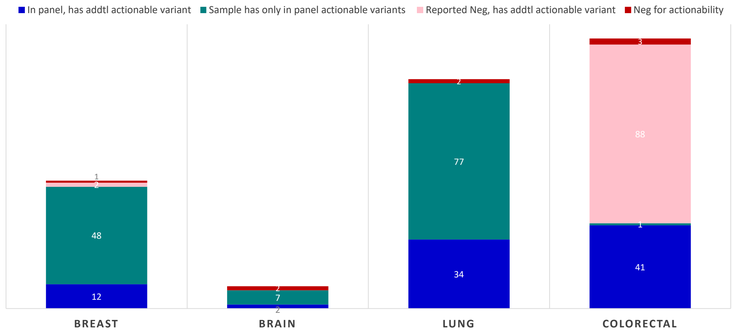


Variant Level Analysis

B. Figure 2,3: Intersection of pathogenicity, actionability, and disease-specific variants according to primary tumor indication.



Sample Level Analysis



C. Figure 4: Distribution of actionability for unique clinical sample

D. Figure 5: Samples (n= 1484) tested with a 44 genes, Lung–Specific panel were de-identified and unmasked to a Comprehensive gene panel (517 genes) to gain an understanding of (1) 'how many samples would have had additional actionable genes?' and (2) 'how many would have been reported as 'Not Detected' but have actionable alterations outside of a given panel?'

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Reference: https://www.oncokb.org/actionable-genes (166 actionable genes)
OncoKB™: Suehnholz et al., Cancer Discovery 2023 and Chakravarty et al., JCO PO 2017.

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