Empowering people, **informing** care decisions

March 23, 2026

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Forward Looking Statements

This presentation contains forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended, which are subject to the "safe harbor" created by those sections. These forward-looking statements include, but are not limited to, statements concerning: our positioning for continued growth and value creation; our estimated U.S. total addressable market for our commercially available tests; our ongoing studies generating data and their impact on driving adoption of our tests; study observations and interpretations of study data, including conclusions about the benefits and impact of our tests on treatment decisions and patient outcomes; our ability to advance penetration of our tests with clinicians and payers; our ability to carry out our commercial strategies; our future approach to capital allocation; pipeline opportunities to expand screening and diagnostic support for patients; our test volume growth strategy and expectations; our ability to maintain strong adjusted gross margin and a strong balance sheet; and the timing and achievement of program milestones. The words "anticipates," "can," "could," "estimates," "expects," "may," "potential," "target" and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. We may not actually achieve the plans, intentions, or expectations disclosed in our forward-looking statements and you should not place undue reliance on our forward-looking statements. Actual results or events could differ materially from the plans, intentions and expectations disclosed in the forward-looking statements that we make. These forward-looking statements involve risks and uncertainties that could cause our actual results to differ materially from those in the forward-looking statements, including, without limitation: our estimates and assumptions underlying our estimated U.S. total addressable market for our commercially available tests; our assumptions or expectations regarding continued reimbursement for our products and subsequent coverage decisions; Novitas' local coverage determination signifying non-coverage by Medicare of our DecisionDx-SCC test; our estimated total addressable markets for our products and product candidates; the expenses, capital requirements and potential needs for additional financing; the anticipated cost, timing and success of our product candidates; our plans to research, develop and commercialize new tests; our ability to successfully integrate new businesses, assets, products or technologies acquired through acquisitions or developed through collaborations; the effects of macroeconomic events and conditions, including inflation and monetary supply shifts, tariffs and disruptions to trade, labor shortages, liquidity concerns at, and failures of, banks and other financial institutions or other disruptions in the banking system or financing markets and recession risks, supply chain disruptions, outbreaks of contagious diseases and geopolitical events (such as the ongoing conflicts in the Middle East and Ukraine-Russia conflict), among others, on our business and our efforts to address its impact on our business; the possibility that subsequent study or trial results and findings may contradict earlier study or trial results and findings or may not support the results discussed in this presentation, including with respect to the diagnostic and prognostic tests discussed in this presentation; our planned installation of additional equipment and supporting technology infrastructures and implementation of certain process efficiencies may not enable us to increase the future scalability of our TissueCypher Test; the possibility that actual application of our tests may not provide the anticipated benefits to patients; the possibility that our newer gastroenterology and mental health franchises may not contribute to the achievement of our long-term financial targets as anticipated; and the risks set forth under the heading "Risk Factors" in our Annual Report on Form 10-K for the year ended December 31, 2025, and our subsequent Quarterly Reports on Form 10-Q, each filed or to be filed with the SEC, and in our other filings with the SEC. The forward-looking statements are applicable only as of the date on which they are made, and we do not assume any obligation to update any forward-looking statements, except as may be required by law.

Speakers/Agenda

J. Michael Guenther, M.D., Surgical Oncologist
St. Elizabeth Physicians, Edgewood, Kentucky

Study Co-author

Matthew Goldberg, M.D. Dermatologist/ Dermatopathologist and Senior Vice President, Medical, Castle Biosciences

Agenda

Dr. Goldberg:

- Early- stage melanoma decision making
- DecisionDx-Melanoma:
  - Answers two important clinical questions
  - Prospective validation data
- DECIDE study introduction

Dr. Guenther:

