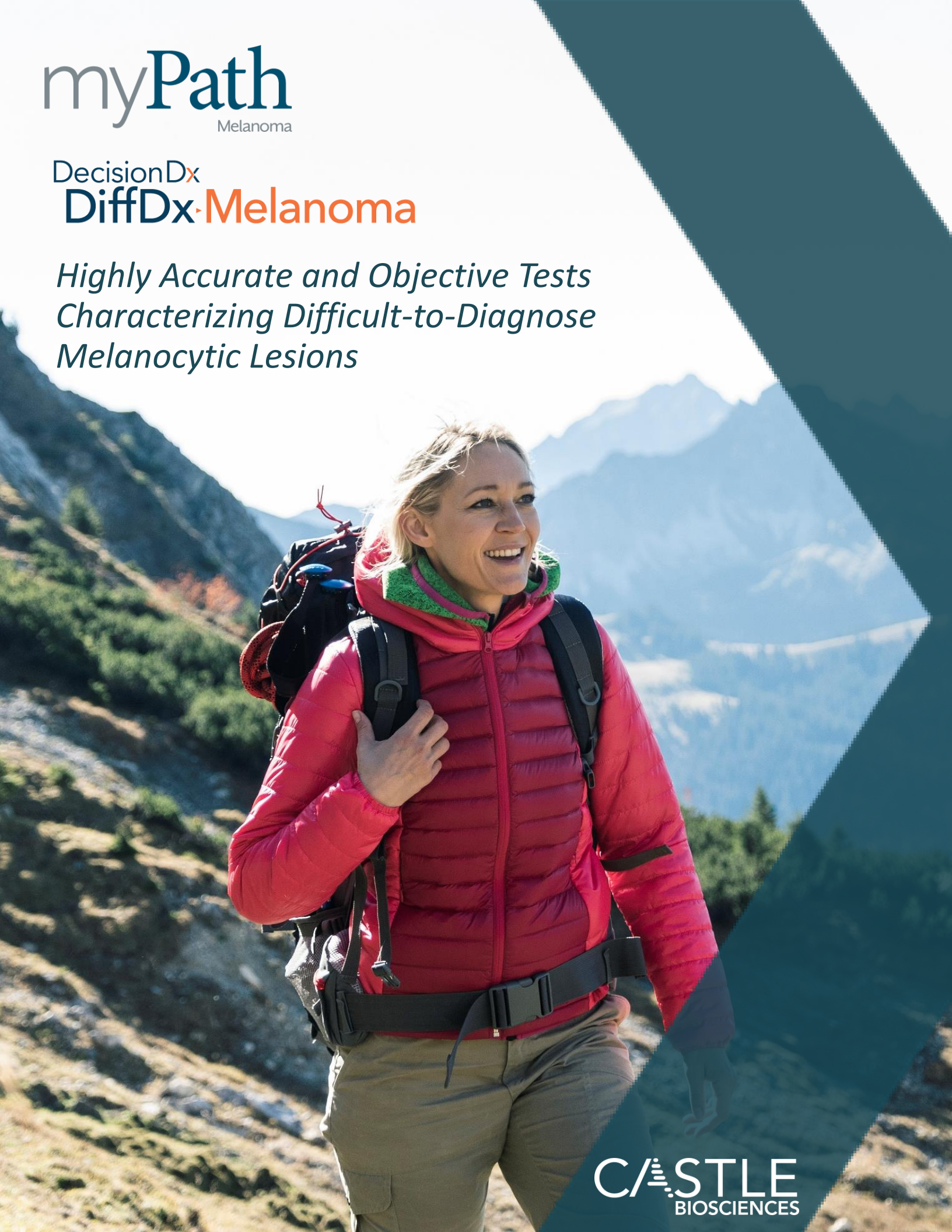
myPath
Melanoma

DecisionDx
DiffDx·Melanoma

Highly Accurate and Objective Tests Characterizing Difficult-to-Diagnose Melanocytic Lesions



CASTLE BIOSCIENCES

myPath Melanoma

DecisionDx DiffDx·Melanoma

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For Healthcare Professionals

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

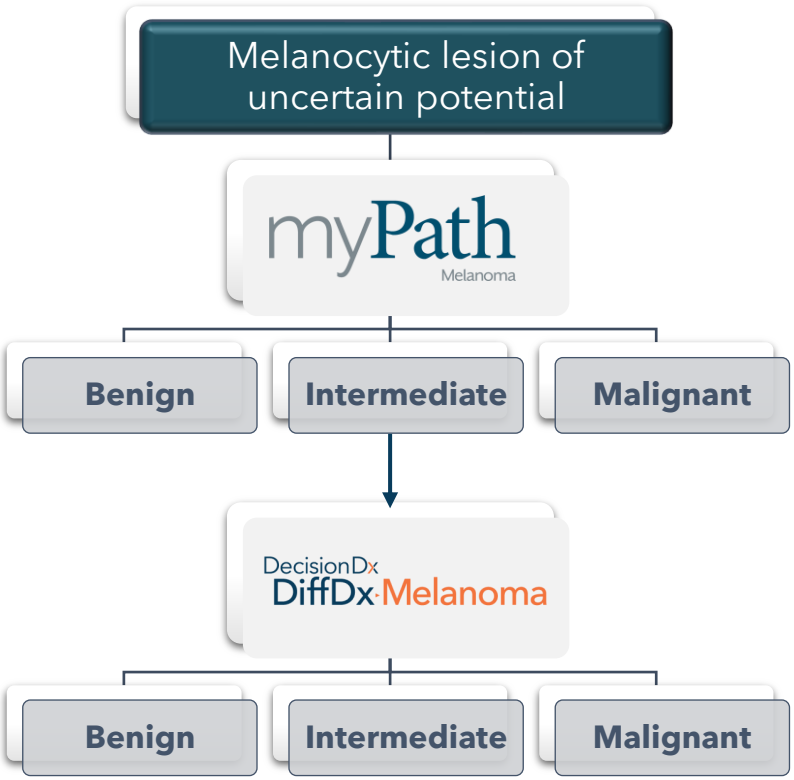
- ✓ Broad differential diagnosis
- ✓ "Borderline" or "Equivocal" or "Challenging" or "uncertain" cases
- ✓ Uncertain malignant potential (eg: MELTUMP)
- ✓ Histologically equivocal lesions
- ✓ Ancillary testing inconclusive or discordant*
- ✓ Benign nevi or melanocytic neoplasm of uncertain potential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

