

Characterizes difficult-to-diagnose
lesions of uncertain malignant
potential



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Comprehensive Diagnostic Offering

Highly accurate and objective gene expression profile tests for melanocytic lesions of uncertain malignant potential

myPath
Melanoma

Quantifies expression of 23 genes from primary melanocytic lesion biopsy using RT-PCR

Includes 2 variants of PRAME

Designed to classify lesions objectively and accurately as benign, intermediate or malignant

DecisionDx
DiffDx-Melanoma

Quantifies expression of 35 genes from primary melanocytic lesion biopsy using RT-PCR

Applies a validated neural network algorithm

Designed to classify lesions objectively and accurately as benign, intermediate or malignant

Intended Use for GEP Testing

Gene expression profile testing aids in characterizing these lesions as suggestive of benign or malignant and can aid with better management decisions. It should be interpreted in the context of other clinical, laboratory and histopathologic information.

Cases that are appropriate for testing

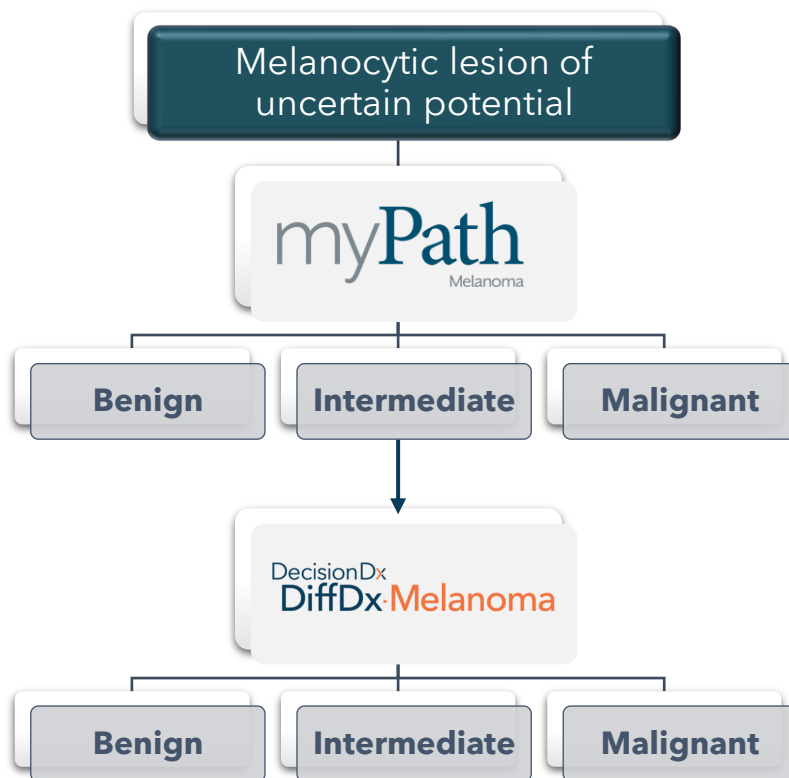
- ✓ Broad differential diagnosis
- ✓ "Borderline" or "Equivocal" or "Challenging" or "uncertain" cases
- ✓ Uncertain malignant potential (eg: MELTUMP)
- ✓ Histologically equivocal lesions
- ✓ Ancillary testing inconclusive or discordant*
- ✓ Benign nevi or melanocytic neoplasm of uncertain potential with re-excision recommendation that suggests diagnostic uncertainty
- ✓ Moderately or severely dysplastic nevi with recommendation to re-excite that suggests diagnostic uncertainty
- ✓ Cases within 6 months of the original biopsy date

Cases not included above may also be appropriate for testing.**

*Immunohistochemistry, FISH, aCGH

**Castle may request an accompanying statement of clinical rationale.

Comprehensive Diagnostic Offering



Leveraging the Strengths of both myPath Melanoma and DiffDx-Melanoma

myPath Melanoma

- ✓ Over 35,000 lesions tested in the clinical setting
- ✓ Validated in over 1,300 melanocytic neoplasms
- ✓ Reported sensitivity of 94% and specificity of 96% when compared to clinical outcomes
- ✓ Can be used with pediatric patients
- ✓ Measured an 80% reduction in excisions with benign test results

DiffDx-Melanoma

- ✓ Provides increased clarity in cases when the myPath Melanoma result is intermediate*
- ✓ Developed using neural networks - an artificial intelligence approach to machine learning for model development
- ✓ Validated on a wide variety of subtypes
- ✓ Low rate of intermediate cases

