Genetic Approaches to the Prognosis of Cutaneous Melanoma

Aaron Farberg, MD, FAAD

Bare Dermatology

Baylor Scott & White Health System

UNT Health Science Center

Dallas, Texas

Conflicts of interest

- Investigator and consultant for Castle Biosciences

Outline

- Cutaneous melanoma staging
- Staging and patient management
- 31-gene expression profile test for cutaneous melanoma (31-GEP)
- Incorporating GEP into clinical practice

Precision/Personalized Medicine:
“Finding your unique disease risks and treatments that will work best for you” - CDC

How are patients with cutaneous melanoma currently staged and selected for the different management strategies?

TABLE 6. AJCC Pathological (pTNM) Prognostic Stage Groups[a]

WHEN T IS...	AND N IS...	AND M IS...	THEN THE PATHOLOGICAL STAGE GROUP IS...
Tis	N0[b]	M0	0
T1a	N0	M0	IA
T1b	N0	M0	IA
T2a	N0	M0	IB
T2b	N0	M0	IIA
T3a	N0	M0	IIA
T3b	N0	M0	IIB
T4a	N0	M0	IIB
T4b	N0	M0	IIC
T0	N1b, N1c	M0	IIIB
T0	N2b, N2c, N3b or N3c	M0	IIIC
T1a/b-T2a	N1a or N2a	M0	IIIA
T1a/b-T2a	N1b/c or N2b	M0	IIIB
T2b/T3a	N1a-N2b	M0	IIIB
T1a-T3a	N2c or N3a/b/c	M0	IIIC
T3b/T4a	Any N ≥N1	M0	IIIC
T4b	N1a-N2c	M0	IIIC
T4b	N3a/b/c	M0	IIID
Any T, Tis	Any N	M1	IV

[a]Used with permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original and primary source for this information is the AJCC Cancer Staging Manual, eighth edition (2017) published by Springer International Publishing (Gershenwald JE, Scolyer RA, Hess KR, et al. Melanoma of the skin. In: Amin MB, Edge SB, Greene FL, et al, eds. AJCC Cancer Staging Manual. 8th ed. New York: Springer International Publishing; 2017:563-585[4]). [b]Pathological stage 0 (melanoma in situ) and T1 do not require pathological evaluation of lymph nodes to complete pathological staging; use clinical N information to assign their pathological stage.

Stage IA–IIA NED

- See Common Follow-up Recommendations for All Patients[jjj]
- H&P (with emphasis on nodes and skin)
  - every 6–12 mo for 5 y, then
  - annually as clinically indicated
- Routine blood tests are not recommended
- Routine imaging to screen for asymptomatic recurrence or metastatic disease is not recommended
- Imaging[kkk] as indicated to investigate specific signs or symptoms

Stage IIB–IV NED

- See Common Follow-up Recommendations for All Patients[jjj]
- H&P (with emphasis on nodes and skin)
  - every 3–6 mo for 2 y, then
  - every 3–12 mo for 3 y, then
  - annually as clinically indicated
- Routine blood tests are not recommended
- Imaging[kkk] as indicated to investigate specific signs or symptoms
- Consider imaging[kkk] every 3–12 months for 2 years, then every 6–12 months for another 3 years[nnn] (unless otherwise mandated by clinical trial participation) to screen for recurrence or metastatic disease (category 2B)
- Routine imaging to screen for asymptomatic recurrence or metastatic disease is not recommended after 3–5 years, depending on risk of relapse

Sentinel Lymph Node Biopsy (SLNB)
How are patients currently selected for the SLNB surgical procedure?