- Review of DECIDE study results as published in *Future Oncology*

- Q&A

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DecisionDx Melanoma®

Dr. Matthew Goldberg

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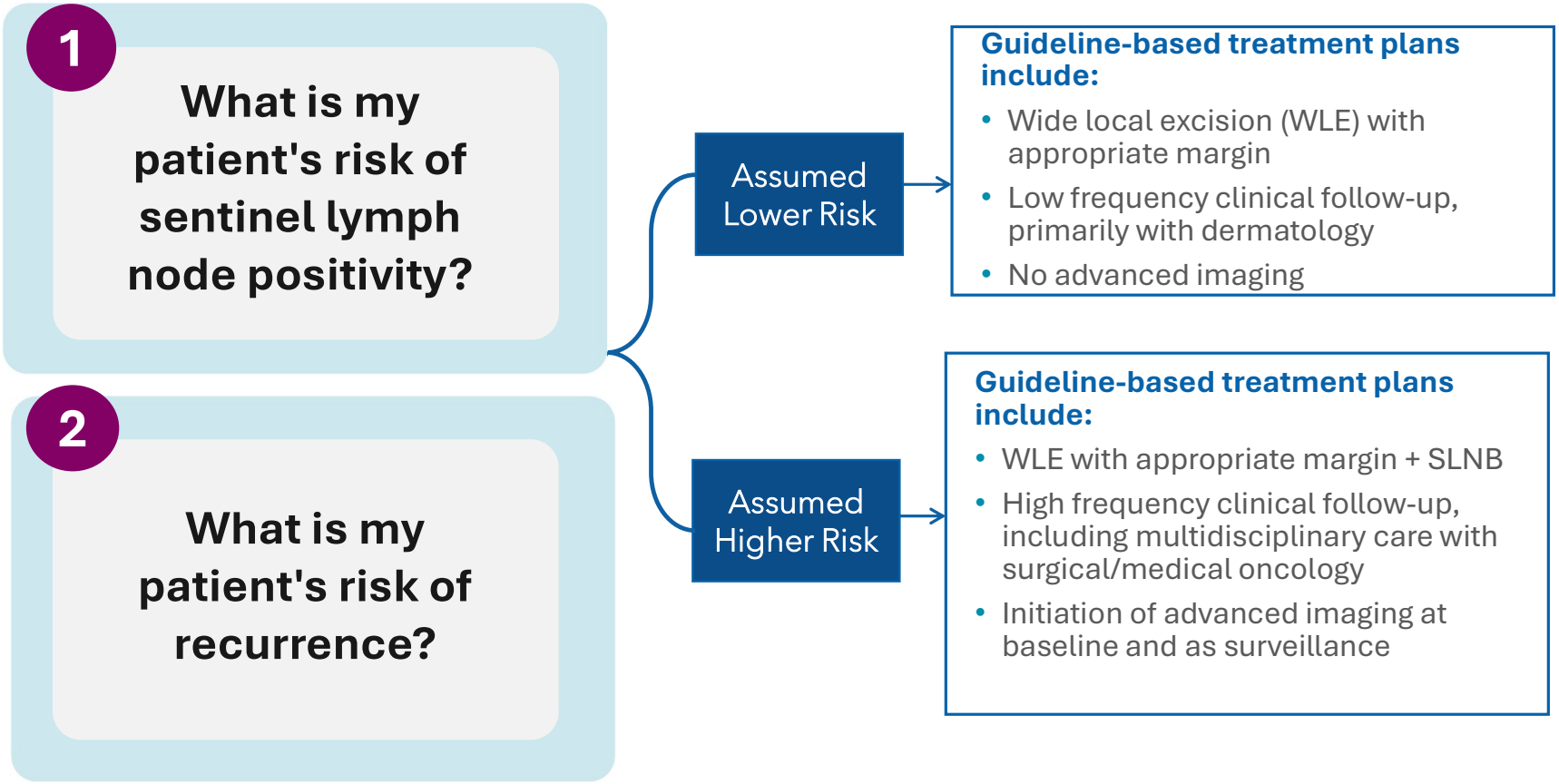
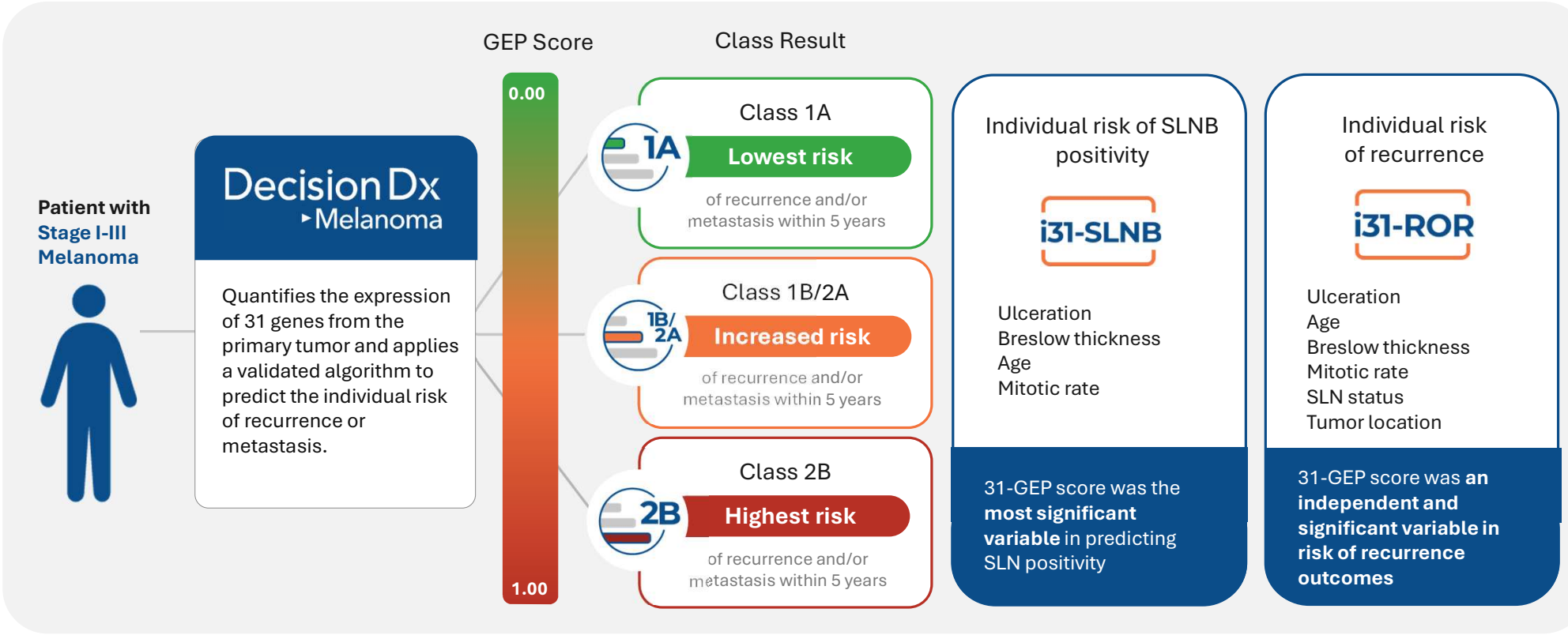
Traditionally, staging and clinicopathology factors answer two key treatment questions following diagnosis of cutaneous melanoma



