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NCCN Guidelines Panel: Cutaneous Melanoma

Re: Clinical Utility of the DermTech Pigmented Lesion Assay

My experience as the director, Melanoma Center, Washington Hospital Center, Washington DC from 1996 to 2015 included accruing about 2000 melanoma patients and a greater number of patients with multiple atypical nevi, with an average lesion count of 100. Many of my patients had more than 200 nevi including one with 1300. We found that upon long-term monitoring of this high-risk group of patients with multiple nevi that about 2/3 of melanomas arose de novo from previously uninvolved skin and only about 1/3 arose from pre-existing nevi. We concluded that it did not make good medical sense to remove large numbers of nevi in order to attempt to decrease the risk of melanoma formation. Many of our patients at the Melanoma Center had a history of numerous biopsies of benign or mildly atypical nevi. The patients objected to these biopsies because of 1) the pain of the procedure, 2) the time for wound healing, 3) the appearance of the scar, and 4) the anxiety caused by the time waiting for the biopsy result. Moreover, two patients had histories of 500 biopsies of benign lesions prior to entry into our clinic. Since 1996, we have relied upon dermoscopic evaluation of our patients' nevi to determine which lesions to biopsy. The routine use of dermoscopy has increased our diagnostic ability and has reduced the number of unnecessary biopsies, but there remains room for improvement. Specifically, dermoscopy and other methods available rely largely on the clinician's experience, education and training, and there is a large disparity within the medical community in the ability to utilize such diagnostic tools accurately in the diagnosis of early stage melanoma. After retiring from the Melanoma Center, Washington Hospital Center, I now continue to care for high-risk patients with large numbers of nevi at the Dermatologic Surgery Center of Washington, which I joined in July, 2015. For almost 5 years, we have routinely performed the Pigmented Lesion Assay ("PLA"), as a pre-biopsy tool for the testing of clinically and dermoscopically atypical lesions to improve our diagnostic accuracy. As such, we are able to diagnose smaller melanomas at an earlier stage and avoid unnecessary surgical procedures. Almost all the melanomas we have diagnosed since we began using PLA have been small (less than 6mm) melanomas in situ. Since all members of our clinical staff use PLA frequently, we have found that only about 10% of the lesions we test are reported as PLA-positive. Thus, 90% of our patients are saved from an unnecessary surgical biopsy. It is reasonable to suggest that gene expression changes may occur prior to the development of a histopathologically diagnosable melanoma. Therefore, it is quite possible that the PLA test may be finding pre-melanoma lesions that eventually would have evolved into pathologically diagnosable melanomas. In fact, most of the PLA-positive lesions labeled as false positives on biopsy are reported as severely atypical nevi. I believe that, while PLA is capable of identifying small

melanomas in situ, it can do so while still dramatically reducing biopsy rates. Regarding the issue of false negative diagnosis, part of the problem might be the difficulty in the differential diagnosis between melanoma in situ and severely atypical nevi by pathologists. For example, do pathologists have different thresholds for the number of cells exhibiting pagetoid spread leading to a diagnosis of MIS rather than an atypical nevus'? In addition to variations in evaluating pagetoid spread, pathologists may also vary in the evaluation of other criteria, such as the degree of cytologic atypia. This highlights the value the PLA brings to our practice: if the PLA provides a negative result, we choose not to biopsy at that time but to monitor closely on a regular schedule. Patients are also informed to return to clinic immediately if any lesion changes prior to their next scheduled visit. At each follow-up examination, we always re-examine all lesions that we have previously tested with the PLA and that were reported to be negative. If there is a change in appearance of a previously PLA-negative lesion on follow-up examination, we either repeat PLA testing or biopsy the lesion depending on the nature of the change. We have found that the PLA rule-out testing is sensitive and reliable and is a useful adjunct to dermoscopy. The use of PLA enables earlier diagnoses of melanomas, including those that did not meet all of the usual clinical and dermoscopic criteria of malignancy. This test can be an asset to any clinician involved in the diagnosis of skin cancer, not just experts in dermoscopy, as it creates an objective standard. I have provided care to patients with melanoma for over 50 years and having a test like the PLA that provides objectivity, particularly for the difficult to diagnose cases, is transformative for the evaluation of pigmented skin lesions.

Please allow me to offer the information above and the specific requests below to the NCCN melanoma guidelines panel for recommending inclusion of the PLA as a helpful tool in the updated cutaneous melanoma guidelines.

Specific Change (to v3 2020, p19, ME-11, pre-diagnostic clinical modalities): Recommend deleting the last sentence to replace with: “The clinical utility of pre-diagnostic biopsy-guiding noninvasive genomic patch testing is established, and the use of this technology is warranted to support biopsy decisions.”
FDA: The PLA is a CLIA LDT test, the sample collector is an FDA compliant Class I device.
Rationale: The availability of an abundance of peer reviewed evidence on the clinical validity and clinical utility of the noninvasive PLA in guiding biopsy decisions and reducing avoidable pigmented lesion biopsies by about 90% while missing fewer melanomas (NPV of over 99%). I am providing key validation (Gerami, JAAD; Ferris JID) and key utility (Ferris, DOJ; Brouha, JDD) peer reviewed publications to facilitate your review.

If you have any questions regarding my use if the PLA, please do not hesitate to contact me.

Sincerely,

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