Impact on clinical practice of a non-invasive gene expression melanoma rule-out test: 12-month follow-up of negative test results and utility data from a large US registry study

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Abstract

The Pigmented Lesion Assay (PLA, sensitivity 91-95%, specificity 69-91%, negative predictive value >99%) is a commercially available, non-invasive gene expression test that helps dermatologists guide pigmented lesion management decisions and rule out melanoma. Earlier studies have demonstrated high clinical utility and no missed melanomas in a 3-6-month follow-up period. We undertook the current investigations to provide 12-month follow-up data on PLA(-) tests, and to further confirm utility. A 12-month chart review follow-up of 734 pigmented lesions that had negative PLA results from 5 US dermatology centers was performed. Thirteen of these lesions (1.8%) were biopsied in the follow-up period and submitted for histopathologic review. None of the lesions biopsied had a histopathologic diagnosis of melanoma. The test's utility was studied further in a registry (N=1575, 40 US dermatology offices, 62 participating providers), which demonstrated that 99.9% of PLA(-) lesions were clinically monitored, thereby avoiding a surgical procedure, and 96.5% of all PLA(+) lesions were appropriately biopsied, most commonly with a tangential shave. This long-term follow-up study confirms the PLA's high negative predictive value and high utility in helping guide the management of pigmented lesions to avoid unnecessary surgical procedures.

Keywords: melanoma, rule-out test, clinical utility, non-invasive, gene expression, pigmented

Introduction

To correctly assess and adjudicate melanocytic skin lesions to rule out melanoma via the current standard of care of visual assessment plus histopathology remains challenging even for pigmented lesion experts because of inherent limitations of image recognition [1-11]. Tools such as dermoscopy, confocal microscopy, or computer-aided image analysis of skin lesions can reduce, but do not overcome some of these inherent limitations. Therapeutic challenges continue even after a decision has been made to biopsy a pigmented lesion suspicious for melanoma because

Abbreviations:
PLA – Pigmented Lesion Assay
PLA(+) – PLA positive
PLA(-) – PLA negative
US – United States
MPath-Dx – Melanocytic Pathology Assessment Tool and Hierarchy for Diagnosis
RNA – Ribonucleic Acid
PRAME – Preferentially Expressed Antigen in Melanoma
LINC00518, LINC – Long Intergenic Non-Coding RNA 518

histologic evaluation relies on pattern recognition and poorly reproducible histologic criteria to distinguish between benign and malignant [4, 6]. This issue and the resulting performance of histopathologic assessment of melanocytic lesions between Melanocytic Pathology Assessment Tool and Hierarchy for Diagnosis (MPath-Dx) Class II and MPath-Dx Class IV (e.g. moderately dysplastic nevi to early invasive pT1a melanomas, respectively) is exemplified in a 2017 US study by Elmore and colleagues [4]. In this study, 187 pathologists reviewed histopathology slides of 240 melanocytic lesions including 118 diagnosed early-stage melanomas. Overall, the sensitivity of diagnosis for early-stage lesions (MPath-Dx Class III and IV) compared to consensus reads established by an expert panel was 65%; this was lower than expected by many, including healthcare providers and patients [4]. Interestingly, intra-observer reproducibility within these MPath-Dx classes showed similarly discouraging discordance [4]. Although a growing number of investigators have demonstrated that immunohistochemistry and molecular analysis techniques, such as fluorescence in situ hybridization, comparative genomic hybridization, and messenger ribonucleic acid (RNA) expression profiling of surgically obtained specimens, can help to somewhat improve our prediction on the behavior of melanocytic neoplasms, these techniques fall short of truly impacting pigmented lesion management because of their performance characteristics and because the tests depend on tissue samples from surgical biopsies [7]. Currently, and based on recent data, up to 90% of all biopsies are performed on benign lesions and are avoidable [8]. A simple, yet accurate, non-invasive commercially available test [12], in our case to guide biopsy decisions and rule out melanoma, is attractive to health care providers and patients alike.