Adapted from Pathak S and Puckett Y. Cutaneous Malignant Melanoma: Guideline-Based Management and Interprofessional Collaboration. *StatPearls*. 2026.
SLN(B)=sentinel lymph node (biopsy)

DecisionDx-Melanoma uses tumor biology to assess a patient's risk

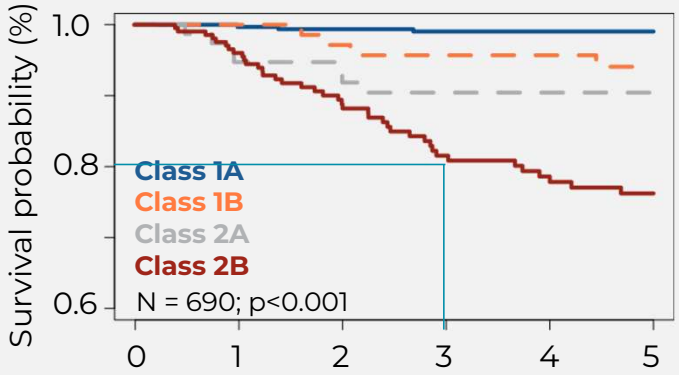


Gerami et al. Clin Cancer Res 2015; Hsueh et al. JCO PO 2021; Bailey et al. JCO PO 2023; Yamamoto et al. CMRO 2023; Guenther et al. Cancer Med. 2025; Jarell et al. JAAD 2022; Whitman et al. JCO PO 2021; Kriza et al. WJSO 2024; Guenther et al. WJSO 2025; Beard et al. Future Oncology 2026
SLN(B)=sentinel lymph node (biopsy) GEP=Gene Expression Profiling

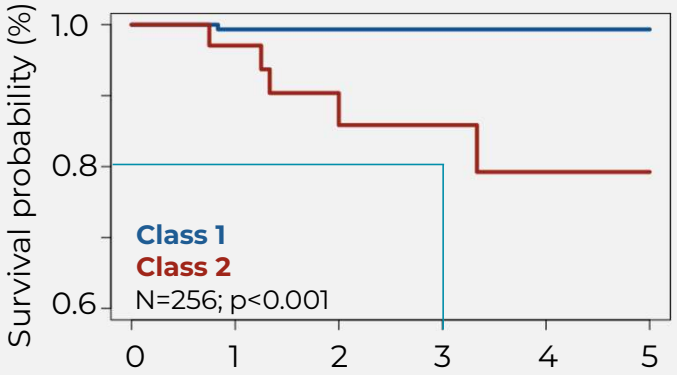
DecisionDx-Melanoma demonstrates validated risk stratification

DecisionDx Melanoma

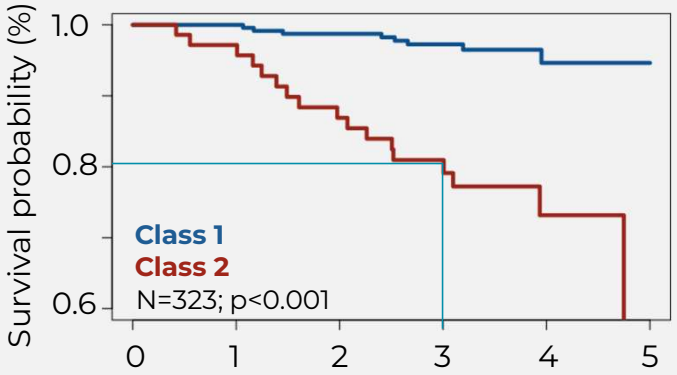
Gastman, 2019 - MSS



Greenhaw, 2018 - MSS



Hsueh, 2021 - OS



Risk stratification across retrospective and prospective studies

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Gastman et al. *JAAD*. 2019, Greenhaw et al. *Dermatologic Surgery*. 2018, Hsueh et al. JCO *Precis Oncol*. 2021.

Patients who receive DecisionDx-Melanoma testing show improved survival compared to those not tested

32% **Lower 3-year melanoma-specific mortality rate** in patients clinically tested vs untested

Melanoma-specific survival	Hazard ratio (95% CI)	P-value
Untested, 2016-2019	Reference	--
31-GEP tested, 2016-2019	**0.68 (0.57-0.81)**	**<0.001**

Key takeaways from this data

- In a large, real-world cohort of clinically tested stage I-III CM patients, **the 31-GEP effectively stratified mortality risk within AJCC sub-stage groups**
- The 31-GEP demonstrated **significant prognostic value for MSS beyond traditional CP factors**
- The 31-GEP is the **only GEP test in melanoma associated with improved survival**

Hasanov et al. Presented at ASCO 2025

Current guidelines for SLNB patient selection

Stage	SLN+Risk	SLNB Eligible
T1a	<5%	***No***
T1a-HR* **T1b**	5-10%	***Discuss and Consider***
T2a **T2b** **T3** **T4**	>10%	***Discuss and Offer***

Guidelines† recommend that the SLNB procedure can be avoided for patients with an expected risk of <5%

To safely forego the SLNB procedure, any test must demonstrate an ability to predict SLN positivity with a risk of <5%.

