Non-Invasive Detection of Genomic Atypia Increases Real-World NPV and PPV of the Melanoma Diagnostic Pathway and Reduces Biopsy Burden

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ABSTRACT

Background: Management of pigmented lesions currently relies on visual assessment with surgical biopsy and histopathologic examination for those lesions suspicious for melanoma. A non-invasive genomic assay that detects two melanoma-associated biomarkers (PLA, 2-GEP) has recently been validated as an adjunct to visual assessment for distinguishing high-risk pigmented lesions appropriate for biopsy from those that can be safely monitored via clinical surveillance.

Methods: Real-world NPV was determined by following a cohort of 1,233 PLA-negative pigmented lesions for evidence of malignancy for up to 36 months and by re-testing a separate prospective cohort of 302 PLA-negative lesions up to 2 years after initial testing. Real-world PPV was determined by identifying melanoma diagnoses among PLA-positive lesions within a US-based registry of 3,418 PLA-tested cases.

Results: Ten early-stage melanomas (4 in situ and 6 pT1a) were identified among 1,233 PLA-negative lesions (0.8%), corresponding to a real-world NPV of 99.2% (CI 95% = 98.5 - 99.6). Of 302 initially PLA-negative lesions subjected to repeat testing an average of 15 months later, 34 were PLA-positive. Biopsy revealed 3 melanomas (all in situ), further confirming an NPV of > 99%. Among 316 PLA-positive lesions, 59 were diagnosed as melanoma by histopathology, corresponding to a PPV of 18.7%. Of all PLA-positive lesions, 30.5% had histopathologic diagnoses corresponding to high-risk MPATH-Dx categories (Classes III-V).

Conclusions: The PLA has an NPV of >99% within the real-world intended use population. The PLA has a PPV of 18.7% for melanoma and also detects high-risk lesions such as dysplastic nevi with severe / high-grade atypia that are generally targeted for complete excision.

INTRODUCTION

Cutaneous melanoma is responsible for more than 7,000 deaths in the United States each year¹. Accurate detection of melanoma in its earliest stages is critical to optimizing patient outcomes, since 5-year survival of 98-99% for early-stage melanoma can be achieved with wide local excision.¹ However, melanoma detection relies primarily on
subjective visual assessment of pigmented lesions clinically suspicious of melanoma. Clinicians use e.g. ABCDE criteria or ‘ugly duckling’ signs to identify those lesions that need additional evaluation by biopsy where malignancy is confirmed by histopathologic evaluation within only a small proportion of specimens. In a study by Anderson involving 4,039 pigmented lesions selected for biopsy based on visual criteria, just 149 (3.7% or 1 in 27) were confirmed as melanoma. \(^2\) Dermoscopy and other in vivo diagnostic aids have been shown to reduce biopsies of benign neoplasms when applied by skilled users, but many pigmented lesions are evaluated by providers who lack dermoscopy expertise.

Few, if any studies exist in which melanocytic lesions considered benign by visual assessment undergo biopsy to determine the proportion of true negatives, and thus the real-world negative predictive value (NPV) of visual assessment is difficult to establish. Most investigations estimate NPV by comparing histopathologic diagnoses of biopsied lesions to clinical images. A study by Nachbar and colleagues evaluated 172 lesions and calculated an NPV of 73% for unaided clinical assessment and 85% for clinical assessment with dermoscopy. \(^3\) Regardless of the precision of such estimates, there is a need for technologies and approaches that effectively differentiate pigmented lesions that need further evaluation by biopsy from those that can be safely managed with clinical surveillance.