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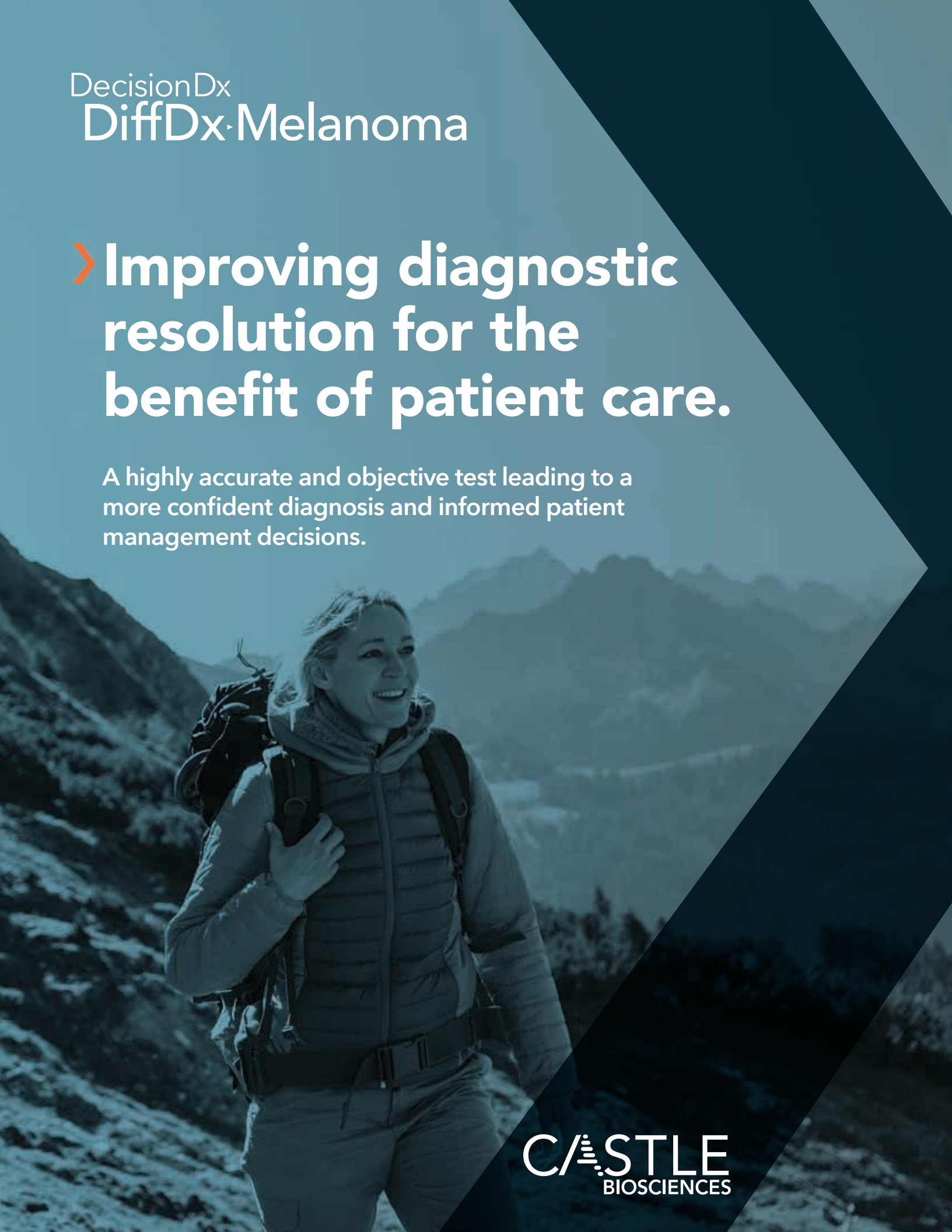
CDO-002v1-052021

DecisionDx
DiffDx·Melanoma

Improving diagnostic resolution for the benefit of patient care.

A highly accurate and objective test leading to a more confident diagnosis and informed patient management decisions.



