Large US Registry Study Confirms 2-GEP Negative Predictive Value Over 99%

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Winter Clinical Dermatology Miami
February 16-19, 2024

Abstract

It remains difficult to assess equivocal melanocytic skin lesions and unambiguously rule out melanoma through the existing standard of care of visual assessment and histopathology due to the inherent limitations of image and pattern recognition. The non-invasive 2-GEP test helps clinicians rule out melanoma through objective precision genomics. The 2-GEP can inform the clinical management of equivocal pigmented lesions with a negative predictive value (NPV) of over 99%.

In a large US registry study, Trust 2, we sought to further evaluate the 2-GEP in a real-world clinical study. The Trust 2 study included 19,653 lesions tested with the 2-GEP. Follow-up evaluations occurred for more than 5,000 tested lesions with median and mean follow-up durations of 348 and 337 days, respectively. Follow-up evaluations included pathology diagnosis for lesions that were biopsied and visual examinations for lesions that were monitored. Lesions that were monitored were classified as either unchanged or changed in a manner concerning for melanoma.

The Trust 2 study demonstrated an NPV of 99.7% for the 2-GEP test which is comprised of LINC00518 *long intergenic non-coding RNA 00518* and PRAME *preferentially expressed antigen in melanoma*. The NPV of 99.7% was observed (rather than calculated from an assumed prevalence) and was associated with a narrow 95% confidence interval of 99.5% to 99.9%. This NPV is higher than other currently available methods, e.g., dermoscopy. The Trust 2 Study results also included a sensitivity of 95.8%, a specificity of 69.4% and a positive predictive value (PPV) of 13.4%. The Trust 2 Study results further validate the 99% NPV observed in a similar real-world study (Trust 1) published in 2021, which evaluated the tested lesions of more than 1,500 patients.

Introduction and Objective

The 2-GEP assay further studied here is a non-invasive genomic rule-out test that can help clinicians improve diagnostic outcomes when melanoma cannot be excluded by visual examination.[1]

The 2-GEP assay uses RT-qPCR to detect the gene expression of PRAME and LINC00518 RNA, two biomarkers that are common in melanomas but uncommon in their benign simulators, extracted from skin cells collected with non-invasive adhesive patches.[1] This approach improves pigmented lesion management beyond visual inspection with a negative predictive value of 99%, a sensitivity of 91%, and by enriching biopsied lesions for melanoma almost 5-fold. The real-world performance of the test and its impact on clinical practice has been addressed in a previously completed patient registry completed in 2020 and summarized in 3 peer reviewed publications.[2-4]

The objective of the current study was to further assess the 'real-world' performance of the 2-GEP and to understand how 2-GEP test results influence clinician decision making with respect to management of the pigmented lesion as well as to determine the outcomes of 2-GEP tested lesions with correlate histopathology results.

Methods

The Trust 2 multi-center study, initiated in 2021, utilized patient data compiled through a large US registry.

The 2-GEP test is comprised of **LINC00518** *(long intergenic non-coding RNA 00518)* and **PRAME** (preferentially expressed antigen in melanoma).

Most 2-GEP-negative lesions were followed with clinical surveillance and not biopsied. To determine whether a negative 2-GEP result was correct or incorrect, the status of 2-GEP-negative lesions upon follow-up examinations (unchanged / stable versus changing in a manner concerning for melanoma) was recorded. In some cases, follow-up evaluations included pathology diagnosis for lesions that were biopsied.

The 95% confidence intervals for NPV and PPV were calculated using the Clopper-Pearson Exact Binomial Test, using the R function "binom.test". The 95% confidence intervals for the difference in NPV and PPV between the groups were calculated using the Farrington-Manning method, using the function "farrington.manning" in R (DescrTab2).

Results

The Trust 2 Study included 19,653 lesions in which the 2-GEP was performed in real-world clinical settings.

Follow-up evaluations of 2-GEP performance were assessed from 5,096 lesions with biopsy results or confirmed clinical follow up with median and mean follow-up durations of 348 days and 337 days, respectively.

The Trust 2 Study demonstrated an NPV of 99.7% which was observed (rather than calculated from an assumed prevalence) and was associated with a narrow 95% confidence interval of 99.5% to 99.9%. The results also included a sensitivity of 95.8%, a specificity of 69.4% and a positive predictive value (PPV) of 13.4% (Table 1).

	2-GEP Test (LINC00518 and PRAME) N=5096
Sensitivity	95.8%
Specificity	69.4%
Positive Predictive Value (PPV)	13.4%
Negative Predictive Value (NPV)	**99.7%**

Table 1. Trust 2 Study 2-GEP test performance metrics.

The NPV of 99.7% is higher than other currently available methods (e.g., dermoscopy).[5]

Conclusion

The Trust 2 Study results further validate the 99% NPV observed in a similar real-world study (Trust 1) published in 2021, which evaluated the tested lesions of more than 1,500 patients.[4]

NPV is considered the most relevant metric for a rule-out test[6,7] since a negative test result is often used to defer intervention (such as biopsy or excision) in favor of surveillance.[2,8,9]

The Trust 2 Study results reaffirm the DMT's real-world clinical utility to rule out melanoma with a negative predictive value (NPV) that is higher than other currently available methods.[5]

As a non-invasive test that has demonstrated an NPV of 99% or higher in multiple, large studies, the DMT provides actionable genomic information for a suspicious pigmented lesion that a clinician may be hesitant to biopsy for a variety of reasons.

References

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