Differentiation of melanomas from the benign nevi that may simulate them may also present challenges at the histopathologic level. Early-stage lesions in particular generate considerable uncertainty and diagnostic disagreement among pathologists. \(^4,5\) In an effort to improve pathologist concordance, the recently-introduced MPATH-Dx classification scheme categorizes melanocytic lesions by recommended treatment rather than specific diagnosis. Based on histopathologic features and perceived risk of progression, pathologists assign lesions to one of five classes, each with a corresponding treatment recommendation. \(^6\) Melanomas and high-risk lesions constitute classes III-V, with Class III encompassing in situ melanomas as well as other high-risk lesions such as dysplastic nevi with severe or high-grade atypia. In a study by Lott et al. involving 18,715 biopsies of melanocytic lesions, 4.5% were categorized as MPATH-Dx Class III lesions while 8.6% were classified as Class III-V lesions. \(^7\) Figure 1 summarizes the typical current care pathway and Figure 2 outlines relevant aspects of the MPATH-Dx classification. \(^6\)

A non-invasive genomic assay that detects two melanoma-associated biomarkers (the Pigmented Lesion Assay, PLA, or 2-GEP test) has recently been validated as an adjunct to visual assessment in differentiating high-risk pigmented lesions appropriate for biopsy from those that are benign and suitable for clinical surveillance. In the current study, we derived the test’s ‘real-world’ NPV within the intended use population using follow-up data from a large cohort of patients with PLA-negative lesions. We also re-tested a separate cohort of initially PLA-negative lesions to evaluate result consistency and the potential value of repeat testing for clinically evolving lesions. In addition, we determined the test’s real-world PPV and its ability to detect high-risk / MPATH-Dx Class III lesions using a previously-described cohort of PLA-positive lesions.
Figure 1. Current assessment and management of pigmented lesions suspected of melanoma. The traditional pathway uses visually assessed atypia to guide biopsy decisions and 83.1% of biopsies are MPATH-Dx Class I lesions with no or mild cellular atypia based on histopathology and 8.3% being MPATH-Dx Class II lesions with moderate atypia. Being able to accurately identify especially MPATH-Dx Class III is key to patient outcome as these lesions, designated as and high-risk, may receive a benign diagnosis while actually being true melanomas. Currently, the proportion of surgically biopsied lesions that fall in these categories is low (4.5%). MPATH-Dx Class IV and V lesions should also be referred to medical and/or surgical oncology if appropriate.

METHODS

Data were obtained from cohorts of PLA-negative and PLA-positive lesions. PLA-negative lesions were evaluated to determine the proportion of true negatives among negative tests, or NPV, for melanoma diagnosis. PLA-positive lesions were evaluated to determine the proportion of true positives among positive tests, or PPV, as well as the proportion of lesions considered high-risk / MPATH-Dx Class III (melanoma in situ, lesions with severe / high-grade atypia).
PLA-Negative Lesion Study Cohorts (TRUST Study)

A total of 2,104 pigmented lesions that tested PLA-negative between August 2017 and August 2020 were identified for study enrollment at five geographically dispersed clinical sites. Of these, 1,781 were evaluated for long-term follow-up up to 36 months after initial testing by medical chart review (Figure 3). PLA-negative lesions were evaluated for any melanoma diagnosis, development of later-stage disease, and melanoma death. Additional 323 PLA-negative lesions were enrolled in a prospective arm (NCT04563949) and subjected to repeat clinical evaluation and PLA testing. PLA-positive lesions in the repeat testing cohort were biopsied and evaluated for melanoma diagnosis. This study was approved by Western and Copernicus Group Institutional Review Boards and conducted according to the Declaration of Helsinki principles.

PLA-Positive Lesion Study Cohort

Between July 2018 and June 2019, a total of 3,418 pigmented lesions clinically suspicious for melanoma were entered in a prospective registry, evaluated and tested with the PLA. The registry was conducted by 90 licensed healthcare providers within 53 practices throughout the US. Of the lesions registered, 324 tested positive. Pathology reports were collected and reviewed for any melanoma diagnosis. Diagnoses were then categorized according to the MPATH-Dx classification scheme (Figure 2). The PPV was determined by calculating the number

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**Figure 2.** MPATH-Dx classification, histopathological diagnosis, and treatment recommendations. The listed histopathologic diagnoses are common examples for the MPATH-Dx classes.4,6,7

