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 PLA*plus*. PLA*plus* 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). Additional 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. PLA*plus* 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 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 PLA*plus*.

PLA*plus* 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). PLA*plus* conservatively focuses on maximizing sensitivity while maintaining a high specificity of 62%. Adding TERT promotor 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.

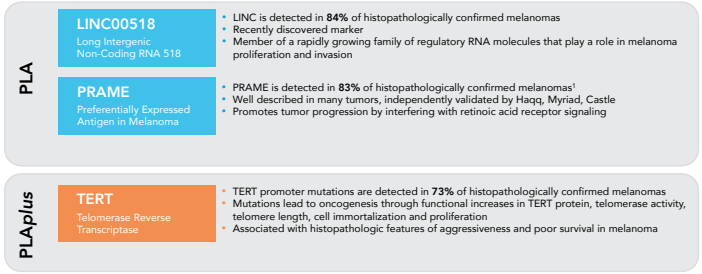

Figure 1: PLA*plus* genomic targets.

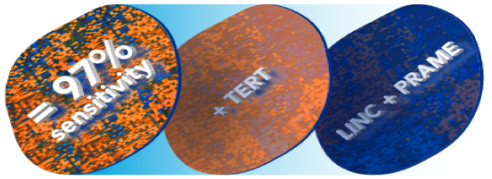

Figure 2: PLA*plus* combines gene expression and mutation analyses to further enhance early melanoma detection.

CONCLUSIONS

- Adding TERT promotor 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 promotor 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 PLA*plus* lend themselves to remote sample collection under physician guidance in teledermatology environments.

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Conflict of interest disclosures: SRJC and LKF are advisors and/or investigators, ZY, CI, MDH and BJ are employees of DermTech

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