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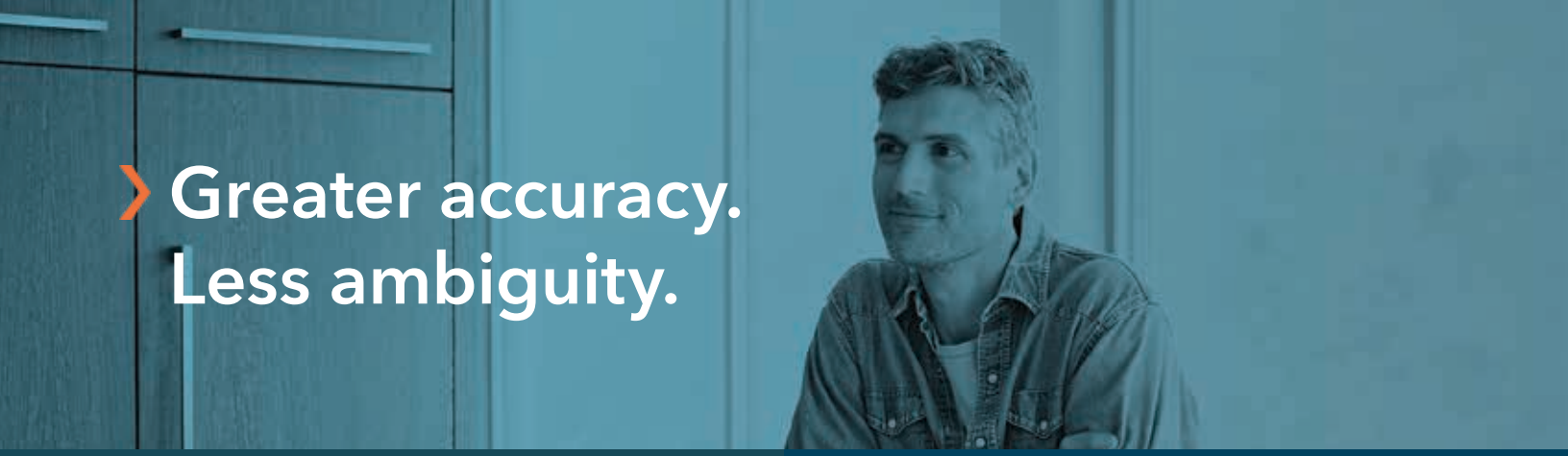


Greater accuracy. Less ambiguity.

With over 300,000 suspicious pigmented lesions every year that can't be confidently diagnosed with a routine H&E,[1] it is reasonable that even the most expert dermatopathologists and dermatologists can become frustrated.

Leveraging artificial intelligence-based technology, we set out to help by providing an objective test with a high level of accuracy, low technical failure, low intermediate-risk, and an inclusion of a variety of both benign nevi and malignant lesions.

Artificial intelligence meets biology.

35 Genes

Neural networks are used to identify 32 genes over 6 areas of gene function and 3 controls to best classify melanocytic lesions

2 Algorithms

The 2 proprietary algorithms are applied to the gene expression patterns to identify malignant potential of a lesion

1 Result

A clinically actionable result in over 96% of the cases including multiple types of benign nevi and malignant melanoma

Unmatched diagnostic performance.

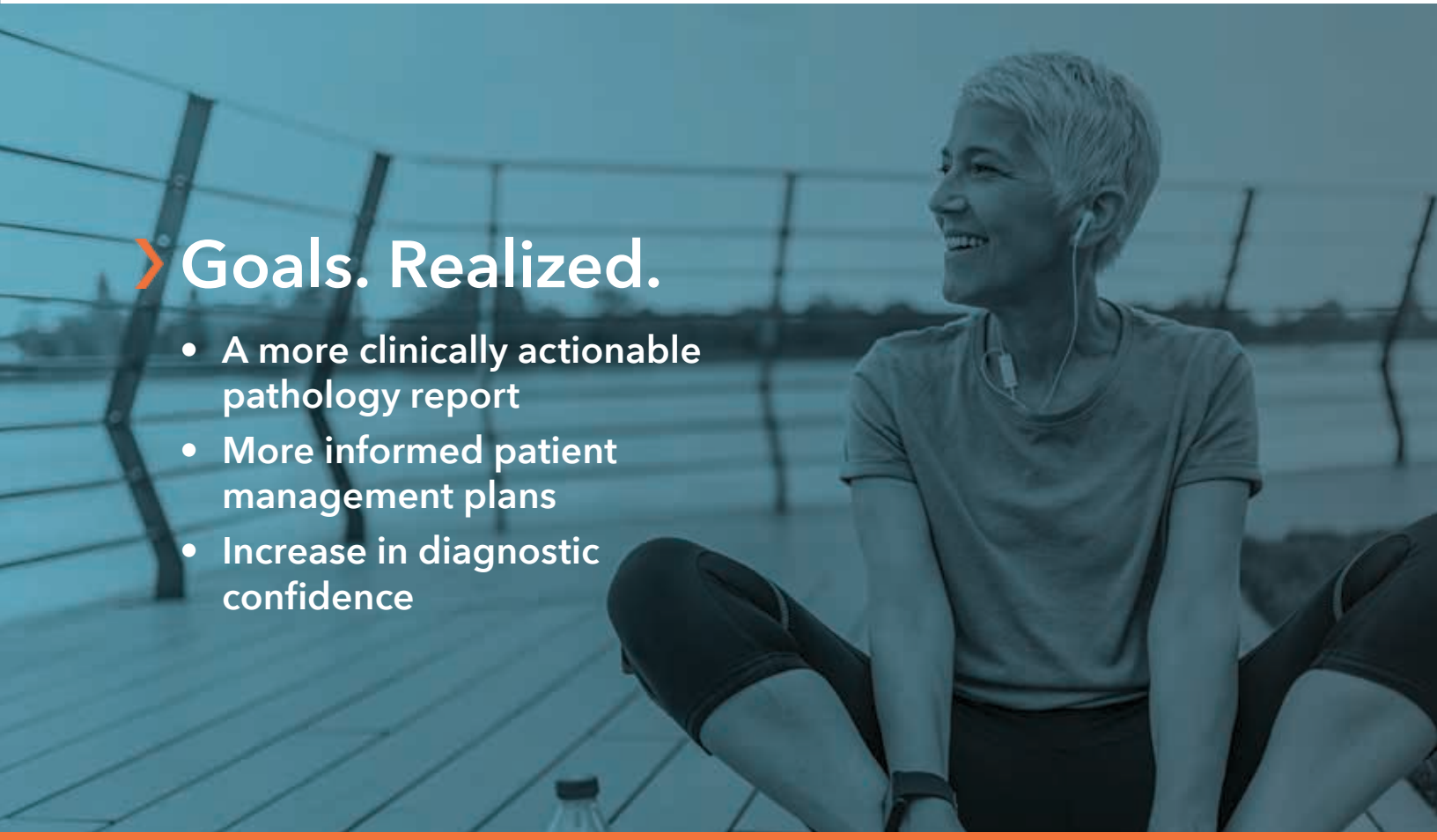
DecisionDx® DiffDx™-Melanoma provides a highly accurate and objective evaluation resulting in a benign or malignant result in >96% of lesions receiving a test result.