†NCCN Guidelines for Melanoma v1.2026, ASCO/SSO Guidelines for Sentinel Lymph Node Biopsy 2017, AAD Guidelines for Melanoma 2018; 1 Morton *NEJM.* 2014; 2 Ellis *Am J Surg.* 2010; 3 Bamboat *Ann Surg Oncol.* 2014; 4 Joyce Ir *J Med Sci.* 2017, 5 Chen et al. *Oncotarget.* 2016.

DecisionDx-Melanoma i31-SLNB result can accurately stratify risk

Key clinical objectives evaluated in the DECIDE study:

1. Prospectively confirm the performance of the i31-SLNB result in predicting sentinel lymph node (SLN) positivity
2. Evaluate real-world use of the i31-SLNB result to guide SLNB decisions
3. Assess recurrence outcomes among patients with <5% i31-SLNB predicted risk, who did not undergo SLNB

Study design:

31-GEP testing

Patient/Physician Decision
(Evaluating both Class call & i31-SLNB result)

Study visit 1:
Informed consent
- Melanoma Dx within 2 months
- Age ≥18 years
- Considering SLNB
- Ordering 31-GEP to guide SLNB decision

→

Study visit 2:
31-GEP and/or
i31-SLNB result

→

Study visit 3:
SLNB decision
- SLNB
- No SLNB

→

Track clinical outcomes
- SLN positivity rates
- RFS, DMFS, and MSS outcomes in <5% risk patients

Beard et al. *Future Oncol* 2026

Beard T, Guenther JM, Leong SP, et al. The integrated 31-gene expression profile test identifies low-risk patients with cutaneous melanoma who can forego the SLNB procedure: results from a prospective, multicenter trial. *Future Oncol.* Published online March 13, 2026.
doi: https://doi.org/10.1080/14796694.2026.2640227

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Dr. J Michael Guenther

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Review of publication data from DECIDE: a prospective, multicenter clinical utility study

Beard T, Guenther JM, Leong SP, et al. The integrated 31-gene expression profile test identifies low-risk patients with cutaneous melanoma who can forego the SLNB procedure: results from a prospective, multicenter trial. *Future Oncol.* Published online March 13, 2026.
doi: https://doi.org/10.1080/14796694.2026.2640227

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DecisionDx-Melanoma i31-SLNB result accurately stratifies risk

In a prospective, multicenter study, the test accurately predicts both SLN positivity and identifies low-risk patients who can forgo an SLNB

Key clinical objectives evaluated in the DECIDE study:

1. Prospectively confirm the performance of the i31-SLNB result in predicting sentinel lymph node (SLN) positivity
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→

Study visit 3:
SLNB decision
- SLNB
- No SLNB

→

Track clinical outcomes
- SLN positivity rates
- RFS, DMFS, and MSS outcomes in <5% risk patients

Beard et al. *Future Oncology* 2026

Patient demographics: n=912

	All Patients (n=912)
Age, years, median (range)	65 (20-90)
Breslow thickness, mm, median (range)	0.8 (0.1-12)
Transected base, n (%)	
Absent[a]	526 (57.7%)
Yes	386 (42.3%)
SLN status assessed, n (%)	430 (47.1%)
Negative	386 (89.8%)
Positive	44 (10.2%)
SLN not performed, n (%)	482 (52.9%)
T stage, n (%)	
T1a[b]	335 (36.7%)
T1b	330 (36.2%)
T2a	162 (17.8%)
T2b	24 (2.6%)
T3a	23 (2.5%)
T3b	16 (1.8%)
T4a	7 (0.8%)
T4b	15 (1.6%)

	All Patients (n=912)
Ulceration present	
Absent	814 (89.3%)
Present	82 (9.0%)
Unknown	16 (1.8%)
Mitotic rate (/mm^2), median (range)	1 (0-26)
i31-SLN predicted risk, n (%)	
<5%	474 (52.0%)
5-10%	294 (32.2%)
>10%	144 (15.8%)

Beard et al. Future Oncology 2026

[a]Includes patients with other clinicopathologic features leading the clinician to consider an SLNB.

[b]All patients with T1a tumors had high-risk features or other concerns that led their clinician to consider SLNB for the patient.

DECIDE Study Results: Predicting SLNB Positivity

A subset analysis of **Stage IB (T1b-T2a)**

DecisionDx-Melanoma (i31-SLNB)

Beard et al. *Future Oncology* 2026

Patient Population	SLN Positivity %*
Low Risk by GEP	1.4%
High Risk by GEP	18.5%

13.2x higher SLN positivity

A subset analysis of patients with **Stage IB disease** demonstrates that DecisionDx-Melanoma can identify....

- **Low risk patients** well below the **5% NCCN low-risk threshold**
- **High risk patients** that are **~13x more likely to have a positive node**

Beard et al. SSO Annual Conference 2026. Phoenix, AZ.

*Low risk for DecisionDx-Melanoma defined as <5% i31-SLNB score & high risk defined as ≥10%

Comparing two prospective SLNB trials (DECIDE vs MERLIN_001)

A subset analysis of **Stage IB (T1b-T2a)**

Patient Population	DecisionDx-Melanoma (i31-SLNB) Beard et al. *SSO Annual Conference 2026.* SLN Positivity %*	CP-GEP Heiken et al., *JAMA Surg.* 2025 SLN Positivity %
Low Risk by GEP	1.4%	6.5%
High Risk by GEP	18.5%	18.3%
	13.2x higher SLN positivity	2.8x higher SLN positivity

A subset analysis of patients with **Stage IB disease** demonstrates that DecisionDx-Melanoma can identify....

