*NEW i31-GEP INTEGRATED TEST RESULT FOR LIKELIHOOD OF SLN POSITIVITY WITH EXPANDED DATA COHORT*

# DecisionDx-MELANOMA HCP Guide to the Patient Report

## Personalized Risk Prediction Beyond Clinicopathologic Factors

### DecisionDx-Melanoma Class Result

| | |
|---|---|
| **Class 1A** | **Lowest risk** of recurrence and/or metastasis within 5 years |
| **Class 1B/2A** | **Increased risk** of recurrence and/or metastasis within 5 years |
| **Class 2B** | **Highest risk** of recurrence and/or metastasis within 5 years |

*SLNB positivity information now on page 2*

### 5-Year Outcomes

**NEW Expanded validation cohort** (total n=1,477) for 5-year outcomes from published meta-analysis (Greenhaw et al. *JAAD* 2020).

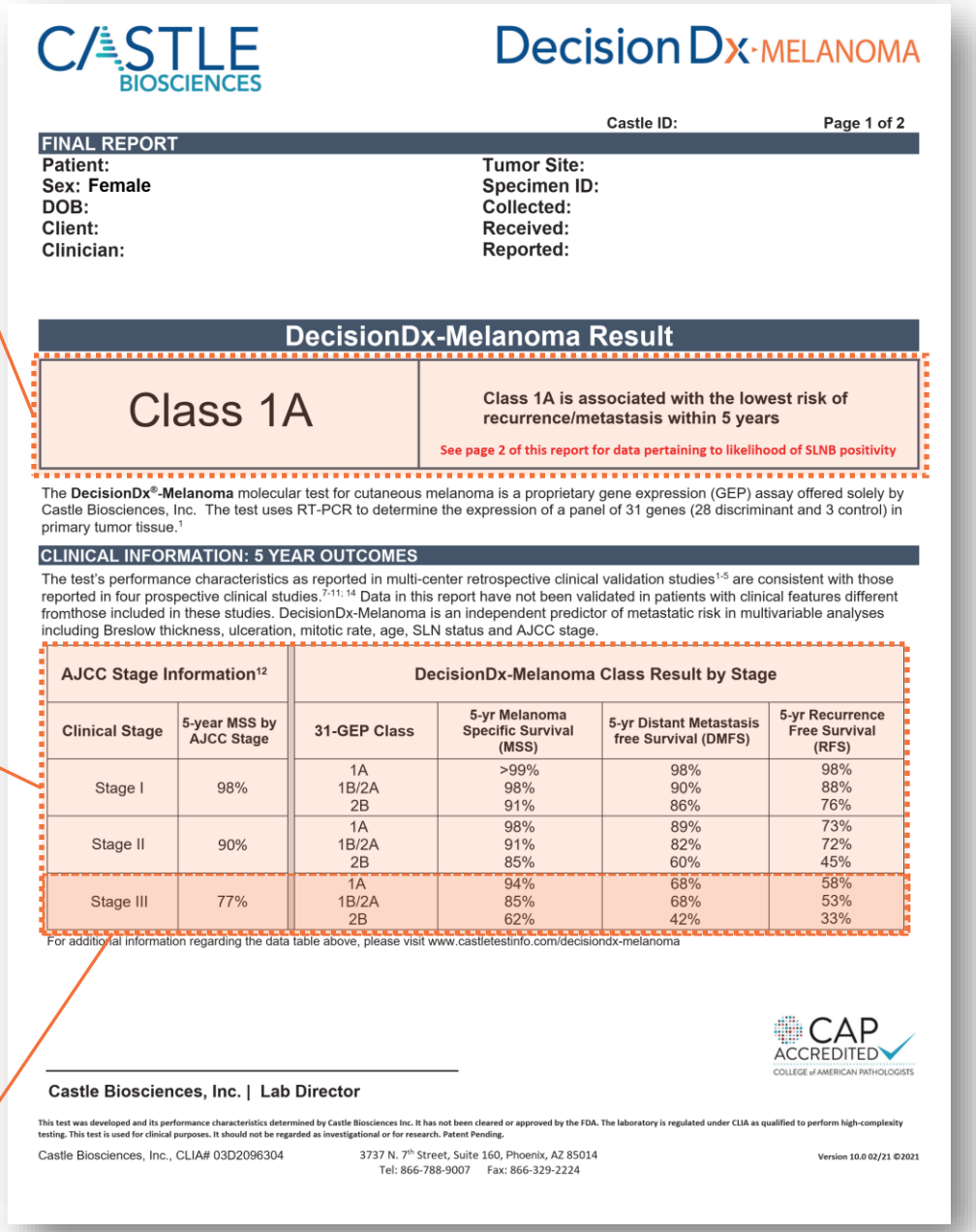
- Includes 4 independent patient cohorts
- DecisionDx-Melanoma is an **independent predictor of metastatic risk** in multivariate analyses including Breslow thickness, ulceration, mitotic rate, age, SLN status and AJCC stage.