The clinical validation study contained a variety of benign nevi and malignant lesions, and lesions with full diagnostic concordance (3/3 dermatopathologists) as well as a smaller subset of lesions with 2/3 diagnostic concordance.[2]

Melanoma subtypes included: acral lentiginous, desmoplastic, lentiginous, lentigo maligna, nevoid, nodular, spitzoid, superficial spreading, and melanoma in situ.[2]

Benign subtypes included: blue nevus, common nevus (compound, junctional and intradermal), deep penetrating nevus, dysplastic nevus (compound and junctional), and Spitz nevus.[2]

All Ages (N = 503)			
99.1%	**94.3%**	**93.6%**	**99.2%**
Sensitivity 95% CI: 97.9–100%	Specificity 95% CI: 91.5–97.1%	PPV 95% CI: 90.5–96.7%	NPV 95% CI: 98.1–100%
3.6% Intermediate-Risk			



Goals. Realized.

- A more clinically actionable pathology report
- More informed patient management plans
- Increase in diagnostic confidence

DecisionDx DiffDx-Melanoma

Don't settle for ambiguity.

- Development and validation included many benign and melanoma subtypes, including lesions confined to the epidermis[2]
- Provides a clinically actionable result in >96% of cases[2]
- Low rate of intermediate-risk cases[2]
- Sensitivity and Specificity (for all ages): 99.1% and 94.3%, respectively[2]
- Performance consistent in lesions with full concordance as well as those with only a 2 out of 3 agreement[2]

Easily integrated.

At the time of the diagnostic work-up, provide either 10 consecutive slides (1 H&E, 9 unstained 5 µm cuts) or the tissue block along with the following:

- A completed requisition form
- The pathology report of the primary biopsy
- Copy of patient's insurance information
- Letter of medical necessity

Online submission is also available. Test results are typically available within 5 days.

Patient access.

Castle Biosciences works with all insurance providers, including Medicare, Medicaid, commercial insurers, and the VA, to secure coverage and payment for the DiffDx-Melanoma test. Castle will submit insurance claims and manage the insurance billing process on behalf of patients. The company also sponsors an industry-leading Patient Assistance Program with the belief that quality care should not depend on financial considerations.

You can get more information about insurance coverage, claims processing, and financial assistance by calling 866-788-9007 and selecting option #3.

Order now at CastleTestInfo.com

References:

1. Shoo et al., *J Am Acad Dermatol* 2010;62:751-6
2. Estrada et al., *SKIN: J Cutaneous Med* 2020;4:506-22

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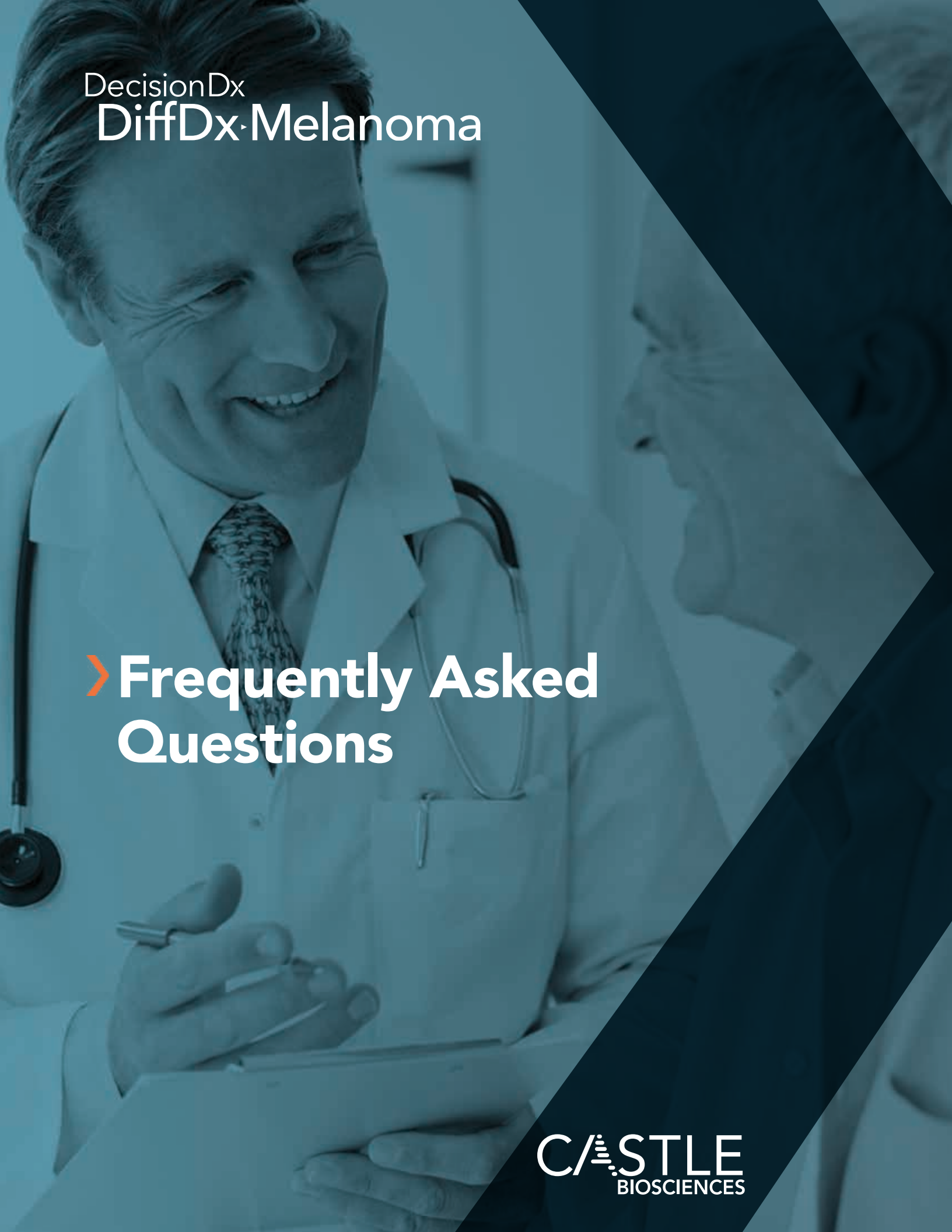