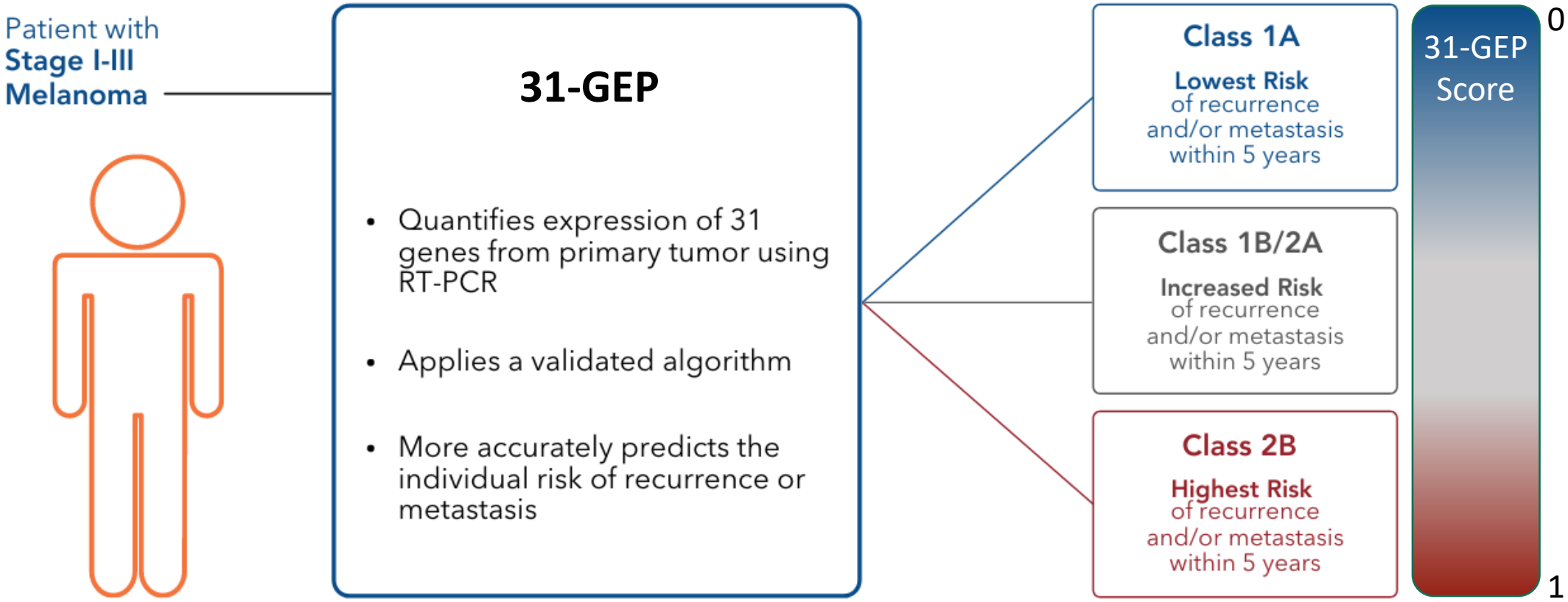
Stage	SLN+ Risk	SLNB Eligibility
T1a	<5%	No
T1a-HR* T1b	5-10%	Eligible (consider or offer)
T2a T2b T3 T4	>10%	