The recently described Pigmented Lesion Assay (PLA), a non-invasive PRAME (Preferentially Expressed Antigen in Melanoma) and LINC (Long Intergenic Non-Coding RNA 518,) based gene expression assay using an adhesive patch sample collection platform for obtaining epidermal RNA, is such a test [13-21]. This test is comprehensively validated (sensitivity 91-95%, specificity 69-91%, negative predictive value [NPV] >99%) and has shown encouraging data on utility as well as cost savings [13-21]. We previously reported on the real-world utility of the PLA and 3-6 month follow-up data on 330 PLA(-) tests demonstrating high utility and confirming the test's high NPV in a 3-6 month follow-up period [14]. The focus of the current work is to expand the follow-up period to 12 months and to confirm the test's high NPV in the real-world setting. Additionally, we also report on a large US registry study of commercially obtained results and management decisions to further define the test's clinical utility.

Methods

We here expand on PLA follow-up and utility findings previously reported to include long-term follow-up and US registry data [13]. Approval was obtained from the Western-Copernicus Group's independent review board.

We enrolled 734 PLA(-) negative pigmented skin lesions clinically suspicious for melanoma from 5 US dermatology practices that use the PLA commercially. Each of the centers had used the PLA test commercially for over 12 months. A clinical monitor was sent to each site to conduct a detailed chart review for each patient once they had reached the 12-month follow-up time point. Charts were

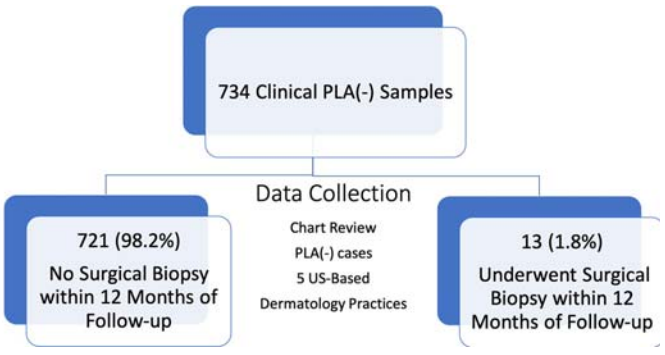

Figure 1. *Twelve-month follow-up of Pigmented Lesion Assay [PLA](-) pigmented skin lesions clinically suspicious for melanoma (N=734). Clinicians followed the guidance of the test also during long-term follow-up and biopsied only 1.8% of PLA(-) lesions. None of the PLA(-) lesions biopsied during the follow-up period carried the histopathologic diagnosis of melanoma.*

reviewed for lesion characteristics and current lesion disposition. Any action taken with respect to a previously tested lesion was recorded. If a given lesion was subsequently surgically biopsied, histopathology was reviewed. When available, the clinical reason for subsequent biopsy was ascertained. We also update findings on 61 PLA(+) cases, a subset of which we previously reported [13].

Starting in June of 2018, we initiated a registry study on the management of pigmented lesions after testing with the commercially available PLA. Forty US dermatology practices (and 62 providers within these practices including board certified dermatologists, primary care physicians, physician assistants, and nurse practitioners) participated in the registry and we report here on 1575 pigmented lesions clinically suspicious for melanoma that were evaluated by PLA between June and December of 2018. The PLA results and management decisions (clinical monitoring of a given lesion or biopsy) were uploaded to a web portal. The web portal supported the collection of lesion PLA results, biopsy decision, biopsy type, and requested 3, 6, or 12 month follow up if the lesion was marked. Lesion location and patients' sex was also recorded

All lesion samples were obtained using a non-invasive adhesive skin collection kit (DermTech, La Jolla, CA) according to package insert instructions. In brief, a selected pigmented lesion suspicious for melanoma is cleansed with an ethanol swab and dried, and four adhesive patches from the sample collection kit are applied sequentially to collect one sample. Gentle pressure from about 5 circular thumb motions ensures contact between the adhesive and skin; no wait time is required. To enable separation of lesional from non-lesional surrounding skin tissue, the lesion is demarcated with a marker pen on each one of the applied adhesive patches. Patches are placed in a pre-addressed courier envelope and shipped to a central processing laboratory without need for refrigeration or special handling. The sample collection process takes about 1-2 minutes. A molecular pathology report is generally available within 48-72 hours.

