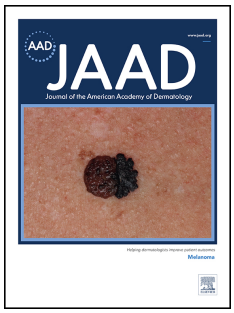
Journal Pre-proof



Clinical Performance of a Noninvasive Melanoma Rule-Out Test Across Fitzpatrick Skin Types

Maral K. Skelsey, MD, Brent Loftis, DO, Mark D. Kaufmann, MD, Daniel M. Siegel, MD, MS, Neal Bhatia, MD, Michael Wangia, MD, Michael Walker, PhD, Andrew Rigby, John W. Whitaker, PhD, Steven Stone, PhD, Mary Moccia, MS, FNP-C, Kaleigh A. O'Brien, BS, Burkhard Jansen, MD, Loren E. Clarke, MD

PII: S0190-9622(24)03157-8

DOI: https://doi.org/10.1016/j.jaad.2024.11.007

Reference: YMJD 19202

To appear in: *Journal of the American Academy of Dermatology*

Received Date: 4 May 2024

Revised Date: 22 October 2024

Accepted Date: 1 November 2024

Please cite this article as: Skelsey MK, Loftis B, Kaufmann MD, Siegel DM, Bhatia N, Wangia M, Walker M, Rigby A, Whitaker JW, Stone S, Moccia M, O'Brien KA, Jansen B, Clarke LE, Clinical Performance of a Noninvasive Melanoma Rule-Out Test Across Fitzpatrick Skin Types, *Journal of the American Academy of Dermatology* (2024), doi: https://doi.org/10.1016/j.jaad.2024.11.007.

Article Type: Research Letter (Resubmission as Research Letter Instead of Original Article JAAD-D-24-00896

Title: Clinical Performance of a Noninvasive Melanoma Rule-Out Test Across Fitzpatrick Skin Types

Maral K Skelsey, MD[1,2], Brent Loftis, DO[3], Mark D Kaufmann, MD[4], Daniel M Siegel, MD, MS[5], Neal Bhatia, MD[6], Michael Wangia, MD[7,8], Michael Walker, PhD[9], Andrew Rigby[10], John W Whitaker, PhD[10], Steven Stone, PhD[10], Mary Moccia, MS, FNP-C[10], Kaleigh A O'Brien, BS[10], Burkhard Jansen, MD[10], Loren E Clarke, MD[10]

Department of Dermatology, Georgetown University School of Medicine, Washington, DC[1]; Dermatologic Surgery Center of DC, Chevy Chase, MD[2]; Wine Country Dermatology, Napa, CA[3]; Icahn School of Medicine, Mount Sinai, New York City, NY[4]; SUNY Downstate Medical Center, Brooklyn, NY[5]; Therapeutics Clinical Research, San Diego, CA[6]; University of Florida College of Medicine, Gainesville, FL[7]; Howard University College of Medicine, Washington, DC[8]; Walker Bioscience, Carlsbad, CA[9]; DermTech, San Diego, CA[10]

Corresponding Author:

Maral K Skelsey, MD

5530 Wisconsin Avenue #820

Chevy Chase, MD 20815

Email: Dr.Maral.Skelsey@mohs-md.com

Funding Sources: This study was supported by DermTech.

Conflicts of Interest: MKS, BL, MDK, DMS, NB, MW, MW are investigators and / or consultants of DermTech; AR, JW, SS, MM, KAO, BJ and LEC are employees of DermTech.

IRB Approval Status and Patient Informed Consent: On March 3, 2021, the WCG IRB approved a request for a waiver of authorization for use and disclosure of protected health information (PHI) for this study via expedited review. The need for patient consent does therefore not apply. No recognizable patient photographs or other identifiable materials were used.

Reprint Requests: Maral K Skelsey, MD

Manuscript Word Count: 455

References: 5

Figures: 0, **Tables:** 2

Conference Presentation: 2024 AAD Annual Meeting, San Diego, CA (March 8-12, 2024)

Keywords: Fitzpatrick skin type; melanoma; rule-out test; genomic test; noninvasive test; medical dermatology; skin cancer; oncology.

Numerous studies suggest that melanoma in individuals with higher Fitzpatrick skin types (FST) is more likely to present at an advanced stage and result in higher mortality[1]. A non-invasive genomic rule-out test assessing gene expression of *LINC00518* and *PRAME* has been introduced to help augment detection of melanoma at an early stage while reducing the number of biopsies performed for benign pigmented lesions that simulate melanoma[2, 3]. Clinical validation using histopathologic consensus diagnoses as a reference standard demonstrated the test has a ≥99% negative predictive value (NPV), indicating that a lesion that tests negative is unlikely to be a melanoma[4, 5]. Although patients of all skin types were eligible for inclusion in the validation study, the cohorts consisted mostly of samples from individuals with FST I, II, or III. The purpose of the current study was to assess the performance of this noninvasive rule-out melanoma test across all Fitzpatrick skin types, with a particular focus on NPV in FST IV-VI patients.