**NEW MSS, DMFS and RFS risk prediction** provided by AJCC clinical stage for each DecisionDx-Melanoma class result.

- DecisionDx-Melanoma class **refines risk estimates** for survival when compared to AJCC v8.
- **Significant difference** between lowest risk (Class 1A) and highest risk (Class 2B) for all stages and all outcomes.
- For reference, the table now includes 5-year MSS by AJCC stage.

### Stage III Clinical Experience (n=312)

Now includes Class Result sub-classification (A/B)



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**FINAL REPORT**

| | |
|---|---|
| **Patient:** | **Tumor Site:** |
| **Sex: Female** | **Specimen ID:** |
| **DOB:** | **Collected:** |
| **Client:** | **Received:** |
| **Clinician:** | **Reported:** |

**DecisionDx-Melanoma Result**

| | |
|---|---|
| Class 1A | Class 1A is associated with the lowest risk of recurrence/metastasis within 5 years<br>See page 2 of this report for data pertaining to likelihood of SLNB positivity |

The **DecisionDx®-Melanoma** molecular test for cutaneous melanoma is a proprietary gene expression (GEP) assay offered solely by Castle Biosciences, Inc. The test uses RT-PCR to determine the expression of a panel of 31 genes (28 discriminant and 3 control) in primary tumor tissue.[1]

**CLINICAL INFORMATION: 5 YEAR OUTCOMES**

The test's performance characteristics as reported in multi-center retrospective clinical validation studies[1-5] are consistent with those reported in four prospective clinical studies.[7-11; 14] Data in this report have not been validated in patients with clinical features different fromthose included in these studies. DecisionDx-Melanoma is an independent predictor of metastatic risk in multivariable analyses including Breslow thickness, ulceration, mitotic rate, age, SLN status and AJCC stage.

| AJCC Stage Information[12] | | DecisionDx-Melanoma Class Result by Stage | | | |
|---|---|---|---|---|---|
| Clinical Stage | 5-year MSS by AJCC Stage | 31-GEP Class | 5-yr Melanoma Specific Survival (MSS) | 5-yr Distant Metastasis free Survival (DMFS) | 5-yr Recurrence Free Survival (RFS) |
| Stage I | 98% | 1A | >99% | 98% | 98% |
| | | 1B/2A | 98% | 90% | 88% |
| | | 2B | 91% | 86% | 76% |
| Stage II | 90% | 1A | 98% | 89% | 73% |
| | | 1B/2A | 91% | 82% | 72% |
| | | 2B | 85% | 60% | 45% |
| Stage III | 77% | 1A | 94% | 68% | 58% |
| | | 1B/2A | 85% | 68% | 53% |
| | | 2B | 62% | 42% | 33% |

For additional information regarding the data table above, please visit www.castletestinfo.com/decisiondx-melanoma

CAP ACCREDITED COLLEGE of AMERICAN PATHOLOGISTS

Castle Biosciences, Inc. | Lab Director

This test was developed and its performance characteristics determined by Castle Biosciences Inc. 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. Patent Pending.

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# DecisionDx-MELANOMA HCP Guide to the Patient Report

## Personalized Risk Prediction Beyond Clinicopathologic Factors

**NEW Integrated Test Result** incorporating clinicopathologic factors with the 31-GEP continuous score to provide **precise, personalized likelihood of positive SLNB**.

- Artificial intelligence-based neural network algorithm (i31-GEP)
- Independently validated in patients with T1-T4 cutaneous melanoma.
- Algorithm was developed in 1,398 patients and validated in 1,674 consecutively tested patients.