Results

Of 734 PLA(-) pigmented skin lesions clinically suspicious for melanoma enrolled in the study, 721 (98.2%) were monitored without biopsy whereas 13 (1.8%) were subjected to surgical biopsies (13 shave/scoop procedures) within the 12-month follow-up period (**Figure 1**). Six of 13 (46.2%) surgical biopsies were performed at the patients' request, whereas 7 biopsies were performed to provide clinicians with more information on changing lesions. Histopathology results for the biopsied PLA(-) lesions indicated that 11 lesions were nevi with various degrees of cellular atypia, one was a basal cell carcinoma, and one was a squamous cell carcinoma in situ. All lesions removed at patients' requests were nevi histopathologically. In line with previously observed PLA use characteristics, 36.9% of studied patients were male and 63.1% were female (**Table 1**). Most lesions evaluated by PLA in this study were located on the trunk (47.5%), followed by extremities (35.1%), and face/head/neck areas (17.3%), (**Table 1**). Although not the focus of this study, it is nevertheless of interest to note that all 61 PLA(+) cases also recorded were surgically biopsied. Sixty-six percent of patients returned within the 12-month follow-up period at varied intervals.

Table 1. *Summary of patient characteristics and lesion locations of evaluated Pigmented Lesion Assay (PLA) cases from (a), a 12-month follow-up chart review study of Pigmented Lesion Assay [PLA](-) lesions (N=734) and (b), a PLA registry (N=1575).*

	Male/Female	Median Age (Years)	Lesion Location
12-Month Follow-Up PLA(-) Lesions (N=734)	271 / 463 36.9% / 63.1%	52	Face/Head: 129 (17.5%) Trunk: 351 (47.5%) Extremities: 259 (35.0%)
Registry (N=1575)	558 / 1017 35.4% / 64.6%	48	Face/Head: 290 (18.4%) Trunk: 822 (52.2%) Extremities: 463 (29.4%)

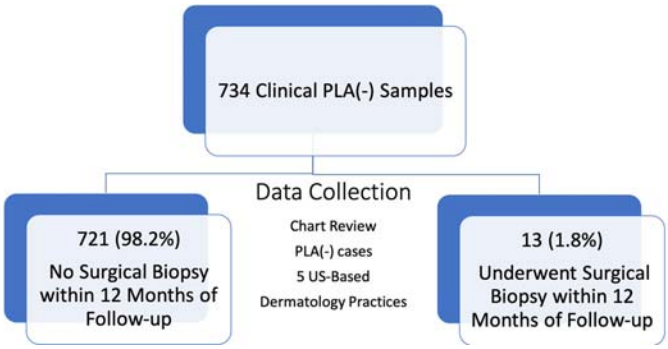

Figure 2. *Data summary from the Pigmented Lesion Assay registry study (N=1575, data sets collected between July and December of 2018).*

Data on 1575 patients and their lesions were uploaded to the registry (**Figure 2**; patient characteristics summarized in **Table 1**). Of these, 1433 PLA(-) cases were reported. Notably, 1431 of 1433 (99.9%) of patients with PLA(-) test results were appropriately managed with a lesion monitoring approach avoiding surgical procedures. Of these, 132 (9.2%) were scheduled for follow-up in three months, whereas 383 (26.7%) and 732 (51.0%) were scheduled for follow-up in 6 and 12 months, respectively. In addition, 184 of patients (12.8%) were scheduled for follow-up at other time frames. Of the two PLA(-) cases subjected to surgical procedures, one was a melanocytic nevus subjected to a shave/scoop biopsy and the second was a squamous cell carcinoma in situ removed by MOHS surgery.

Data on 142 PLA(+) tests results (9.0% of all lesions assessed by PLA in this cohort) were uploaded to the registry, and 96.5% were surgically biopsied. Of these biopsies, 51.1% were shave/scoop, 13.1% were punch, and 35.8% were excisional procedures. Thirty-one (21.8%) of all assessed PLA(+) had detectable levels of LINC and PRAME transcripts, whereas 85 (59.9%) showed detectable levels of the LINC transcript only and 26 (18.3%) had detectable levels of the PRAME transcript only. **Table 2** summarizes gene expression and biopsy results. Regarding lesions not subjected to biopsy (N=5, 3.5% of PLA positive cases), all were LINC-only cases, which have a lower probability of being melanomas histopathologically [14].