Test performance metrics for patients with FST I-III (n=4152) and IV-VI (n=130) across 73 US clinical practice sites were compared using biopsy results and follow-up information compiled through the DermTech Melanoma Test Registry Protocol (WCG IRB waiver obtained 3/3/2021). Performance metrics were also calculated for a cohort limited to lesions with at least 6 months follow-up or biopsy results.

Full cohort characteristics and follow-up details are summarized in **Table 1**, and performance of the test in all subjects is summarized in **Table 2.** In in the full cohort (N=4282), sensitivity was 0.9429 (66/70), specificity was 0.9086 (3709/4082), PPV was 0.1503 (66/439), and NPV was 0.9989 (3709/3713) for FST I-III. For FST IV-VI, sensitivity was 1.0 (3/3), specificity was 0.9449 (120/127), PPV was 0.3 (3/10), and NPV was 1.0 (120/120). Three of three melanomas (0.55mm, 0.40mm, and melanoma *in situ* in non–sun-exposed areas on the trunk) in the IV-VI group diagnosed by histopathology were correctly identified as positive with the test. The 95% confidence intervals for the differences in sensitivity, specificity, NPV, and PPV between the two groups included 0, indicating no significant difference in any of the performance metrics.

Additional analyses limited to subjects with either a biopsy result or at least 6 months (≥182 days) of follow-up after testing (N=2266) confirmed the results observed in the full cohort for sensitivity, specificity, PPV and NPV, and no statistically significant differences between groups were observed (**Table 2**).

The results of this study demonstrate that performance of the noninvasive test in FST IV-VI patients does not differ from that in FST I-III patients. These findings support the test's utility of guiding biopsy

decisions for ambiguous pigmented skin lesions of all skin types without a need to limit access for patients with Fitzpatrick skin types IV-VI.

	FST I-III (N=4152)	FST IV-VI (N=130)
Median Age, y (range)	59 (18-99)	58 (18-93)
Female Sex, n (%)	2564 (62%)	69 (53%)
Subjects With Test-Positive Lesions, n (%)	439 (11%)	10 (8%)
Subjects With Test-Negative Lesions, n (%)	3713 (89%)	120 (92%)
Subjects With Follow-Up, n (%)	2525 (61%)	75 (58%)
Subjects With ≥6 Months Follow-Up, n (%)	2197 (53%)	69 (53%)

*Subjects with non-melanomas as determined by either biopsies of gene expression positive or negative lesions or follow-up of gene expression negative lesions that were not biopsied.

Table 1. Characteristics of subjects by Fitzpatrick skin type (FST) groups.

	Lesions with biopsy or any follow-up			Lesions with biopsy or ≥ 6 months follow-up		
	FST I-III (N=4152)	FST IV-VI (N=130)	Significant Difference?	FST I-III (N=2197)	FST IV-VI (N=69)	Significant Difference?
SENSITIVITY	94.3%	100%	No	94.3%	100%	No
SPECIFICITY	90.9%	94%	No	82.5%	89.4%	No
PPV	15%	30%	No	15%	30%	No
NPV	99.9%	100%	No	99.8%	100%	No

Table 2. Test performance in patients with all Fitzpatrick skin types. The full data set (N=4282) included all cases with Fitzpatrick skin type (FST) information (biopsied or not and any length of follow-up). The most stringent data set summarized (N=2266) includes cases that were either biopsied or have ≥6 months (≥182 days) of follow-up. No statistically significant differences were observed between groups with either dataset.

REFERENCES

1. Stubblefield J, Kelly B. Melanoma in non-caucasian populations. *Surg Clin North Am*. Oct 2014;94(5):1115-26, ix. doi:10.1016/j.suc.2014.07.008
2. Skudalski L, Waldman R, Kerr PE, Grant-Kels JM. Melanoma: How and when to consider clinical diagnostic technologies. *J Am Acad Dermatol*. Mar 2022;86(3):503-512. doi:10.1016/j.jaad.2021.06.901
3. Fried L, Tan A, Bajaj S, Liebman TN, Polsky D, Stein JA. Technological advances for the detection of melanoma: Advances in molecular techniques. *J Am Acad Dermatol*. Oct 2020;83(4):996-1004. doi:10.1016/j.jaad.2020.03.122
4. Gerami P, Yao Z, Polsky D, et al. Development and validation of a noninvasive 2-gene molecular assay for cutaneous melanoma. *J Am Acad Dermatol*. Jan 2017;76(1):114-120 e2. doi:10.1016/j.jaad.2016.07.038
5. Skelsey M, Brouha B, Rock J, et al. Non-Invasive Detection of Genomic Atypia Increases Real-World NPV and PPV of the Melanoma Diagnostic Pathway and Reduces Biopsy Burden. *SKIN The Journal of Cutaneous Medicine*. 2021;5(5):512-523.