### DecisionDx-Melanoma Class Result

31-GEP Score (range 0-1)

**Class 1A:** Lowest risk 0-0.41
**Class 1B/2A:** Increased risk >0.41 to <0.59
**Class 2B:** Highest risk 0.59-1.0

### Patient-Specific Clinicopathologic Factors

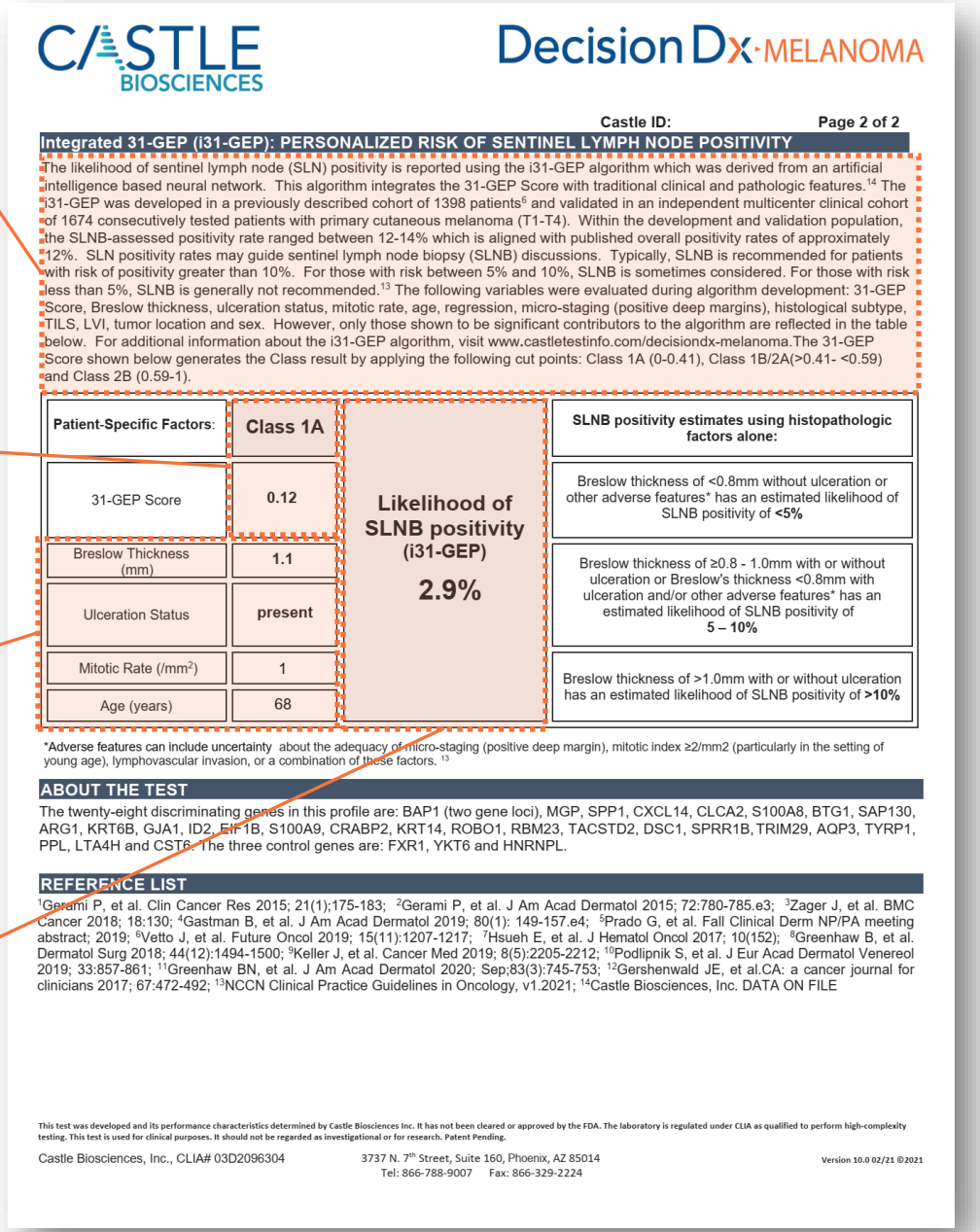
Castle populates algorithm using information from the pathology report(s) submitted with the tissue to be tested.

### Likelihood of SLNB positivity (%)

- The newly validated algorithm (i31-GEP) integrates the DecisionDx-Melanoma 31-GEP score (range 0-1) with clinicopathologic factors to provide a more precise and personalized SLN positivity risk prediction.