Discussion

The PLA is a rule-out test that helps clinicians assess and manage pigmented skin lesions non-invasively. Of critical importance for a rule-out test is the test's negative predictive value or NPV, which assesses the probability that a negative test result was incorrect (leading to a false negative diagnosis). Based on previous validation work, the PLA has a predicted NPV of >99% based on a melanoma prevalence in biopsied pigmented lesions ranging from 3-7% [13-15, 21]. The current study was undertaken to understand the long-term follow-up of PLA(-) pigmented lesions and help confirm the rule-out test's NPV. Findings from 734 PLA(-) lesions reviewed at 12 months demonstrated that only 1.8% of PLA(-) lesions were biopsied in this follow-up period. None of the lesions biopsied had a melanoma diagnosis by histopathology consistent with PLA's high NPV. Pigmented lesions that are suspicious for melanoma and that are being clinically followed often manifest visible changes, such as size increase, border changes, or color variation within 3-6 months providing a rationale for 3-6-month follow-up

Table 2. *Non-invasive gene expression test characteristics and selected biopsy types after Pigmented Lesion Assay [PLA](+) test results of PLA registry cases (N=1575). The PLA is positive if either Long Intergenic Non-Coding RNA (LINC) or Preferentially Expressed Antigen in Melanoma (PRAME) or both LINC and PRAME are detected.*

	Total PLA(+)	Total LINC and PRAME(+)	Total LINC(+)	Total PRAME (+)
PLA Registry (N=1575)	142	31 (21.8%)	85 (59.9%)	26 (18.3%)
Biopsy Type after PLA(+) Test	Shave: 70 (51.1%) Punch: 18 (13.1%) Excision: 49 (35.8%) No Biopsy: 5	Shave: 11 (35.5%) Punch: 4 (12.9%) Excision: 16 (51.6%) No Biopsy: 0	Shave: 49 (57.6%) Punch: 11 (12.9%) Excision: 20 (23.5%) No Biopsy: 5 (0.6%)	Shave: 10 (38.5%) Punch: 3 (11.5%) Excision: 13 (50.0%) No Biopsy: 0

periods [1, 22, 23]. Thus, this 12-month follow-up period should be sufficient for any new changes to manifest, indicating the presence of an emerging melanoma in a previously tested PLA(-) lesion. In addition, patients with atypical pigmented lesions that are being followed are instructed to identify changes that may indicate the presence of melanoma making patient concern about a pigmented lesion an additional risk factor for melanoma that can trigger assessment by biopsy [25, 26]. We therefore believe the results of this study reflect and further support the high NPV of the PLA. Inherent limitations of the data presented include the assumption that lesions of patients not returning to follow-up visits at the site of PLA testing within a 12-month follow-up period are true negatives. Additionally, we cannot rule out that some PLA(-) lesions may not have been adequately re-assessed within the 12-month follow-up period and we recommend erring on the side of caution and surgically biopsying a lesion in question if additional risk factors and further clinical suspicion or patient concern mandate such a step. Further limitations inherent to studies designed to assess melanoma rule-out tests and platforms in real-world settings include the low prevalence of melanoma compared to how common benign lesions of clinically similar appearance are in given target populations. However, it is comforting to consider that the non-invasive gene expression platform used here lends itself to validation study comparisons that can exceed the quality level of randomized control groups. With this platform it is possible to obtain non-invasive gene expression information and histopathology reads from the same lesion [13]. The performance of the PLA relative to consensus reads (91% sensitivity) compares favorably to primary site histopathology performance (84% sensitivity), [13, 21]. The PLA also reduces the number needed to biopsy (NNB, the number of biopsies needed to detect a melanoma) by a factor of about 10 from 25 to 2.7 [7, 14, 21]. Cost savings of the PLA are primarily driven by a reduction in initial biopsies and excisions as well as reduced stage-related treatment costs from missing fewer melanomas. A recent cost savings analysis by Hornberger and Siegel demonstrates that a cost reduction of 47% per assessed lesion suggestive of melanoma versus the current histopathologic standard of care is achievable if the PLA priced at $500 per test is used [20]. Although pigmented lesions can evolve over time, it is helpful to again contemplate that only 13 of 721 or 1.8% of PLA(-) lesions followed for 12 months were surgically biopsied for any reason (6 of 13 were biopsied at patients' requests). These data sets appear to suggest that the pool of cases where repeat PLA testing may be considered as an alternative to the performed surgical biopsies in a real-world setting is very small.

