Key Summary of Published Article

Analytical Validation and Performance Characteristics of a 48-Gene Next-Generation Sequencing Panel for Detecting Potentially Actionable Genomic Alterations in Myeloid Neoplasms

Background

- Myeloid neoplasms are a heterogenous group of malignant disorders that develop in the bone marrow and peripheral blood. They include acute myeloid leukemia (AML), myelodysplastic syndromes (MDSs), and myeloproliferative neoplasms (MPNs).
- Analysis of genetic variants can help guide clinical management, and next-generation sequencing (NGS) panels have been developed for analysis of myeloid neoplasms.
- However, some technical challenges remain for these panels.[1,2] For example, some genes commonly altered in myeloid neoplasms, such as *CEBPA*, *CARL*, and *FLT3*, are particularly difficult to sequence.
- **Objectives:** Investigators developed and validated an NGS panel of 48 genes, including those that are technically difficult to sequence by NGS, for variant analysis of AML, MDSs, and MPNs.

Methods

- The 48 gene targets included in the NGS panel were selected based on being associated with the diagnosis or clinical management (including therapy selection) of myeloid neoplasms.
  - Technically difficult-to-sequence genes included *CEBPA*, *CARL*, and *FLT3*.
- Single-nucleotide variations, insertions/deletions, and *FLT3* internal tandem duplications were detected using a bioinformatics pipeline developed in-house.
- For analytical validation, 184 deidentified specimens were analyzed for variants.
- To allow for comparison relative to an existing panel, another 137 specimens were selected because at least 1 pathogenic variant in a gene included in the 48-gene panel was detected with a 35-gene hematologic neoplasm panel.
- To assess clinical performance, 2,053 submitted specimens from patients with probable myeloid neoplasms were tested using the 48-gene NGS panel.

Results

- Analytical validation studies demonstrated that the 48-gene NGS panel had 99.6% (95% CI, 98.9-99.9%) sensitivity and 100% (95% CI, 100%) specificity, with no false-positive results.
- The 48-gene panel showed 100% agreement for variants detected with the 35-gene hematologic panel.
- Of 2,053 submitted patient specimens
  - 55.6% (n=1,142/2,053) had ≥1 pathogenic variant.
  - 51.7% (n=1,062/2,053) had clinically significant (prognostic, diagnostic, actionable) variants.
  - 41.7% (n=856/2,053) had ≥1 variant that was actionable (available therapy or experimental drug).

Conclusions

- The findings of this study show that the 48-gene NGS panel can detect actionable variants, including those in genes that are difficult to sequence.

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