*T1a with High-Risk Features

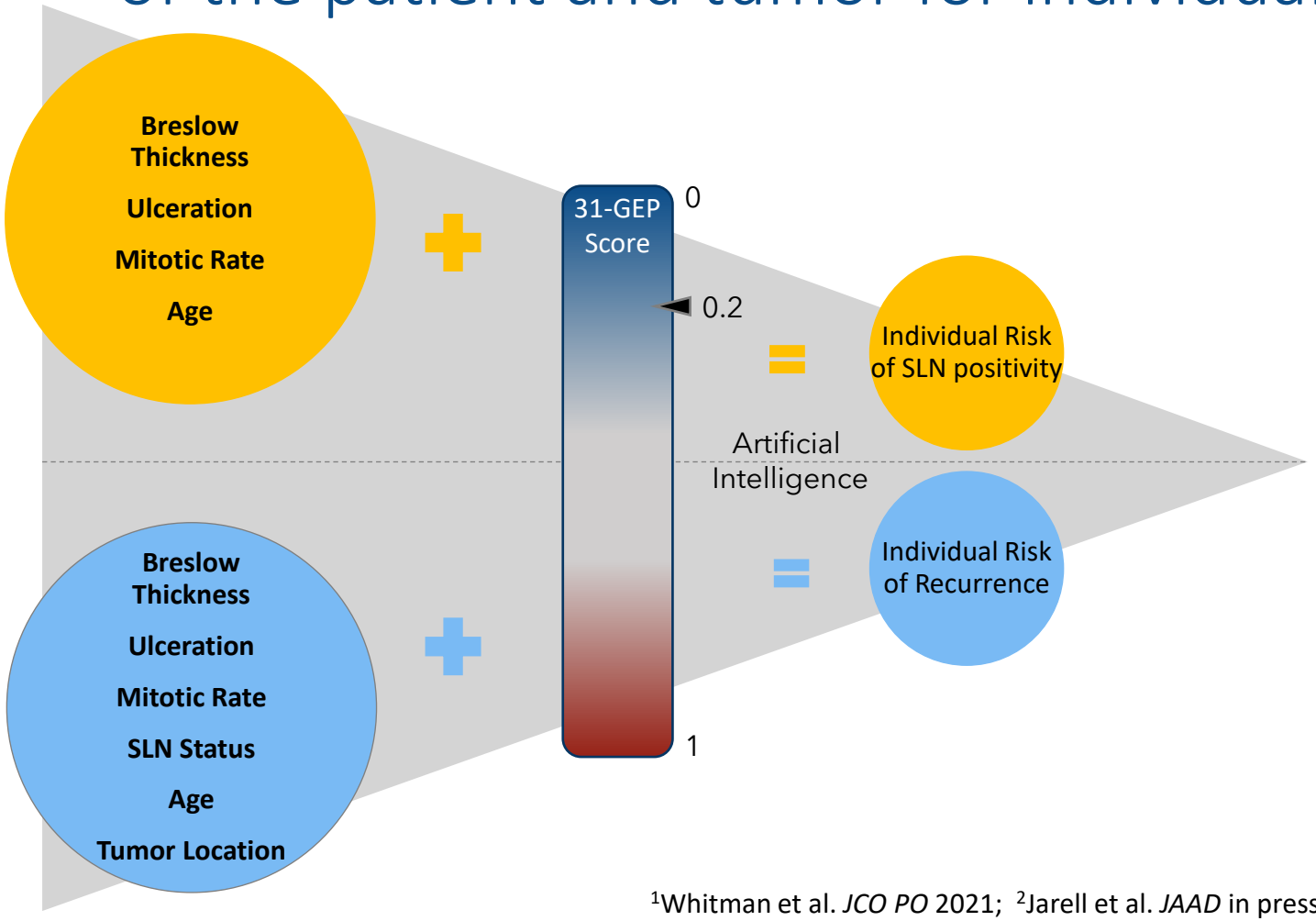
Guidelines† recommend that the SLNB procedure can be considered for patients (T1-T4) with an expected risk of being SLN positive above 5% based on Breslow thickness and ulceration status

†NCCN Guidelines for Melanoma v2.2022, ASCO/SSO Guidelines for Sentinel Lymph Node Biopsy 2017, AAD Guidelines for Melanoma 2018;

The 31-GEP further stratifies patient risk through molecular biology



Combining the validated 31-GEP molecular algorithm with features of the patient and tumor for individualized risk



i31-GEP Clinical Report
Integrated 31-GEP

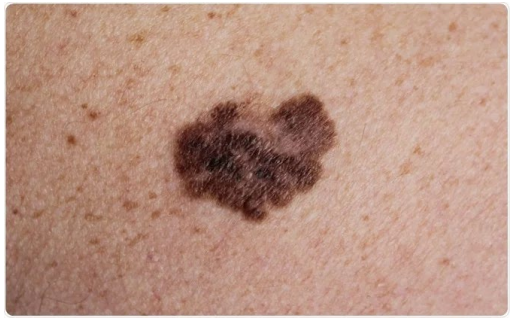
31-GEP score was the most significant variable in predicting SLN positivity[1]