- **Low risk patients** well below the **5% NCCN low-risk threshold**
- **High risk patients** that are **~13x more likely to have a positive node**

Beard et al. *SSO Annual Conference 2026.* Phoenix, AZ., Adapted from Heiken et al., *JAMA Surgery* 2025
*Low risk for DecisionDx-Melanoma defined as <5% i31-SLNB score & high risk defined as ≥10%

DECIDE study showed up to 13-fold difference in predicting SLNB positivity rates between lowest and highest categories

Decision Dx Melanoma

SLN positivity rates by i31-SLNB result				
	<5%	5-10%	>10%	Fold Difference <5% vs. >10%
T1-T4 % SLN+	2.6%	7.0%	21.4%	8x higher
T1b-T2a % SLN+	1.4%	7.4%	18.5%	13x higher

Patients with <5% predicted risk had very low SLN positivity

Patients with >10% predicted risk had 8-13x higher SLN positivity

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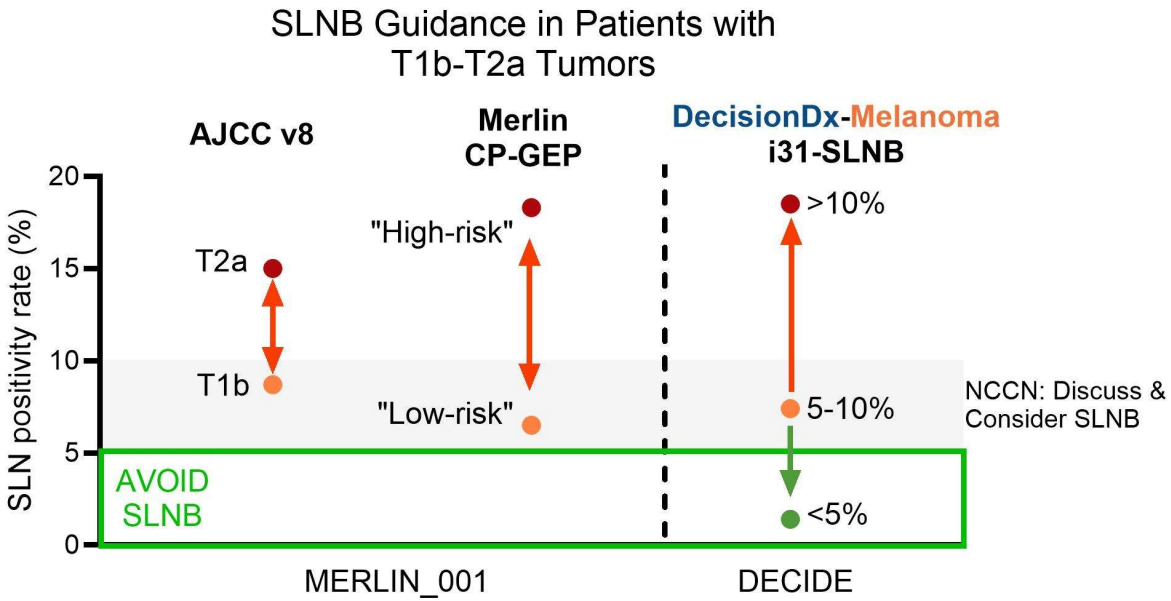
Beard et al. *Future Oncology* 2026, Beard et al. *SSO Annual Conference 2026*. Phoenix, AZ.

DecisionDx-Melanoma can identify patients with T1b-T2a tumors who can avoid a SLNB

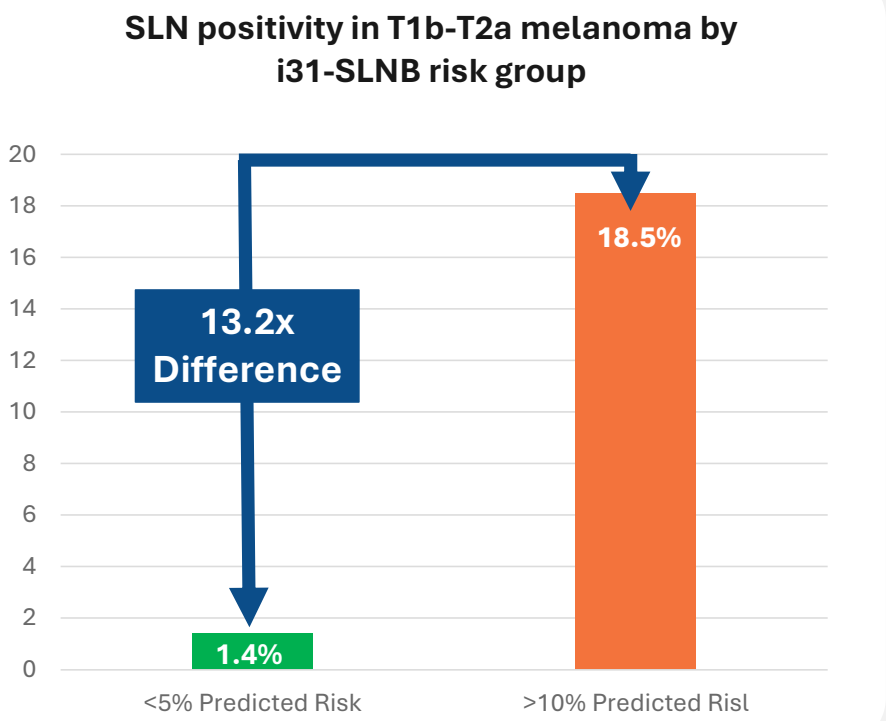


The i31-SLNB result provided superior risk stratification because…

- **It can more precisely identify truly high-risk patients**
  - Patients with an i31-SLNB score >10% have a markedly higher likelihood of SLN positivity.
- **It can identify a truly low-risk (<5%) population**
  - Identifying patients below a <5% SLN-positivity threshold allows clinicians to **confidently consider forgoing SLNB**, rather than placing low risk patients in the "discuss and consider" category

Adapted from: Beard et al. *Future Oncology* 2026, Heiken et al. *JAMA Surgery* 2025

DecisionDx-Melanoma can accurately predict SLN positivity in T1b-T2a patients



~13x higher SLN positivity

in T1b-T2a patients with a >10% predicted risk compared to patients with a <5% predicted risk.