<table>
<thead>
<tr>
<th>MPATH-Dx</th>
<th>Histopathology Diagnosis</th>
<th>Treatment Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>Common and mildly dysplastic nevi</td>
<td>Typically requiring no further treatment</td>
</tr>
<tr>
<td>Class II</td>
<td>Moderately dysplastic and spindle cell/epithelioid nevi</td>
<td>May merit excisions &lt; 5mm margins</td>
</tr>
<tr>
<td>Class III</td>
<td>Severely dysplastic nevi, melanoma in situ cases</td>
<td>Excision with 5mm to 1cm margins</td>
</tr>
<tr>
<td>Class IV</td>
<td>Stage pT1a invasive melanomas</td>
<td>Excisions ≥ 1cm margins</td>
</tr>
<tr>
<td>Class V</td>
<td>Stage pT1b (or greater) invasive melanomas posing more significant risk of metastasis</td>
<td>Excisions ≥ 1cm margins and potential adjunctive therapy</td>
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</tbody>
</table>
of histopathologically confirmed melanomas among PLA-positive lesions.

Sample Collection and Analysis

All lesions were tested using the Pigmented Lesion Assay (PLA) (DermTech; La Jolla, CA). Non-invasive sampling occurred per the standard instructions for use with DermTech’s adhesive skin collection kit. Samples were submitted to DermTech’s CLIA certified and CAP accredited high complexity molecular pathology laboratory for gene expression testing (La Jolla, CA). Following the extraction of RNA, samples were analyzed using quantitative PCR to assess the expression of two genes, LINC00518 and PRAME. The PLA is considered positive when one or both genes are detected; positive lesions subsequently undergo biopsy or excision for histopathologic review. PLA-negative tests have no target gene expression detected and are typically monitored per standard clinical follow-up. Per standard procedures, samples with insufficient RNA quantity or quality and those with contamination (e.g. excessive blood or non-vellus hair) that cannot undergo gene expression analysis are reported as such and these lesions are recommended to undergo biopsy.

RESULTS

Here, we determine the real-world NPV and PPV of the 2-GEP PLA by studying appropriate TRUST study cohorts (n=2,572 lesions total; focus on long-term follow-up with chart review and long-term follow-up

Figure 3. Real-world, long-term follow-up study to define the NPV for the PLA (TRUST Study). PLA-negative lesions were separated into 2 cohorts for long-term follow-up. 1,781 PLA-negative lesions were identified by chart review and followed for up to 36 months following their initial PLA test; 1,233 of these patients additionally received confirmed follow-up visits. Additional 323 PLA-negative lesions were prospectively enrolled into a clinical study (NCT04563949) for repeat PLA testing up to 24 months following the initial PLA-negative test result. NPV’s for both cohorts were >99%. Lesions not included in the analysis were either protocol deviations (e.g. sample not collected according to the instructions for use) or lacked sufficient RNA for analysis.
with re-testing of PLA-negative lesions) as well as from a registry (n=3,418 lesions) to determine the test’s real-world performance. The median age of the re-tested TRUST study cohort was 58 years (41.7% male, 58.3% female patients). The median age of patients in the registry was 48 years (39.2% male, 60.8% female).

**PLA-Negative Lesion Study Cohorts**

A total of 2,575 clinically suspicious pigmented lesions tested with the PLA were identified by chart review and used to establish PLA-negative lesion study cohorts for further evaluation (n=2104, Figure 3). PLA-positive lesions (n=276) and samples of 195 lesions (97 which could not undergo gene expression analysis due to insufficient genomic material or contamination due to excessive hair or blood, and 98 in which medical charts were not available for review) were excluded from NPV analyses.

The 1,781 PLA-negative lesions identified and monitored by medical charts were reviewed for a time period of up to 36 months following the initial PLA-negative test. No melanoma deaths or late-stage melanoma diagnoses were reported in this PLA-negative lesion cohort. A subset of 1,233 lesions (69%) had confirmed follow-up evaluations within the 36 months of the initial PLA-negative test. Ten lesions (0.8%) in this subset cohort were subsequently biopsied (an average of 15.1 months after initial negative PLA) and received an early-stage melanoma diagnosis (4 in situ and 6 pT1a invasive melanomas were identified) (Figure 3) establishing an NPV for melanoma diagnosis of 99.2% (CI 95%= 98.4 - 99.6).