DecisionDx
DiffDx·Melanoma

Frequently Asked Questions

CASTLE BIOSCIENCES

General FAQs

What is the DecisionDx DiffDx-Melanoma test?

DecisionDx® DiffDx™-Melanoma is a new gene expression profile test to aid dermatopathologists in characterizing difficult-to-diagnose melanocytic lesions by providing a highly accurate, objective evaluation.

The test development process harnessed the capabilities of artificial intelligence, applying deep learning and neural networks to refine the final gene set. The result is a test with a high level of accuracy, low technical failure rate and low intermediate-risk zone.

Dermatopathologists can experience a definitive result from DiffDx-Melanoma in >96% of lesions submitted for testing.

Which types of lesions are eligible for the test?

This test is intended for the in vitro analysis of primary cutaneous melanocytic lesions for which malignant potential is uncertain. It should not be ordered for lesions which are metastatic or non-melanocytic in nature. Test performance has not been validated in patients receiving immunosuppressant or radiation therapy.

What information does the test provide?

The DiffDx-Melanoma gene expression profile test provides a highly accurate, objective evaluation of melanocytic lesions with unknown malignant potential. 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.

The results are listed as:

BENIGN: Gene Expression Profile suggestive of benign neoplasm

INTERMEDIATE-RISK: Gene Expression Profile cannot exclude malignancy

MALIGNANT: Gene Expression Profile suggestive of melanoma

Clinical Evidence

What studies support the validation of the test?

The development and training of the DiffDx-melanoma assay occurred in a set of 416 lesions. Validation occurred in an independent set of 503 lesions is described in:

Estrada et al. Development and validation of a diagnostic 35-gene expression profile test for ambiguous or difficult-to-diagnose suspicious pigmented skin lesions. *SKIN: J Cutan Med* 2020 (in press).

How accurate is the test?

DiffDx-Melanoma has been demonstrated to provide:

- Very high accuracy with a low intermediate-risk result: the test demonstrated 99.1% sensitivity, 94.3% specificity, 93.6% positive predictive value and 99.2% negative predictive value in patients of all ages (Table 1). Only 3.6% (18/503) of cases were classified as intermediate-risk.
- Inclusion of a wide variety of subtypes in the study improved the classification of lesions as benign or malignant and led to a limited intermediate-risk zone
- A total of 96.4% of cases from patients of all ages had a clinically actionable benign or malignant test result
- High technical success: 96% of all specimens were successfully processed

Table 1: Clinical Validation Accuracy Metrics

DiffDx-Melanoma	All ages N=503		>18 years old N=478	
	35-GEP	95% CI	35-GEP	95% CI
Sensitivity	99.1%	97.9–100	99.1%	97.9–100
Specificity	94.3%	91.5–97.1	96.2%	93.8–98.6
PPV	93.6%	90.5–96.7	96.1%	93.6–98.6
NPV	99.2%	98.1–100	99.1%	97.9–100%
Intermediate-risk result	3.6%		3.8%	

Given the potential biological transition of melanocytic lesions from a benign to a malignant state, the 35-GEP profile was developed to identify lesions with an intermediate-risk of malignancy. Though a definitive benign or malignant result is advantageous for implementing patient management pathways, samples with probability scores in the intermediate-risk zone cannot be definitively called malignant. Because malignancy cannot be excluded, these lesions warrant careful consideration with a focus on clinicopathologic correlation for patient management decisions.

Clinical Evidence

What genes are included?

DiffDx-Melanoma development included neural network, machine learning to select and prioritize 32 discriminant genes associated with benign or malignant biology. These genes are involved in barrier function, cytoskeletal function, gene regulation, melanin biosynthesis, protein synthesis and tumorigenesis (Table 2). Three control genes are also included.

Table 2: DecisionDx DiffDx-Melanoma Genes

Barrier Function	Cytoskeleton	Gene Regulation	Melanin Biosynthesis	Protein Synthesis	Tumorigenesis	Control Genes
CST6*	ABLIM1	BAP1*	ATP6V0E2	RPL37A	ANXA8L1	FXR1*
CSTA	DSP	GATA3	DCT	RPS16	BCL2A1	HNRNPL*
CLCA2*	KRT2	KLF5	GPR143		BTG1*	YKT6*
GJA1*	KRT17	SAP130*	PTN		CXCL14*	
HAL	NES	SFN	WIPI1		DUSP4	
MGP*	PPL*	TP63			S100A8*	
					S100A9*	

*Included in DecisionDx-Melanoma

Do you include PRAME? Why not?

