

Validation of a Clinically Actionable Cancer Core Gene Test for Solid Tumors Facilitating Targeted Molecular Therapy and Immunotherapy

Background

- Molecular profiling of tumors can distinguish tumor subtypes and guide treatment decisions.¹⁻³
- Most molecular profiling tests do not assess microsatellite instability (MSI), which can indicate a patient's response to immunotherapy.
- **Objective:** The investigators of this study validated a new test that targets mutations in core cancer genes relevant to molecular therapy and determines MSI status, which is relevant to immunotherapy response.

Methods

- This study included formalin-fixed, paraffin-embedded (FFPE) tumor samples and whole blood samples from lung, colorectal, melanoma, and breast cancer tumors.
- Four major types of mutations were assessed: single nucleotide variations (SNVs), insertion/deletions (INDELs), whole gene copy number variations (CNVs), and structural rearrangements (translocations).
- The test analyzed exons from 49 core cancer genes, introns from a subset of genes known to have prevalent gene rearrangements, and the TERT (telomerase reverse transcriptase) promoter region.
- Targeted DNA regions were captured by hybridization with complementary biotinylated RNA baits, and next-generation sequencing was performed.
- Microsatellite instability (MSI) status was evaluated when paired whole blood samples were available.

Results

- Read depth was 700-fold for all targeted regions.
- Analytical sensitivity was
 - $\geq 5\%$ mutation frequency for SNVs and INDELs
 - $\geq 20\%$ for translocations and CNVs
- The test identified 38 of 38 unique variants.
- MSI status determined by this test was compared to MSI status determined by the reference National Comprehensive Cancer Network Bethesda PCR test.
 - Of 59 paired FFPE/blood samples, 58 (98%) were concordant.
- Mutation count was 5-fold higher in MSI-positive samples than MSI-negative samples, which is consistent with previous reports.

Conclusions

- The investigators analytically validated a solid-tumor, next-generation sequencing test that includes 49 core cancer genes and determines MSI status.
- This test has potential to guide treatment decisions for cancer patients.

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