A total of 323 PLA-negative lesions were prospectively enrolled into a clinical study (NCT04563949) for repeat PLA testing up to 24 months following the initial PLA-negative test result. Twenty-one lesions were removed from subsequent testing and analysis due to protocol deviations, insufficient quantity of RNA for analysis, or contamination; however, no melanoma diagnoses were reported among these 21 lesions. Repeat testing was conducted on 302 (93.5%) lesions and 268 (88.7%) remained negative (Figure 3). Thirty-four out of 302 lesions (11.2%) were PLA positive on repeat testing. All 34 PLA-positive lesions underwent surgical biopsy and histopathology. Three of 302 (1%) of PLA-positive re-tested lesions received an in situ melanoma diagnosis. All three lesions exhibited evolution or change by clinical or photographic analysis. The time from initial PLA testing to repeat testing for each lesion was 13, 14, and 19 months (average 15.3 months). If the in situ melanomas identified were present at time of initial diagnosis, the NPV of the original test would be 99.0% (CI 95% = 97.1 - 99.8). All 34 PLA-positive lesions in the repeat test cohort were also categorized according to the MPATH-Dx classification scheme with 20 (59%) in Class I, 5 (15%) in Class II, and 4 (11.8%) in Class III. The proportion of repeat tested high risk Class III lesions (11.8%) is significantly lower than the proportion of lesions in this class in primary tested lesions (26.1%).

**PLA-Positive Lesion Registry Cohort**

Of the 324 lesions (9.5%) that were PLA positive, 316 (97.5%) underwent surgical biopsy and 313 had histopathology reports available for review. Fifty-nine lesions received a melanoma diagnosis (47 in situ, 11 pT1a, and 1 pT2a) yielding a positive predictive value for melanoma diagnosis of 18.7%. Using the MPATH-Dx risk classification scheme of melanocytic lesions to facilitate comparisons among reports from pathologists who use different nomenclature and classifications of lesion atypia, subsets of 272 melanocytic and 41 non-melanocytic
lesions (primarily scars of previously biopsied pigmented lesions and keratoses potentially constituting collision lesions with melanocytic lesions) were identified. The melanocytic lesions were further categorized per MPATH-Dx classification scheme with 43.8% (n=119), 25.7% (n=70), 26.1% (n=71), 4.0% (n=11) and 0.4% (n=1) classified as Classes I–V, respectively. Similar to previously published work on the genomic progression of melanoma, the PLA identified genomic atypia across the full spectrum of categories, including some MPATH-Dx Class I and Class II lesions. Notably, 30.5% (n=83) of PLA-positive lesions had histopathological diagnoses corresponding to the malignant / high-risk Class III-V categories (Figure 4). The proportion of lesions in Class II-V groupings of atypical pathologic features was 56.3%.

Biopsy Burden

Of the 5,993 lesions tested with the PLA in the lesional cohorts assessed (n=2,575 TRUST Study and n=3,418 registry cases), the vast majority of tests were negative and not subjected to surgical biopsy. In this group 3.7% to 6.5% of PLA tests could not be analyzed due to insufficient quantity of RNA, contamination (e.g. hair or blood), and sample collection protocol deviations. Thus, in these cohorts the PLA reduced surgical biopsies by 83.5% to 86.3%.

DISCUSSION

The PLA (2-GEP test) is intended as ‘rule-out’ test for melanoma and should therefore have a high NPV within the intended use population. NPV is often derived from a test’s sensitivity and specificity in conjunction with estimates of disease prevalence, but this approach may not accurately reflect the NPV observed in actual clinical use. In this study, we sought to calculate ‘real-world’ NPV by examining a large cohort of PLA-negative lesions from five geographically dispersed clinical sites for any evidence of melanoma detected during a protracted follow-up period. Within a cohort of 1,781 patients, including 1,233 patients with confirmed follow-up visits, 10 early stage melanomas (6 in situ, 4 pT1a) were identified 12-24 months after the initial testing. Importantly, no late-stage melanoma diagnoses or melanoma deaths were reported. Calculations restricted to the 1,233 patients with confirmed follow-up visits yielded an NPV of 99.2% (CI 95% = 98.4 - 99.6). Analysis of the entire cohort of 1,781 PLA-negative lesions produced an NPV of 99.4% (CI95% = 99.0 – 99.7). These results suggest the PLA’s NPV is superior to that of visual assessment alone (NPV = 75-83%).