31-GEP score was an independent and significant variable in prognostication for precise RFS, DMFS, and MSS[2]

[1]Whitman et al. *JCO PO* 2021; [2]Jarell et al. *JAAD* in press

NCCN guidelines recognize that a patient's individual risk of recurrence and individual risk of SLN positivity drive management recommendations including SLN biopsy decisions

What are the two initial decision points after diagnosis?

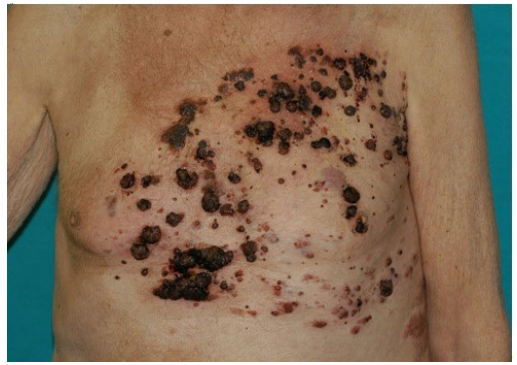


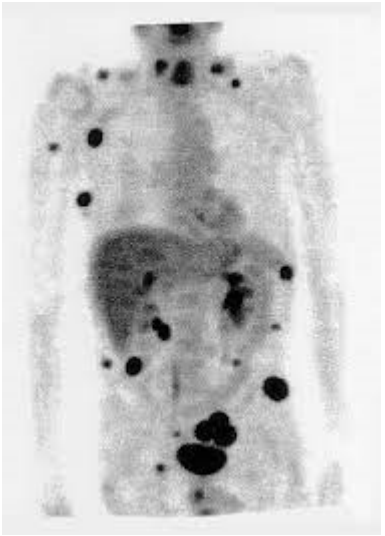
What's the risk for a positive SLN?

Traditionally, tumor thickness and ulceration are used to make this decision.

What's the risk of recurrence (follow up, imaging and referral decisions)?

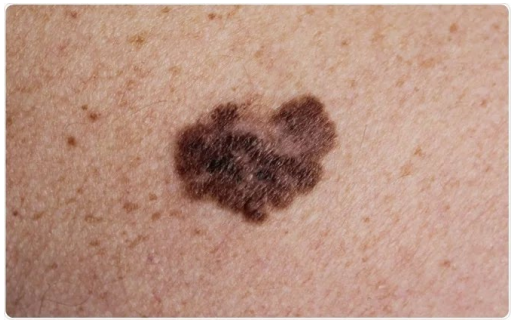
Traditionally, tumor thickness, ulceration, and SLN status are used to make this decision





NCCN guidelines recognize that a patient's individual risk of recurrence should drive management decisions and that a patient's individual risk of SLN positivity drives SLN biopsy recommendations

First, let's focus on sentinel lymph node biopsy

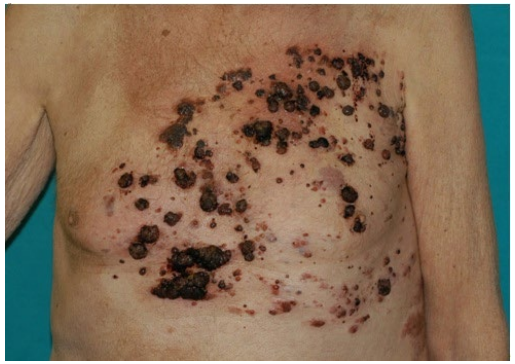


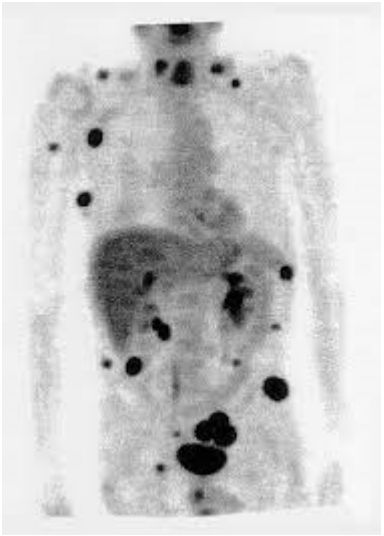
What's the risk for a positive SLN?