Regardless of the assessment used for the management of atypical pigmented lesions, routine clinical follow up is a critical component of quality care. Surveillance follow-up schedules for monitored or potential new lesions vary depending on clinical setting, physician specialty, stage of disease, number and nature of nevi, and risk factors [22, 23]. In the absence of evidence-based guidelines, many clinicians arrange follow-up according to a schedule with which they and their patients are most comfortable and surveillance plans generally include a follow-up after 3, 6, or 12 months as also evidenced by data from follow-up periods in our own registry study presented here [22, 23]. The vast majority of planned pigmented lesion follow-up visits therefore fall within the conservatively chosen 12-month period of the chart review study that is at the core of the data presented here.

Understanding the clinical utility of a novel diagnostic test or diagnostic aid relative to the established standard of care is paramount to assess how a test is used in clinical practice and to evaluate the test's impact on clinical management and patient benefit. In the presented registry study, 99.9% of PLA(-) cases were scheduled for follow up surveillance within a 12- month time period. Only two of 1433 PLA(-) lesions (0.1%) were not observed but biopsied or excised. One was a nevus that was biopsied and the other case was a squamous cell carcinoma in situ removed via MOHS surgery where the PLA may have been used to rule out melanoma prior to selecting a MOHS procedure. The clear clinical benefit is that these patients avoided a surgical biopsy procedure as well as the attendant

risks of scarring, infection, bleeding, and abnormal wound healing, which may occur in a small subset of patients, but which is magnified by the extremely high number of surgical biopsies performed on pigmented lesions [7, 21]. Perhaps even more importantly, initial surgical biopsy procedures often lead to wider margin excisional removal procedures owing to uncertainty of the initial histopathologic diagnosis. This is related to challenges associated with histopathologic assessment, including limited lesion sampling of only 1-2% of the biopsied tissue, overlapping diagnostic criteria between atypical nevi and early stage melanoma, and variability in assessment of cellular atypia [4, 6, 27, 28]. These wide excisional procedures are much more significant and often require closure repair. Up to 40% of initial biopsy procedures may be followed with a wider margin excision. Therefore, reducing initial surgical biopsies has the added clinical benefit of reducing follow-up full excisions [27].

Of equal importance is ensuring that PLA(+) tests are appropriately followed with a surgical biopsy. In the reported registry study, 96.5% or 137 of 142 PLA(+) cases were biopsied. It is of interest to note that of the 5 PLA(+) registry study cases not biopsied but rather monitored, all were LINC only positive. These cases came from two clinicians at two sites whereas the other 60 participating clinicians biopsied all PLA(+) lesions. Tests with only this single transcript carry a lower probability of being diagnosed histopathologically as melanoma than tests with the PRAME transcript only, or results with both transcripts detected [14]. **Figure 3** depicts a simplified model on how the PLA transcripts LINC and PRAME are involved in the evolution of melanocytic lesions. The model attempts to convey how initial molecular changes at the DNA and RNA level are followed by microscopic changes that enable histopathologic assessment and ultimately manifest themselves as macroscopic changes including ABCDE criteria frequently used to clinically assess pigmented skin lesions [1-4, 13-15]. Overall, 93% of PLA results positive for both LINC and PRAME are diagnosed histopathologically as in situ or invasive melanomas. PRAME-negative only and LINC-negative only lesions are melanomas histopathologically in 50% and 7%, respectively [14]. Both targets are known to be overexpressed in melanoma and mechanistically PRAME promotes melanoma progression by interfering with retinoic acid receptor signaling and LINC is a regulator of oncogenesis affecting melanoma proliferation and invasion [13]. All PRAME only or LINC and PRAME double positive cases were biopsied at all registry study sites. More excisional biopsies were performed on double positive lesions and PRAME positive lesions, which have a higher probability of being diagnosed as melanomas by histopathologic assessment than on LINC only lesions, as mentioned above (**Table 2**). These findings further support that clinicians appropriately follow the guidance of the test and that the types of biopsy conducted were consistent with US practice. Furthermore, it is also of interest to note that most lesions evaluated by PLA were located on the trunk followed by extremities, suggesting that the use of PLA testing was not limited to cosmetically sensitive areas.