To further assess NPV, a separate cohort of 302 PLA-negative lesions underwent clinical evaluation and repeat testing an average of approximately 15 months after initial testing. Of these, 34 lesions were PLA-positive upon repeat testing, three of which were interpreted histopathologically as melanomas in situ. For the calculation of NPV it was assumed that these were melanomas at the time of initial testing and represent initial false-negative results. However, it is also possible they were benign lesions in which in situ melanomas subsequently evolved during the interval between initial and repeat testing (median 15.3 months). In support of this, all three lesions reportedly demonstrated evolution between initial and repeat testing. Further study is warranted but this observation suggests that repeat testing may have value in the rare instance that a lesion clinically evolves and starts to resemble a more concerning higher-risk lesion after an initial negative test result. The ability to re-assess an evolving intact lesion in these rare circumstances may be seen as an additional advantage of non-invasive
Genomic testing over scenarios where a clinician needs to re-assess changing remnants of a previously biopsied lesion.

<table>
<thead>
<tr>
<th>PLA Test</th>
<th>Biopsies</th>
<th>MPATH-Dx Diagnosis of Melanocytic Lesions</th>
<th>PLA Positive Cases</th>
</tr>
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<tbody>
<tr>
<td>PLA Positive Lesions 9.5% (324/3,418)</td>
<td>Biopsies of PLA Positive Lesions 97.5% (316/324)</td>
<td>MPATH-Dx Class I</td>
<td>43.8% 119/272</td>
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<td></td>
<td></td>
<td>MPATH-Dx Class II</td>
<td>25.7% 70/272</td>
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<td></td>
<td></td>
<td>MPATH-Dx Class III</td>
<td>26.1% 71/272</td>
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<td></td>
<td></td>
<td>MPATH-Dx Class IV</td>
<td>4.0% 11/272</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MPATH-Dx Class V</td>
<td>0.4% 1/272</td>
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**Figure 4.** Real-world registry to define the PPV for the PLA. A total of 3,418 lesions were assessed by PLA, and positive melanocytic lesions with corresponding histopathology were further classified by MPATH-Dx.8,9

Many tests require a compromise with respect to NPV and PPV in which optimizing one parameter comes at the expense of the other. Maximum NPV is priority for a test designed to safely rule out melanoma, but this study and prior analyses confirm that the PLA’s high NPV is balanced by a suitable PPV. In addition, the current data demonstrate that the PLA effectively detects the subset of ostensibly benign but high-risk melanocytic lesions such as dysplastic nevi with high-grade atypia (MPATH-Dx Class III) that are typically excised to mitigate potential misdiagnosis and / or risk of progression. While it is obviously most important to identify and excise definitive melanomas, many authorities advocate complete excision for melanocytic lesions with high-grade atypia due to their higher potential for misdiagnosis (ambiguous histopathologic features misinterpreted as benign or focal malignancy not visualized within the available sections) and / or their increased risk for progression (propensity to evolve into melanoma over time).4,6,16,17 Wachsman et al., for example, described a lesion with non-invasively detected genomic atypia that initially received a benign diagnosis but was later found to harbor melanoma upon serial sectioning.17 Early-stage melanoma in particular carries an inherent risk of evading histopathologic detection since it may evolve focally within a pre-existing nevus, yet due to the practical limitations of sectioning and histopathologic examination only up to 2% of biopsied tissue may be examined microscopically.14 Furthermore, early-stage melanocytic neoplasms are more likely than fully-evolved lesions to exhibit ambiguous or conflicting histopathologic features and generate
diagnostic uncertainty or discordance, increasing potential for false-negative or false-positive diagnoses.\textsuperscript{4}

In this study, some lesions categorized as MPATH-Dx Class I and II as well as some pigmented non-melanocytic lesions produced positive test results. The significance of LINC00518 and PRAME overexpression by non-melanocytic lesions and by melanocytic lesions that seemingly lack high-risk or overtly malignant histopathologic features is not yet fully characterized. However, genomic aberrations likely evolve prior to the development of morphologically identifiable malignancy.\textsuperscript{18} In addition, the PLA samples the entire breadth of a lesion and therefore may detect small foci of malignancy not visualized within the limited portion of a biopsy specimen that can be examined by histopathology.\textsuperscript{14,16} Studies in which PLA-positive but histopathologically-benign specimens undergo serial sectioning to evaluate the frequency of occult malignancy are ongoing.