Inform the Entire Patient Management Plan

For patients diagnosed with invasive melanoma, Castle Biosciences' DecisionDx[®]-Melanoma prognostic testing informs clinical and management decisions (studied in 5,700+ patients; 30 peer-reviewed publications)

- ✓ Intensity of follow-up, surveillance imaging, referral and adjuvant therapy
- ✓ Predicts likelihood of SLNB positivity and outcomes

*DiffDx-Melanoma will only be performed on myPath intermediate cases of patients 18 years or older

Comprehensive Diagnostic Offering: myPath Melanoma Report Guide

Leveraging the strengths of gene expression profiling

Castle's Comprehensive Diagnostic Offering

- Initial testing with **myPath Melanoma**, the most extensively researched and validated ancillary diagnostic test for lesions of uncertain malignant potential
- In cases with a myPath Intermediate result, Castle adds value with the **DecisionDx DiffDx-Melanoma** test to provide increased clarity (see reverse)

myPath Melanoma Test Result

- Includes patient test score comparing individual GEP result to those in the independent validation cohort

Benign: -16.7 to -2.1
Intermediate: -2.0 to -0.1
Malignant: 0 to +11.1

myPath Melanoma Validated in 1,300+ Cases

- 4 validation studies, 8+ publications including 2,000+ cases
 - Reported sensitivity = 94%; specificity = 96% compared to clinical outcomes
 - 80% reduction in excisions with benign test results
 - 30 different subtypes
 - Including pediatric cases
- Over 35,000 clinically resulted cases

Inform the entire patient management plan

For patients diagnosed with invasive melanoma, Castle Biosciences' **DecisionDx-Melanoma** prognostic testing informs clinical management decisions (studied in 5,700+ patients; 30 peer-reviewed publications)

- Intensity of follow-up, surveillance imaging, referral and adjuvant therapy
- Predicts likelihood of SLNB positivity and outcomes

More information about the Castle Comprehensive Diagnostic Offering at www.castlebiosciences.com

CASTLE BIOSCIENCES **myPath**
Melanoma

Castle ID: _____ Page 1 of 2

FINAL REPORT

Patient: _____ Tumor Site: _____
 Sex: _____ Specimen ID: _____
 DOB: _____ Collected: _____
 Client: _____ Received: _____
 Clinician: _____ Reported: _____
 Ordered By: _____

Final Test Result

Benign	Gene expression profile suggestive of benign neoplasm	Score: -4.0
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RESULT DESCRIPTION

myPath Melanoma utilizes a molecular signature measured by qRT-PCR that classifies a sample as malignant, benign, or indeterminate. The number shown above is this patient's score relative to the myPath Melanoma scores according to the range of benign and malignant lesions in the independent validation cohort with a threshold of zero.

A score range of -16.7 to +11.1 was established in a validation study and scores within this range will be reported. For scores from -16.7 to -2.1 the resulting classification is benign; for scores from -2.0 to -0.1, classification is intermediate*; for scores from 0 to +11.1, the classification is malignant. Scores outside the validated range require follow-up with the ordering health care professional.

*For purposes of reporting herein, the terms intermediate and indeterminate are equivalent.

TEST VALIDATION AND PERFORMANCE METRICS

Based on an analysis of 437 melanocytic lesions in the validation study, a score threshold of zero was established to classify a sample as malignant, benign, or indeterminate. In the validation cohort, the gene expression signature had a sensitivity of 94% and a specificity of 90%¹.

BACKGROUND AND INTENDED USE

Background: Current methods used for definitive diagnosis of melanoma are sufficient for most lesions. However, histopathologic assessment can be challenging, even for experienced dermatopathologists. High rates of diagnostic discordance have been reported²⁻⁶. myPath Melanoma refines the diagnosis of nevi and melanoma by providing an objective tool to aid in classification of pigmented lesions.

Intended Use: The myPath-Melanoma gene expression test is intended for the in vitro analysis of primary cutaneous melanocytic lesions for which malignant potential is uncertain. This ancillary test aids in characterizing these lesions as benign or malignant and should be interpreted in the context of other clinical, laboratory and histopathologic information. myPath Melanoma has not been validated on metastatic melanomas, re-excision specimens, non-melanocytic neoplasms, or biopsies from a patient receiving immunosuppressant therapy or radiation treatment. Analysis of these samples may result in incorrect test interpretation; therefore, these specimens will not be accepted for testing.