The current standard of care for the management of atypical pigmented lesions attempts to rule out melanoma via visual assessment followed by surgical biopsy and histopathology [1-11]. The aim of this

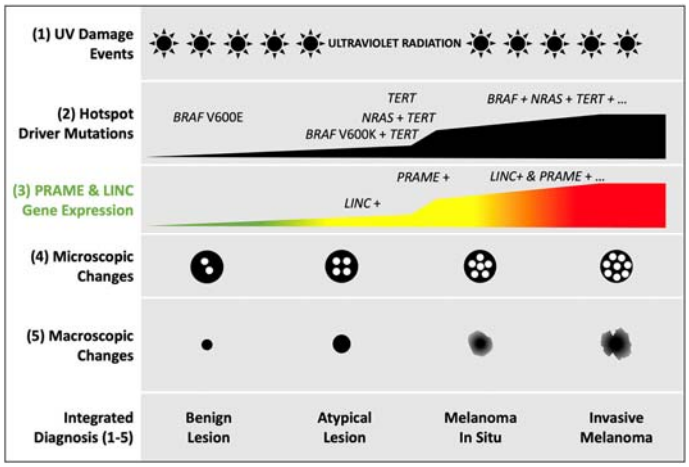

Figure 3. *Simplified model on Long Intergenic Non-Coding RNA (LINC)and Preferentially Expressed Antigen in Melanoma (PRAME) gene expression in the evolution of melanocytic lesions. The model depicts how initial molecular changes at the DNA (2) and RNA level (3) are followed by microscopic changes (4) that enable histopathologic assessment and are followed by macroscopic changes (5) captured within ABCDE criteria frequently used to clinically assess pigmented skin lesions. [1-4, 13-15].*

assessment is to identify melanoma at the earliest stages when a high cure rate is possible by wide excision, while monitoring lesions that don't need to be biopsied [22]. The current visual standard of care pathway has an NPV for early stage melanoma that ranges from 75%-89% [4-8], although the real world NPV may be higher owing to the use of special stains on lesions with difficult histopathology and the default to wide excisions in challenging cases. The PLA provides an alternative assessment that demonstrates a high NPV (>99%) while avoiding surgical procedures.

It is furthermore of interest to note that there is a growing body of evidence that not only clinicians, but also dermatopathologists benefit from the availability of melanoma-associated molecular risk factor information when they approach diagnostic decisions on pigmented lesions since primarily image recognition-based assessment of pigmented lesions remains challenging even for experts [24]. Providing non-invasively obtained results of PLA testing of clinically ambiguous pigmented lesions to pathologists can enable pathologists to even more closely evaluate borderline malignant lesions for histopathologic evidence of malignancy (C. Cockerell MD, personal communication).

Conclusion

Twelve-month follow-up data and findings from a large US registry study described here confirm the PLA's high clinical utility and high negative predictive value. Clinicians follow the guidance of the test and rely on it during long-term follow-up. PLA(-) lesions are monitored clinically and generally not biopsied, avoiding unnecessary surgical procedures; PLA(+) lesions are biopsied as intended. The PLA is a test that transforms the current diagnostic pathway from one that is subjective, invasive, and of low accuracy to one that is objective, non-invasive, and highly accurate.

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Potential conflicts of interest

This study was partially supported by DermTech, Inc. LF, DR, DS, GP, SK and CC are advisors to, and BJ, ZY and JR are employees of DermTech.

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Figure 1 was erroneously used twice; the information described in the legend of Figure 2 corresponds with the correct Figure 2 provided below.

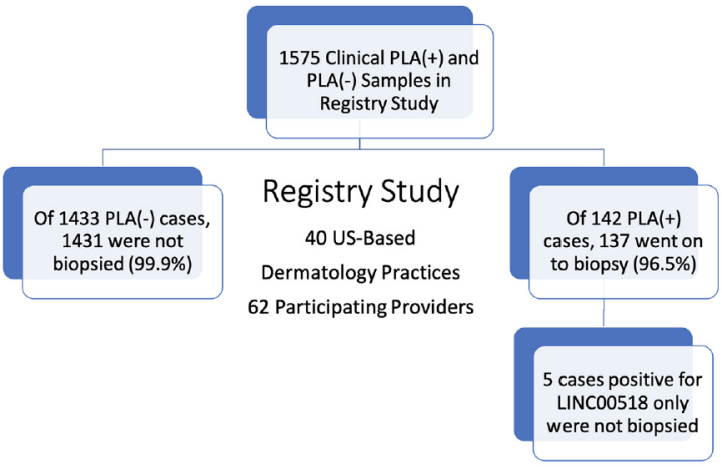

Figure 2. *Data summary from the Pigmented Lesion Assay registry study (N=1575, data sets collected between July and December of 2018).*