- Guidelines suggest:
  - <5% likelihood: avoid SLNB
  - 5-10% likelihood: discuss and consider SLNB
  - >10% likelihood: recommend SLNB

More information about the Integrated Test Result (i31-GEP)
**www.CastleTestInfo.com/DecisionDx-Melanoma**



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**Integrated 31-GEP (i31-GEP): PERSONALIZED RISK OF SENTINEL LYMPH NODE POSITIVITY**

The likelihood of sentinel lymph node (SLN) positivity is reported using the i31-GEP algorithm which was derived from an artificial intelligence based neural network. This algorithm integrates the 31-GEP Score with traditional clinical and pathologic features.[14] The i31-GEP was developed in a previously described cohort of 1398 patients[6] and validated in an independent multicenter clinical cohort of 1674 consecutively tested patients with primary cutaneous melanoma (T1-T4). Within the development and validation population, the SLNB-assessed positivity rate ranged between 12-14% which is aligned with published overall positivity rates of approximately 12%. SLN positivity rates may guide sentinel lymph node biopsy (SLNB) discussions. Typically, SLNB is recommended for patients with risk of positivity greater than 10%. For those with risk between 5% and 10%, SLNB is sometimes considered. For those with risk less than 5%, SLNB is generally not recommended.[13] The following variables were evaluated during algorithm development: 31-GEP Score, Breslow thickness, ulceration status, mitotic rate, age, regression, micro-staging (positive deep margins), histological subtype, TILS, LVI, tumor location and sex. However, only those shown to be significant contributors to the algorithm are reflected in the table below. For additional information about the i31-GEP algorithm, visit www.castletestinfo.com/decisiondx-melanoma.The 31-GEP Score shown below generates the Class result by applying the following cut points: Class 1A (0-0.41), Class 1B/2A(>0.41- <0.59) and Class 2B (0.59-1).

| Patient-Specific Factors: | Class 1A |
|---|---|
| 31-GEP Score | 0.12 |
| Breslow Thickness (mm) | 1.1 |
| Ulceration Status | present |
| Mitotic Rate (/mm²) | 1 |
| Age (years) | 68 |

**Likelihood of SLNB positivity (i31-GEP)**
**2.9%**

| SLNB positivity estimates using histopathologic factors alone: |
|---|
| Breslow thickness of <0.8mm without ulceration or other adverse features* has an estimated likelihood of SLNB positivity of **<5%** |
| Breslow thickness of ≥0.8 - 1.0mm with or without ulceration or Breslow's thickness <0.8mm with ulceration and/or other adverse features* has an estimated likelihood of SLNB positivity of **5 – 10%** |
| Breslow thickness of >1.0mm with or without ulceration has an estimated likelihood of SLNB positivity of **>10%** |

*Adverse features can include uncertainty about the adequacy of micro-staging (positive deep margin), mitotic index ≥2/mm2 (particularly in the setting of young age), lymphovascular invasion, or a combination of these factors. [13]

**ABOUT THE TEST**

The twenty-eight discriminating genes in this profile are: BAP1 (two gene loci), MGP, SPP1, CXCL14, CLCA2, S100A8, BTG1, SAP130, ARG1, KRT6B, GJA1, ID2, EIF1B, S100A9, CRABP2, KRT14, ROBO1, RBM23, TACSTD2, DSC1, SPRR1B, TRIM29, AQP3, TYRP1, PPL, LTA4H and CST6. The three control genes are: FXR1, YKT6 and HNRNPL.

**REFERENCE LIST**

[1]Gerami P, et al. Clin Cancer Res 2015; 21(1);175-183; [2]Gerami P, et al. J Am Acad Dermatol 2015; 72:780-785.e3; [3]Zager J, et al. BMC Cancer 2018; 18:130; [4]Gastman B, et al. J Am Acad Dermatol 2019; 80(1): 149-157.e4; [5]Prado G, et al. Fall Clinical Derm NP/PA meeting abstract; 2019; [6]Vetto J, et al. Future Oncol 2019; 15(11):1207-1217; [7]Hsueh E, et al. J Hematol Oncol 2017; 10(152); [8]Greenhaw B, et al. Dermatol Surg 2018; 44(12):1494-1500; [9]Keller J, et al. Cancer Med 2019; 8(5):2205-2212; [10]Podlipnik S, et al. J Eur Acad Dermatol Venereol 2019; 33:857-861; [11]Greenhaw BN, et al. J Am Acad Dermatol 2020; Sep;83(3):745-753; [12]Gershenwald JE, et al.CA: a cancer journal for clinicians 2017; 67:472-492; [13]NCCN Clinical Practice Guidelines in Oncology, v1.2021; [14]Castle Biosciences, Inc. DATA ON FILE



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