Castle Biosciences, Inc. Sherri Borman, PhD, HCLD, Laboratory Director

CAP
ACCREDITED
COLLEGE of AMERICAN PATHOLOGISTS

The test performance characteristics were verified and confirmed by Castle Biosciences. It has not been cleared or approved by the FDA. The laboratory is regulated under CLIA as qualified to perform high-complexity testing. This test is used for clinical purposes. It should not be regarded as investigational or for research only. Patent Pending.

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Tel: (866) 788-9007 Fax: (866) 712-5207 Version 1.0 04/29/2021

Comprehensive Diagnostic Offering: DiffDx-Melanoma Report Guide

Leveraging the strengths of gene expression profiling

Castle's Comprehensive Diagnostic Offering

- Initial testing with **myPath Melanoma**, the most extensively researched and validated ancillary diagnostic test for lesions of uncertain malignant potential (see reverse)
- In cases with a myPath Intermediate result, Castle adds value with the **DecisionDx DiffDx-Melanoma** 35-GEP test to provide increased clarity

DiffDx-Melanoma Test Result

- Benign:** GEP suggestive of benign neoplasm
Intermediate: GEP cannot exclude malignancy
Malignant: GEP suggestive of malignant neoplasm

DiffDx-Melanoma Validation


- Validation study included independent cohort of 503 cases
 - Diagnoses of experts
 - Extensive variety of subtypes
 - In patients ≥ 18 years of age:
 - Sensitivity = 99.1%
 - Specificity = 96.2%


Inform the entire patient management plan

For patients diagnosed with invasive melanoma, Castle Biosciences' **DecisionDx-Melanoma** prognostic testing informs clinical management decisions (studied in 5,700+ patients; 30 peer-reviewed publications)

- Intensity of follow-up, surveillance imaging, referral and adjuvant therapy
- Predicts likelihood of SLNB positivity and outcomes

More information about the Castle Comprehensive Diagnostic Offering at www.castlebiosciences.com





Castle ID: _____ Page 1 of 2

FINAL REPORT

Patient:	Tumor Site:
Sex:	Specimen ID:
DOB:	Collected:
Client:	Received:
Clinician:	Reported:
Ordered By:	

Final Test Result

Benign	Gene expression profile suggestive of benign neoplasm
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RESULT DESCRIPTION

The proprietary DecisionDx DiffDx-Melanoma test is an empirically derived multi-analyte algorithmic assay (e.g.MAAA). The DiffDx-Melanoma test is a 35 gene qRT-PCR assay that employs a neural network algorithm comprised of two gene expression signatures inclusive of 32 discriminate and three control genes. The algorithm was trained on a set of patients with definitive diagnosis of either benign nevi or malignant melanoma. The test yields one of three results: benign, intermediate-risk* of malignancy, or malignant.

TEST VALIDATION AND PERFORMANCE METRICS

Test Validation: The DiffDx-Melanoma test was validated in an independent cohort totaling 503 pigmented lesions. Within this clinical validation study, adult patients represented 478 cases (230 melanomas and 248 nevi). Test performance was determined in this patient subset through comparison of probability scores to consensus diagnosis via histopathologic review.


For lesions in patients ≥ 18 years of age, sensitivity and specificity for the test are 99.1% and 96.2%, respectively¹.

BACKGROUND AND INTENDED USE

Background: Current methods used for definitive diagnosis of melanoma are sufficient for most lesions. However, histopathologic assessment can be challenging, even for experienced dermatopathologists. High rates of diagnostic discordance have been reported²⁻⁴. The DiffDx-Melanoma test refines the diagnosis of nevi and melanoma by providing an objective tool to aid in classification of melanocytic lesions.

Intended use: The DiffDx-Melanoma gene expression test is intended for the in vitro analysis of primary cutaneous melanocytic lesions for which malignant potential is uncertain. This ancillary test aids in characterizing these lesions as benign or malignant and should be interpreted in the context of other clinical, laboratory and histopathologic information. DiffDx-Melanoma has not been validated on metastatic melanomas, re-excision specimens, non-melanocytic neoplasms, or biopsies from a patient receiving immunosuppressant therapy or radiation treatment. Analysis of these samples may result in incorrect test interpretation. Therefore, these specimens will not be accepted for testing.