PRAME is not included in the test. PRAME was included in our test discovery efforts; however, during the neural network machine learning, PRAME expression levels did not add additional value to the test output and therefore it was not included in the final panel of discriminant genes.

What types of lesions were included in the validation?

A variety of lesions including those with discordant diagnoses, both melanoma and nevi, were included in the initial validation:

Melanoma: acral lentiginous, lentiginous, desmoplastic, lentigo maligna, *in situ*, nevoid, nodular, superficial spreading, spitzoid

Benign: blue, common nevi (compound, intradermal, junctional), deep penetrating, dysplastic (compound and junctional), Spitz

Common and Dysplastic nevi had varied levels of cellular atypia.

Clinical Impact

How does this impact my diagnosis?

By providing additional highly accurate and objective information, DiffDx-Melanoma helps to create a more clinically actionable pathology report for difficult-to-diagnose melanocytic lesions. Just as with other ancillary studies, it is important to interpret GEP results in the context of other clinical, laboratory and histopathologic information.

DiffDx-Melanoma will also help clinicians obtain diagnostic confidence that your patient is receiving a diagnosis aided by objective and dependable gene expression analysis.

How does this impact what the dermatologist will do?

By providing the dermatopathologist with additional, highly accurate and objective information, DiffDx-Melanoma can lead to a more clinically actionable diagnosis. For the dermatologist, this will enhance clinical confidence that your patient is receiving the most appropriate management plan.

In addition, for most patients diagnosed with melanoma, the DecisionDx-Melanoma prognostic test can be run using the same tissue sample as the DiffDx-Melanoma test – no need to send additional slides (tissue must meet the specimen requirements for DecisionDx-Melanoma with 40% tumor density). This can save precious time and resources for healthcare providers who are making important decisions about patient management plans based on information that the DecisionDx-Melanoma test provides regarding risk of sentinel node positivity and risk of recurrence or metastasis.

Ordering Logistics

How is the test ordered?

The test ordering is easy, with minimal burden to you and your office staff office.

The following are needed for every order:

- Requisition Form (complete with physician signature): download from CastleTestInfo.com or via the online portal
- Pathology Report (from the primary biopsy specimen)
- Copy of patient's insurance Information

Ship these materials along with the specimen to Castle Biosciences' laboratory with pre-paid shipping labels.

All test orders are processed within 24 hours of receipt.

How long will it take to receive test results?

On average, results are available within 5 days from the time a sample is received in the Castle Biosciences laboratory. Results will be sent via fax and available via US mail upon request. A secure online results portal is also available.

What type of tissue is required?

We can accept formalin-fixed, paraffin-embedded (FFPE) tissue in the form of block or slides. If sending slides, we require: 1 H&E + 9 unstained slides (5-micron sections).

Performance characteristics of the signature have not been established for tissue other than FFPE primary cutaneous melanocytic lesions. The signature has not been validated on re-excised lesions, metastatic lesions (i.e. non-primary melanomas), non-melanocytic neoplasms, or lesions subjected to prior treatment (e.g. radiation therapy). Therefore, these samples are not suitable for testing.

Results from this test should be used in conjunction with other information from clinical evaluation, histopathological features, and other diagnostic procedures.

Ordering Logistics

What is the technical success rate for the DiffDx-Melanoma test?

The test has a technical success rate of over 96% when there is sufficient tumor present (more than 10% tumor density).

Can the test be performed on tissue from pediatric patients?

No. This is an area currently under research with DiffDx-Melanoma. Until we have that data available, we cannot accept cases from patients 17 years of age and under.

Where is the test performed?

All of our testing is conducted in Castle Biosciences' CAP-accredited, CLIA-certified laboratory in Phoenix, AZ.

How is billing for the test handled? Will Castle Biosciences help with patients' insurance claims?

Our goal is to ensure all patients have access to all our tests. We work with all insurance providers including Medicare, commercial insurers and the VA to secure payment coverage for tests. Castle will submit and track insurance claims on your patients' behalf throughout the billing process, including appeals if necessary. After we process a claim, patients will likely receive an Explanation of Benefits from their insurance company just like they do for other services. This is not a bill. In addition, Castle offers an industry-leading financial assistance program for both insured and uninsured patients.

DecisionDx DiffDx-Melanoma

Don't settle for ambiguity.

- Development and validation included many benign and melanoma subtypes, including lesions confined to the epidermis[1]
- Provides a clinically actionable result in >96% of cases[1]
- Low rate of intermediate-risk cases[1]
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Patient access.

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You can get more information about insurance coverage, claims processing, and financial assistance by calling 866-788-9007 and selecting option #3.