Beard et al. *SSO Annual Conference 2026.* Phoenix, AZ.

<5% Predicted Risk (1/74); >10% Predicted Risk (12/65)

DecisionDx-Melanoma i31-SLNB can accurately identify low-risk patients who can forgo SLNB than AJCC staging alone

Risk stratification method	*False-negative Rate*	TN:FN ratio
NCCN SLNB Guidance	5%	19:1
Previously reported combined studies (Prieto et al.)		
CP-GEP T1–T2*	6.2%	15:1
i31-SLNB/31-GEP T1–T2 *	**2.8%**	**34:1**
Beard et al. *Future Oncol.* 2026		
i31-SLNB T1–T4	**2.6%**	**37:1**
i31-SLNB T1–T2a	**1.8%**	**55:1**

Beard et al. is consistent with prior studies demonstrating that the **DecisionDx-Melanoma i31-SLNB result can accurately identify patients at low risk of SLN positivity compared to the use of AJCC staging and other GEP tests.**

*Prieto et al. *Cancer Diagnosis & Prognosis*. 2025.

Beard et al. *Future Oncology* 2026

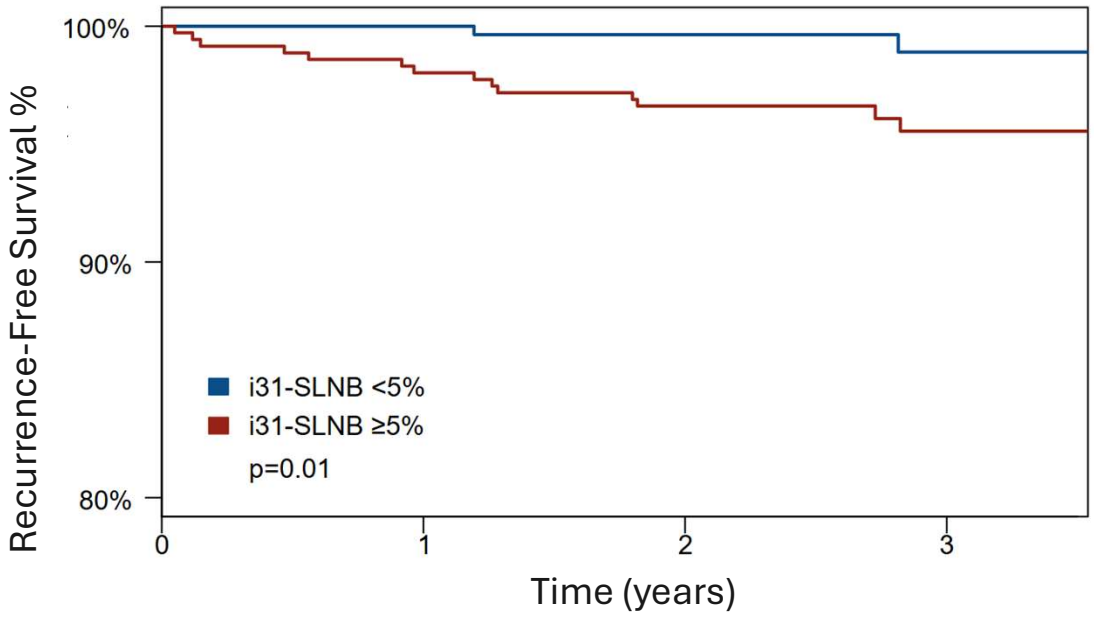
Patients with a low risk DecisionDx-Melanoma result can forego an SLNB

- Patients with a **low-risk i31-SLNB** (<5%) have a low risk of recurrence
  - n=139*

3-year Recurrence Free Survival (RFS) = 97.8%

- Patients with a **high-risk i31-SLNB** (≥5%) have a higher risk of recurrence
  - n=177

3-year Recurrence Free Survival (RFS) = 91.1%



Beard et al. *Future Oncol. 2026*
*102 patients avoided SLNB.
Recurrence-free survival (RFS) definition includes any regional or distant metastasis

Identifying High-Risk Patients in Traditionally Low-Risk Cohorts

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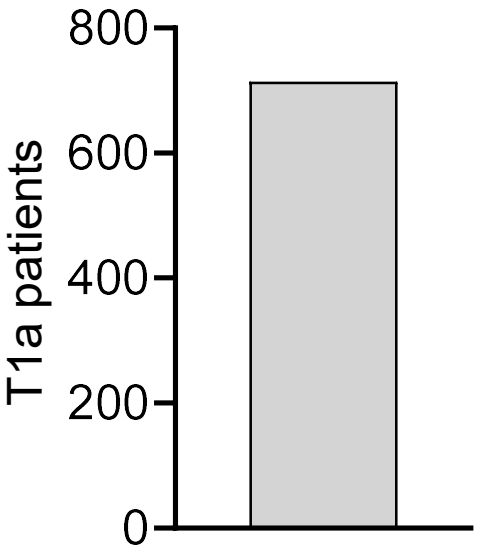
DecisionDx-Melanoma vs CP-GEP: Performance in T1a tumors

Comparing the two largest studies including T1a tumors, DecisionDx-Melanoma identified high-risk patients among T1a tumors and CP-GEP did not.