Castle Biosciences, Inc. Sherri Borman, PhD, HCLD, Laboratory Director



The test performance characteristics were verified and confirmed by Castle Biosciences. It has not been cleared or approved by the FDA. The laboratory is regulated under CLIA as qualified to perform high-complexity testing. This test is used for clinical purposes. It should not be regarded as investigational or for research only. Patent Pending.

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Version 2.0 04/29/2021



Your Patients Have Access to an Industry-Leading Financial Assistance Program

Healthcare Provider Signs Letter of Medical Necessity (LOMN)

- ▶ A signed LOMN will be needed and can be submitted with the test requisition form
- ▶ For your convenience, a LOMN template is available upon request

Castle Biosciences Submits Claim to Patient's Insurance Company

- ▶ After a patient report is issued, Castle Biosciences bills all third party insurance including Medicare/Medicaid and VA
- ▶ Castle Biosciences will send a letter to the patient notifying them of our claim submission

Patient Receives Explanation of Benefits (EOB)



- ▶ Patients will receive an EOB from their insurance plan
- ▶ This is not a bill, but the EOB may show an "Amount Due From Patient" or state "Patient Responsibility"

Patient Asked to Sign Appeal Consent Form

- ▶ Depending on the patient's insurance plan requirements, Castle Biosciences may require assistance during the reimbursement process to file claims and appeals on the patient's behalf

At Castle Biosciences, our goal is to ensure all patients have access to our tests. We believe the availability of testing should not be limited by a patient's ability to pay.

Reimbursement Information or Questions:

 866-788-9007, option 3
 Reimbursement@CastleBiosciences.com

CastleTestInfo.com

Simple Ordering Process

1. **Requisition Form (Completed & Signed)**
- Hard Copy or Utilize Online Portal
2. **Letter of Medical Necessity (Completed & Signed)**
3. **Pathology Report(Primary Biopsy Specimen)**
- Include Excision Report if Available
4. **Copy of Patient's Insurance Information**

Submit all documentation at Portal.CastleBiosciences.com or fax to 866-329-2224

For Dermatology HCPs:

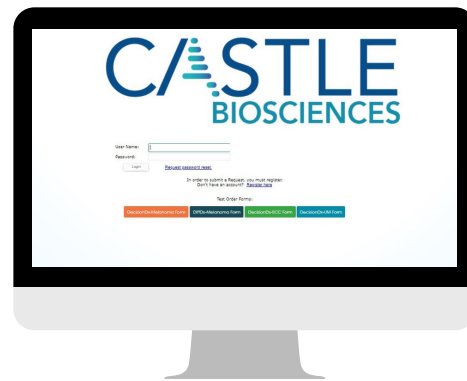
After submitting the above documentation, Castle Biosciences will secure the specimen.

For Dermatopathologists:

Documentation can be submitted as listed above or can be sent with the specimen to the Castle Biosciences Laboratory using a pre-paid shipping label.

Convenient Physician Portal

- ▶ HIPAA compliant and secure
- ▶ Order online or download pdf order forms
- ▶ Easily access patient test information 24/7
- ▶ Upload all supporting documents including LOMN, pathology reports and patient insurance information
- ▶ Receive email notifications when a report is available to view



Results are typically available within 5 days from sample receipt.

Ordering Information, Pre-Paid Shipping Labels or Questions:

☎ 866-788-9007, option 1 or Contact your Area Manager

Requisition Form

Fax completed form to: 866-329-2224
Alternate fax: 602-266-9597

**Required fields*

I. Ordering Entity Information

II. Patient Information

III. Billing Information

Name of Ordering Provider*		Last Name*	First Name*	MI	Please Select Code From Drop Down List	
Specialty	NPI	DOB*	Gender	SSN / MR#	Submitting Diagnosis	ICD-10 Code*
Address*		Address*			Method of Payment:	
City / State / Zip*		City / State / Zip*			<input type="checkbox"/> Private Insurance <input type="checkbox"/> Patient Self-Pay <input type="checkbox"/> Medicare <i>*Section IV required</i> <input type="checkbox"/> Medicaid <input type="checkbox"/> Client Bill (<i>contracted entities only</i>)	
() () Telephone*	() () Fax*	() () Telephone*	() () Telephone*		Primary Insurance Co. Name	Policy#
Institution / Practice Name*		Email			Secondary Insurance? <input type="checkbox"/> Yes <input type="checkbox"/> No (If yes, attach copy of front/back of secondary insurance card)	