Order now at CastleTestInfo.com

References:

1. Estrada et al., *SKIN: J Cutaneous Med* 2020;4:506-22

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Customer Service: 866-788-9007

Requisition Form

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

Required fields

myPath Melanoma DecisionDx DiffDx-Melanoma

I. Ordering Entity Information

Name of Ordering Provider*

Specialty NPI

Address*

City / State / Zip*

( ) ( )
Telephone* Fax*

Institution / Practice Name*

II. Patient Information

Last Name* First Name* MI

DOB* Gender SSN / MR#

Address*

City / State / Zip*

( )
Telephone*

Email

III. Billing Information

Please Select Code From Drop Down List
Submitting Diagnosis ICD-10 Code*

Method of Payment:
☐ Private Insurance ☐ Patient Self-Pay
☐ Medicare ***Section IV required*** ☐ Medicaid
☐ Client Bill *(contracted entities only)*

Primary Insurance Co. Name Policy#

( )
Insurance Co. Phone#

Secondary Insurance? ☐ Yes ☐ 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 *(if different than section I)*

( ) ( )
Phone # Fax#

Mailing Address (☐ same as requestor)

City / State / Zip

Institution/Practice Name

Email address for report notification

Additional Provider *(optional)*

( ) ( )
Phone # Fax#

Mailing Address (☐ same as requestor)

City / State / Zip

Institution/Practice Name

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: _____

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myPath Melanoma
DecisionDx DiffDx-Melanoma

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

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Requisition Form Completion Instructions

1. **Section I**: Complete with information of the ordering Entity.

2. **Section II**: Complete with patient information.

3. **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.

4. **Section IV**: Applicable only for patients with Medicare as their primary insurance.

5. **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.

6. **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.**

7. **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.

8. **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.

ADDING DIAGNOSTIC CLARITY FOR DIFFICULT-TO-DIAGNOSE MELANOCYTIC LESIONS

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

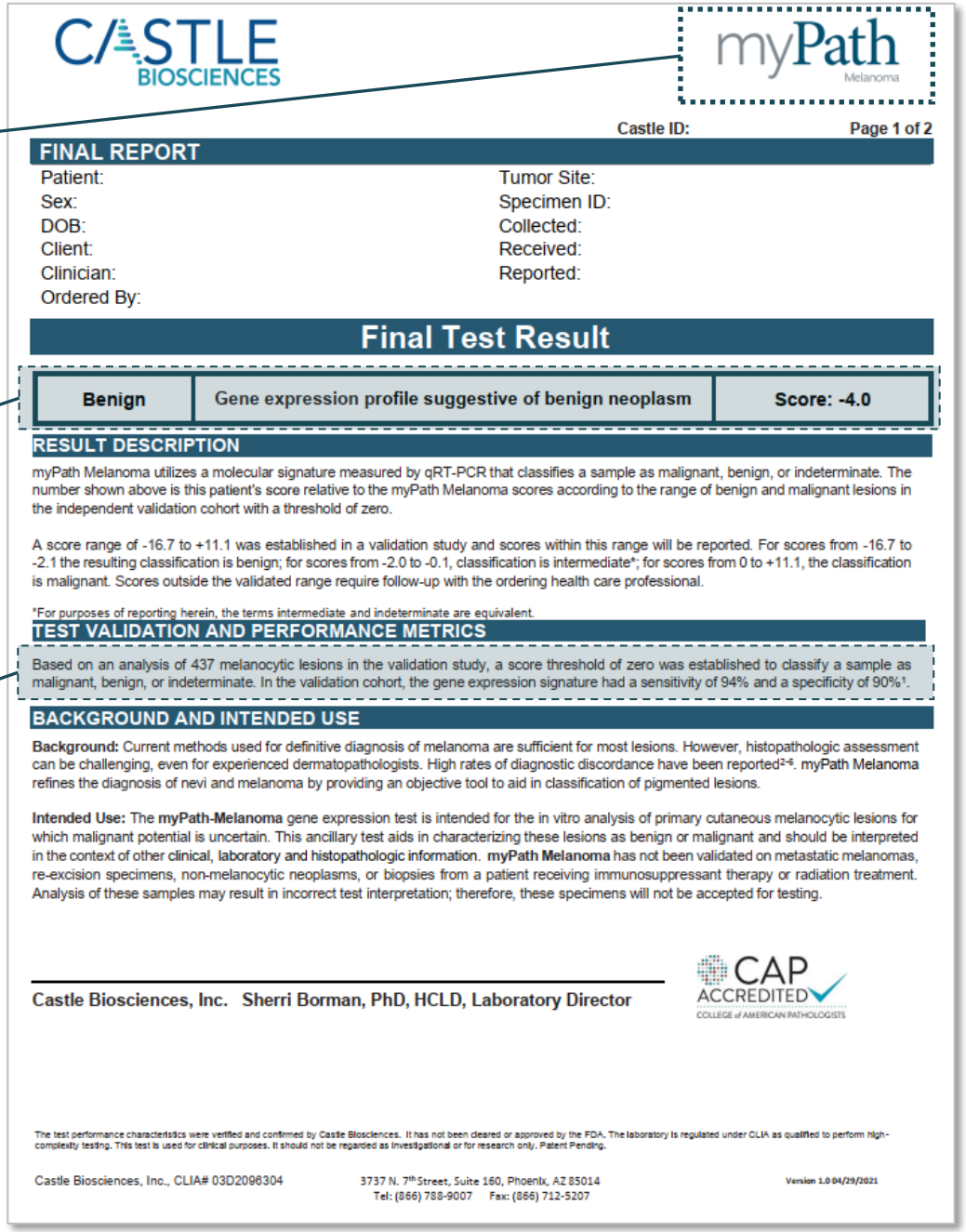
- 4 validation studies, 8+ publications including 2,000+ cases
  - Reported sensitivity = 94%; specificity = 96% compared to clinical outcomes
  - 80% reduction in excisions with benign test results
  - 30 different subtypes
  - Including pediatric cases
- Over 35,000 clinically resulted cases

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**



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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

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 reported[2-6]. 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.