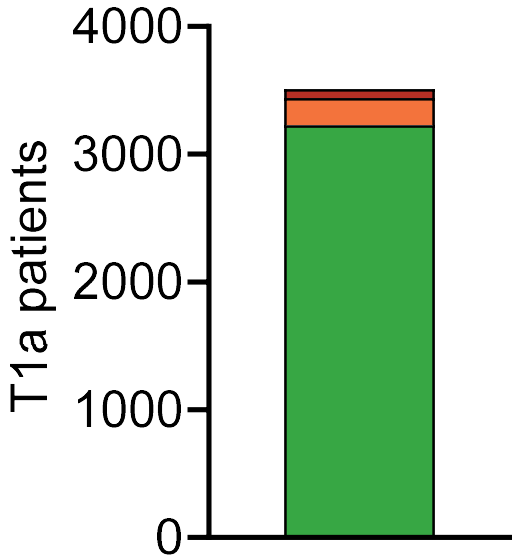
CP-GEP identified **no patients** with T1a tumors as **"high-risk"**

"Low-risk"	714 (100%)
"High-risk"	0 (0%)

CP-GEP
Amaral et al. *EJC* 2025
N = 714



DecisionDx-Melanoma
Joshi et al. *JAAD* 2025
N = 3,512



DecisionDx- Melanoma identified **8% of patients as increased or highest risk.**

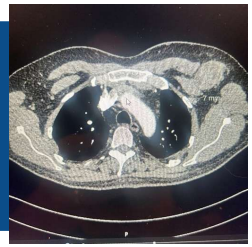
In T1a high-risk tumors, an **intermediate** or **high-risk** score is associated with **5.7x higher risk of death***

*when compared to Class 1A

Joshi et al. *JAAD* 2025, Amaral et al. *EJC 2025*

CASE STUDY

45-year-old male presented with invasive melanoma



DecisionDx Melanoma

FINDINGS

- Breslow depth: 0.4 mm
- Ulceration: Present
- Regression: Present
- Mitotic rate: <1mm^2
- Stage IB (T1b)

MANAGEMENT PLAN

Before GEP testing, the clinician would have followed NCCN guidelines for Stage IB (T1b): Refer for SLNB consult; surgery (i.e. WLE). SLNB result to guide decisions about possible adjuvant therapy.

RATIONALE FOR ORDERING GEP

- Given the patient's thin, ulcerated melanoma (Stage IB, T1b), clinicopathologic factors alone provide limited ability to estimate metastatic risk. The patient fell into the 5-10% SLN+ Risk "discuss and consider" category for SLNB per NCCN guidelines.
- DecisionDx-Melanoma was ordered to provide additional biologic risk stratification, refining risk of metastasis and SLNB positivity beyond clinicopathologic features alone.

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Castle ID: Page 1 of 2

FINAL REPORT

Patient:
Sex:
DOB:
Client:
Provider:
Breslow Thickness:
Age (years):
Ulceration:

Specimen ID:
Collected:
Received:
Reported:
Tumor Site:
Binned Tumor Location:
Nodal Status:
Mitotic Rate (/mm2):

Class 2B
GEP score = 0.91

i31-ROR
MSS: 96.1%
DMFS: 91.1%
RFS: 88.8%

i31-SLNB
19.0%

PAGE 2

i31-ROR Risk Estimates for **SLNB Positive Patients** (5-year AJCC Stage III)

MSS: 93.0% DMFS: 82.1% RFS: 78.8%

IMPACT TO PATIENT CARE

After DecisionDx-Melanoma results

- DecisionDx-Melanoma returned Class 2B (GEP score 0.91), indicating the highest 5-year biologic risk for recurrence and metastasis despite the thin tumor. The i31-SLNB result predicted a 19.0% likelihood of SLNB positivity.
- These results supported a more aggressive clinical approach, reinforcing the decision to pursue SLNB and closer surveillance.

OUTCOME

- SLNB initially demonstrated 1/6 nodes with melanophages, later interpreted as negative on outside pathology review. The patient was lost to follow-up but later re-presented with left axillary adenopathy. After two cycles of immunotherapy, ALND revealed 1/16 nodes positive for melanoma, confirming nodal metastatic disease.
- This case highlights how DecisionDx-Melanoma provides additional biologic insight in thin melanomas traditionally considered lower risk, helping inform more individualized surveillance and guide SLNB referral decisions.