IV. Medicare Only* (Required for patients with traditional Medicare as primary insurance)

At time of tissue collection, was this patient: Non-hospital Hospital Outpatient Hospital Inpatient If hospital inpatient, date of discharge: _____

If specimen is stored for more than 30 days from the date of collection, please provide the date specimen is pulled from archive: _____

V. Clinical Information*

Is the malignant potential of this melanocytic lesion uncertain?* Yes No

Does this lesion have spitzoid features?* Yes No Does this lesion have only a junctional or intraepidermal component?* Yes No

IMPORTANT TO NOTE: *In instances where myPath Melanoma (23-GEP) has an Intermediate result, DiffDx-Melanoma (35-GEP) will be subsequently performed. These tests are intended for the in vitro analysis of primary cutaneous melanocytic lesions for which malignant potential is uncertain. They cannot be ordered for lesions which are metastatic or non-melanocytic in nature. Further, test performance has not been validated in patients receiving immunosuppressant or radiation therapy.*

VI. Required Signature

X

SIGNATURE OF ORDERING PROVIDER*

Printed Name

Date

This signature confirms this test to be medically necessary for this patient. This clinician provides consultation and/or treatment for melanocytic lesions and will use the results in the management of the patient.

I would like to sign-up for online ordering

VII. Additional Order Information

Name of Treating Clinician (<i>if different than section I</i>)	Additional Provider (<i>optional</i>)
() () Phone # Fax#	() () Phone # Fax#
Mailing Address (<input type="checkbox"/> same as requestor)	Mailing Address (<input type="checkbox"/> same as requestor)
City / State / Zip	City / State / Zip
Institution/Practice Name	Institution/Practice Name
Email address for report notification	Email address for report notification

VIII. Laboratory Information

Please fax this requisition along with a copy of the pathology report from the primary biopsy

Facility where tissue is maintained: _____ Date of Collection: _____

Phone: _____ Fax: _____

FOR INTERNAL USE ONLY

Received: _____ Processed by: _____ Materials received: _____

PR/Initials: _____ DTL: _____ Note: _____

**Submit the following forms via the Online Portal at CastleTestInfo.com or
Fax Toll Free 1-866-329-2224 (Alternate fax: 602-266-9597)
These forms may also accompany the specimen upon specimen submission.**

- Completed requisition
- Pathology report(s)*
- Signed letter of medical necessity

*In the absence of a preliminary path report, please submit the following form, or other document containing the following information:

- Pathologist _____
- Pathology lab _____
- Accession#/Specimen ID _____
- Date of collection _____
- Tumor site _____
- Working differential/differential diagnoses _____

Order confirmation will be sent to the ordering clinician via fax within 24 hours of receipt

Requisition Form Completion Instructions

- Section I:** Complete with information of the ordering Entity.
- Section II:** Complete with patient information.
- Section III:** Provide the ICD-10 code and patient's diagnosis. Select Method of Payment. Please complete with billing information including a copy of the front and back of the insurance card (if applicable). If the person completing this requisition is not in possession of the information necessary for completion of the billing information section, please provide the name/department and contact information of the appropriate party from whom this information can be obtained:

Name: _____ Department: _____
Phone: _____ Fax: _____

*If a copy of the front and back of the insurance card is provided, no further information is needed in this section of the requisition. A billing face sheet is also sufficient, in lieu of copy of card.

- Section IV:** Applicable only for patients with Medicare as their primary insurance.
- Section V:** Check the appropriate box confirming unknown malignant potential. Please also indicate if the specimen being submitted has spitzoid features and/or if the lesion has only a junctional or intraepidermal component.
- Section VI:** The ordering provider must sign this section. **For purposes of ordering this test, the "ordering provider" section can be signed by a physician, advanced practice registered nurse (APRN) or representative Physician Assistant (PA)** **Please check the box if you would like access to online ordering.**
- Section VII:** Complete with information for the treating clinician and/or additional clinicians. If the mailing address is the same as for the ordering provider, check the box "same as requestor". Be sure to select the preferred method by which results should be communicated and provide an email address if you wish to receive electronic notification that the report is available.
- Section VIII:** Complete this section with the name of the facility where the tissue from which slides for testing will be requested. Provide the name and phone # of an individual to whom a tissue request should be made.