Castle Biosciences, Inc., CLIA# 03D2096304 3737 N. 7th Street, Suite 160, Phoenix, AZ 85014 Tel: (866) 788-9007 Fax: (866) 712-5207 Version 1.0 04/29/2021

ADDING DIAGNOSTIC CLARITY FOR DIFFICULT-TO-DIAGNOSE MELANOCYTIC LESIONS

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

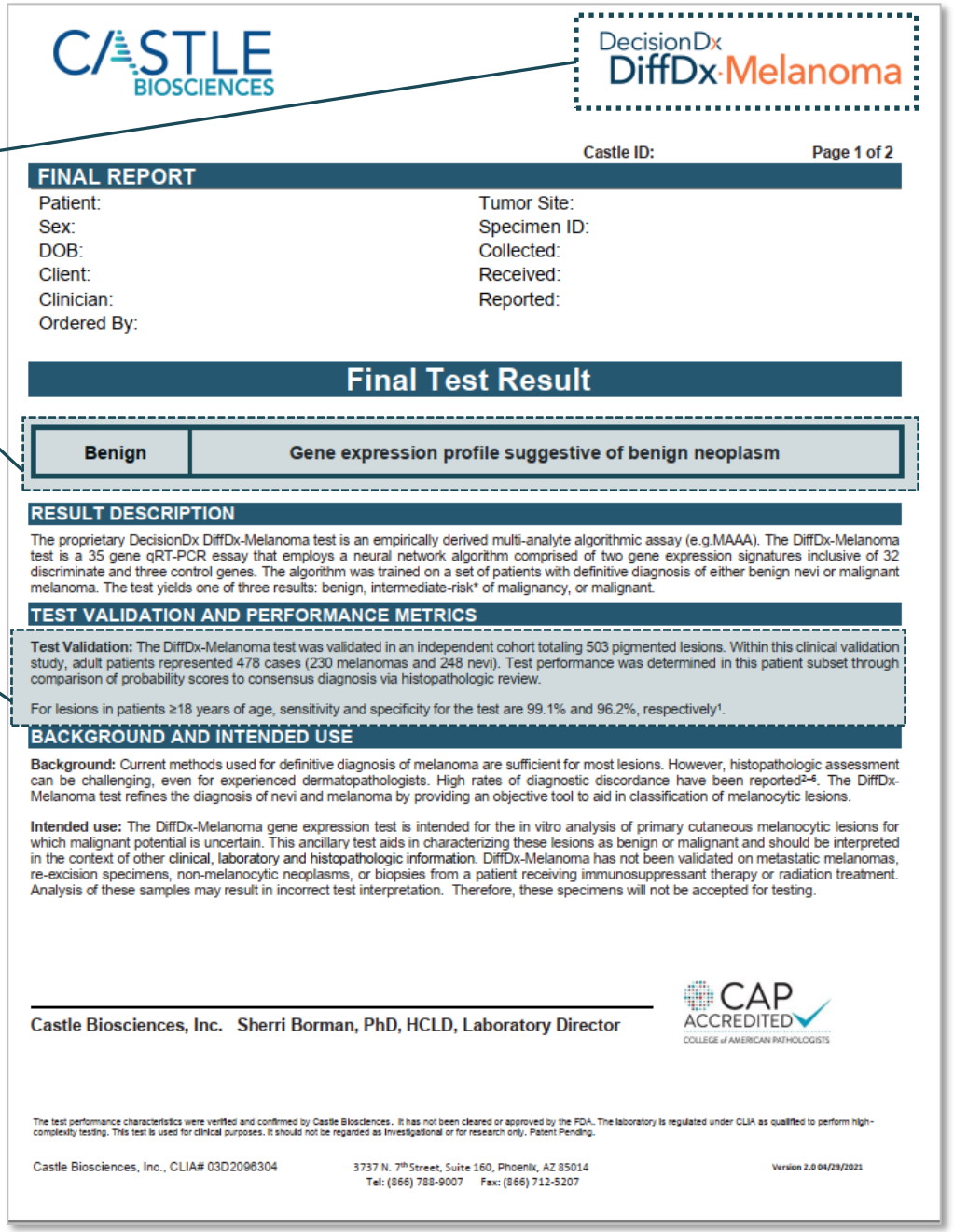
- Validation study included independent cohort of 503 cases
  - Diagnoses of experts
  - Extensive variety of subtypes
  - In patients ≥18 years of age:
    - Sensitivity = 99.1%
    - Specificity = 96.2%

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 BIOSCIENCES

DecisionDx DiffDx-Melanoma

Castle ID: Page 1 of 2

FINAL REPORT

Patient:
Sex:
DOB:
Client:
Clinician:
Ordered By:

Tumor Site:
Specimen ID:
Collected:
Received:
Reported:

Final Test Result

Benign	Gene expression profile suggestive of benign neoplasm

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 essay 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%, respectively[1].

BACKGROUND AND INTENDED USE

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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

myPath Melanoma

DecisionDx DiffDx-Melanoma

Simple Ordering Process

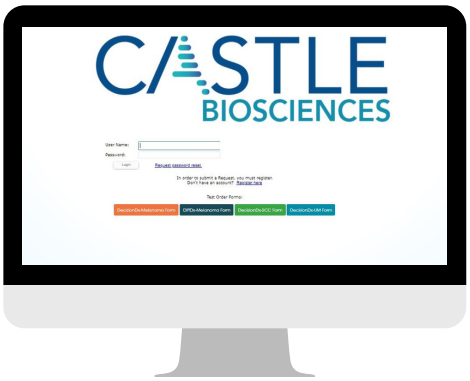
1. **Requisition Form (Completed & Signed)**
   - Hard Copy or Utilize Online Portal
2. **Letter of Medical Necessity (Completed & Signed)**
3. **Pathology Report(Primary Biopsy Specimen)**
   - Include Excision Report if Available
4. **Copy of Patient's Insurance Information**

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

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