Combining DNA and RNA analyses enhances non-invasive early detection of cutaneous melanoma

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SYNOPSIS
The Pigmented Lesion Assay (PLA) is a gene expression test enhancing early melanoma detection. The test uses a proprietary non-invasive sample collection platform to objectively rule out melanoma and guide biopsy decisions. The PLA has been evaluated in over 60,000 patients with approximately 90% (54,000) of patients avoiding surgical biopsies due to negative results. The test's negative predictive value of 99% has been validated in long-term follow-up studies. Combined with the rapid and painless application, the PLA is an attractive solution that misses fewer melanomas while reducing costs. Clinicians follow the guidance of the test in 98% of cases corroborating high clinical utility. To further improve the high performance of the PLA, RNA and DNA analyses were combined in a new test termed PLAplus. PLAplus combines gene expression analyses for LINC00518 and PRAME with TERT promoter mutation analyses thereby elevating the test's overall sensitivity from 91% to 97%. The individual sensitivity numbers of these genomic targets on cases with consensus diagnoses of melanoma were 84% (LINC00518), 83% (PRAME), and 73% (TERT). PLAplus conservatively focuses on maximizing sensitivity while maintaining a high specifity of 62%. Adding TERT promoter mutation analyses to LINC00518 and PRAME further increases the test's negative predictive value from 99.3% to 99.6%.

Studies in real-world use cohorts (n=1,415) demonstrated the presence of TERT promoter mutations in up to 24% of PLA positive and 12% of PLA negative tests. TERT 146G>A mutations were the most frequently observed mutational change (48%). TERT 124G>A (30%) and TERT138G>A (12%) as well as TERT 139G>A mutations (10%) were also detected. PLAplus enhances the early detection of melanoma by combining DNA and RNA analyses of non-invasively collected samples of pigmented skin lesions clinically suspicious of melanoma.

OBJECTIVES
To summarize available data and assess the real-world use of combining LINC00518 and PRAME gene expression analyses with TERT promoter mutation analyses.

METHODS
All clinical studies were IRB approved. Gene expression analyses were performed by RT-PCR as previously described. Mutation analyses were performed by Sanger sequencing.

RESULTS
Efforts to further improve the high performance of the PLA led to a strategy that combines RNA and DNA analyses to create a new test termed PLAplus. PLAplus combines gene expression analyses for LINC00518 and PRAME (two targets overexpressed in melanoma) with TERT promoter mutation analyses (Figure 1) which elevates the test's overall sensitivity from 91% to 97% (Figure 2). Individual sensitivity numbers of these genomic targets on cases with consensus diagnoses of melanoma were 84% (LINC00518), 83% (PRAME), and 73% (TERT). PLAplus conservatively focuses on maximizing sensitivity while maintaining a high specifity of 62%. Adding TERT promoter mutation analyses to LINC00518 and PRAME further increases the test’s negative predictive value from 99.3% to 99.6%.

Studies in real-world use cohorts (n=1,415) demonstrated the presence of TERT promoter mutations in up to 24% of PLA positive and 12% of PLA negative tests. While the biologic significance of different types of TERT mutations is the subject of ongoing studies, TERT 146G>A mutations were the most frequently observed mutational change (48%) in our study cohorts. TERT 124G>A (30%) and TERT138G>A (12%) as well as TERT 139G>A mutations (10%) were also detected. Increasing genomic atypia that may precede morphologic atypia can be found on the spectrum of pigmented skin lesions from benign nevi to melanoma. PLAplus enhances the early detection of melanoma by combining DNA and RNA analyses of non-invasively collected samples of pigmented skin lesions clinically suspicious of melanoma.

CONCLUSIONS

- Adding TERT promoter mutation analyses to LINC00518 and PRAME gene expression analyses further increases test’s sensitivity from 91% to 97%.
- The individual target’s sensitivity numbers are 84%, 83% and 73% for LINC00518, PRAME and TERT, respectively.
- Adding TERT promoter mutation analyses to LINC00518 and PRAME gene expression analyses further increases test’s negative predictive value from 99.3% to 99.6%.
- Both PLA and PLAplus lend themselves to remote sample collection under physician guidance in teledermatology environments.

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