The PLA is intended for analysis of clinically ambiguous lesions, those considered suspicious but not definitive for melanoma, rather than clinically obvious melanomas or banal appearing nevi. The proportion of positive tests that reveal melanoma on subsequent biopsy should therefore be heavily skewed toward \textit{in situ} and pT1a melanomas if the test is being used as intended, and this was indeed demonstrated in the current study. Additionally, clinical utility studies have shown high concordance between the PLA result and subsequent treatment, with 97.5\% of PLA-positive lesions proceeding to biopsy and histopathologic evaluation and 99.99\% of PLA-negative lesions followed with clinical surveillance rather than biopsy.\textsuperscript{8,9}

Importantly, detection of genomic atypia enriches the pool of biopsied lesions for those most likely to be diagnosed as high-risk and/or fully malignant (MPATH-Dx Class III-V). For this group, enrichment was 3.5-fold greater than with visual atypia alone (8.6\% vs. 30.5\%).\textsuperscript{7} \textbf{(Figure 5)} Enrichment is achieved through substantial reduction in the overall biopsy burden (by \textasciitilde85\%), thereby offering a solution to the problem of over-biopsy and over-diagnosis of pigmented lesions recently highlighted by Welch and colleagues.\textsuperscript{5}

An important limitation of this study is that follow-up visits were not documented for 548 of the 1,781 PLA-negative patients, and thus it cannot be confirmed that none of these 548 patients developed a melanoma that remained undetected or was identified and treated elsewhere. For this reason, the most definitive NPV calculation is that derived from the subset of 1,233 patients with documented follow-up visits within the indicated period. In addition, retrospective medical chart review could erroneously evaluate a lesion not tested with the PLA. While real-world data from lesion cohort studies are the most relevant to actual clinical practice, the strategies chosen do not allow for comparisons based on consensus histopathology reads that may reduce variability in histopathologically-determined diagnoses. Lastly, PLA-negative lesions that were negative on repeat testing and by clinical evaluation were considered true negatives for purposes of these analyses, and the possibility that some lesions were in fact melanomas that were negative on both the initial and repeat tests and also by clinical follow-up cannot be entirely excluded.

\textbf{CONCLUSION}

The current study further highlights the PLA's
very high NPV of 99% of critical importance to a robust rule-out test within the intended use population. It demonstrates that non-invasive detection of genomic atypia by the PLA can enhance visual assessment of pigmented lesions, enabling clinicians to more effectively triage high-risk lesions to biopsy while safely managing benign lesions via clinical surveillance. This approach improves the overall NPV and PPV of the current diagnostic pathway while optimizing early detection of melanoma.

Figure 5. Implementation of the PLA improves the assessment and management of pigmented lesions based on genomic atypia information. While the PLA offers benefits across the spectrum of lesions clinically suspicious of melanoma, especially MPATH-Dx Class III high-risk lesions are generally viewed as the most diagnostically challenging where misdiagnoses may occur. It is therefore important to identify these lesions for appropriate
management decisions. The PLA enriches for these lesions with fewer overall biopsies.\textsuperscript{6,9} It is of particular interest to note that the proportion of this MPATH-Dx Class III group is much larger with PLA use (4.5% for the current care pathway summarized in Figure 1 vs. 26.1% with PLA use).\textsuperscript{7} By identifying these lesions as candidates for excision, the chance of a missed or delayed diagnosis is minimized and early melanoma detection is enhanced. MPATH-Dx Class IV and V lesions should also be referred to medical and/or surgical oncology if appropriate.

**Conflict of Interest Disclosures:** Drs. MKS, BB, GP are investigators and advisors to DermTech, MKS and GP are shareholders of DermTech. JR, MDH, LEC and BJ are employees and shareholders of DermTech.

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