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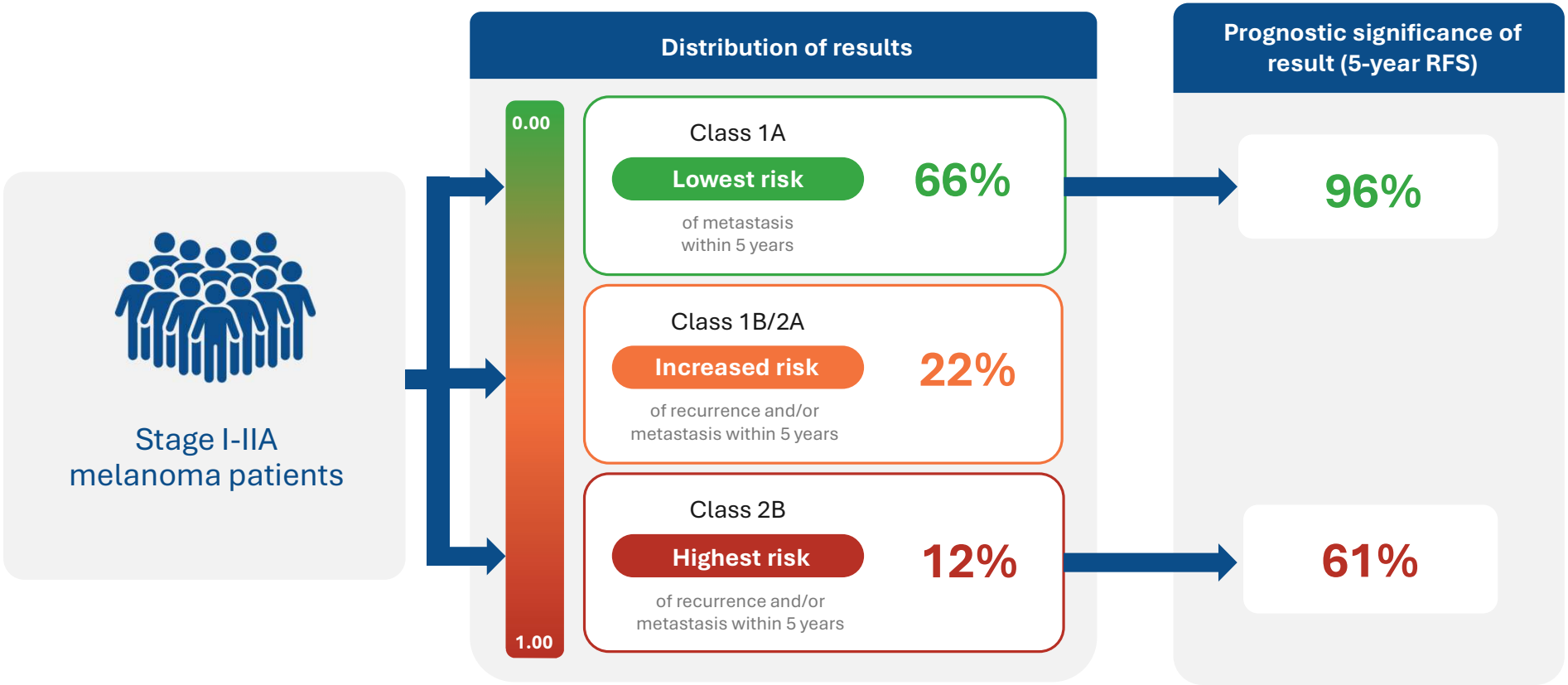
CASE CONTRIBUTED BY: DR. GUENTHER

DecisionDx-Melanoma provides significant risk-stratification to inform management decisions



Gastman et al. *JAAD*. 2019

Prospective data confirm that DecisionDx-Melanoma i31-SLNB result improves SLNB decision-making and supports favorable patient outcomes

Decision Dx Melanoma

1

Accurate risk stratification

Low-risk test results are associated with very low SLNB positive outcomes.

2

Confidence in clinical decision-making

The i31-SLNB gives physicians greater confidence in identifying which patients can avoid SLNB.

3

Favorable patient outcomes

Patients with a <5% i31-SLNB result have **high recurrence-free survival (97.8%) at 3 years**

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Beard et al. *Future Oncology* 2026

Q&A

Dr. Guenther

Dr. Goldberg

Derek Maetzold, Castle Biosciences, CEO

Frank Stokes, Castle Biosciences, CFO

Thank You

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DERMATOLOGY

DecisionDx-Melanoma

Provides comprehensive, personalized, genomic tumor information to guide management for patients with cutaneous melanoma

Clinical Validity, Utility and Demonstrated Patient Outcomes

Demonstrated clinical validity, utility and impact, backed by 58 peer-reviewed publications, including two publications (Bailey et al. 2023 and Dhillon et al. 2023) demonstrating an association with testing and improved patient outcomes

SLNB Guidance and Patient Outcomes[1,2]

DecisionDx-Melanoma successfully identified patients with T1 tumors with a low risk of SLN positivity who can safely forgo SLNB while maintaining high survival rates in a prospective multicenter study and can reduce SLNB-associated complications and healthcare costs.

50%
demonstrated change in management for 1 of 2 patients tested[3]

~231,900
patients with a clinical DecisionDx-Melanoma order from ~16,700 clinicians[4]

~$540M
Estimated U.S. TAM[5]

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1. Marks, The i31-GEP identifies patients with T1 cutaneous melanoma who can safely avoid sentinel lymph node biopsy: Results from a prospective, multicenter study. Video abstract presented at: 2024 American Society for Dermatologic Surgery (ASDS) Annual Meeting; 2. Guenther JM, et al. Patients who forego sentinel lymph node biopsy after 31-GEP testing are not harmed: A prospective, multicenter analysis. Poster presented at: 20th European Association of Dermato-Oncology (EADO) Congress; 3. Dillon et al. 2022; 4. Data as of December 31, 2025; 5. U.S. TAM = Total addressable market based on estimated patient population assuming average reimbursement rate among all payors.

SLN(B)=sentinel lymph node (biopsy)