Traditionally, tumor thickness and ulceration are used to make this decision.

What's the risk of recurrence (follow up, imaging and referral decisions)?

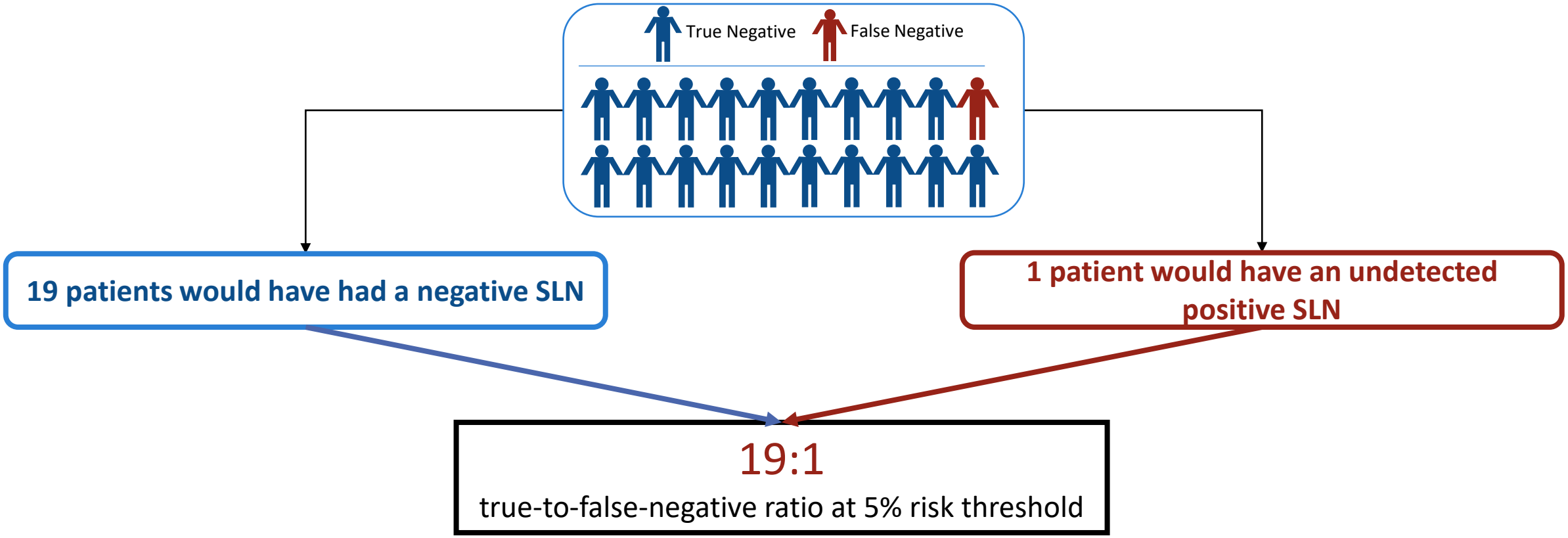
Traditionally, tumor thickness, ulceration, and SLN status are used to make this decision





When discussing SLNB, what does a 5% positivity risk mean?

For every 20 similar patients who are eligible for SLNB, if you do not perform the SLNB…



Any new test must do better than this when selecting patients to forego SLNB!

The i31-GEP for SLNB provides a precise, personalized risk of SLN positivity

B
Th
Ul
Mit

original reports

PRECISION MEDICINE

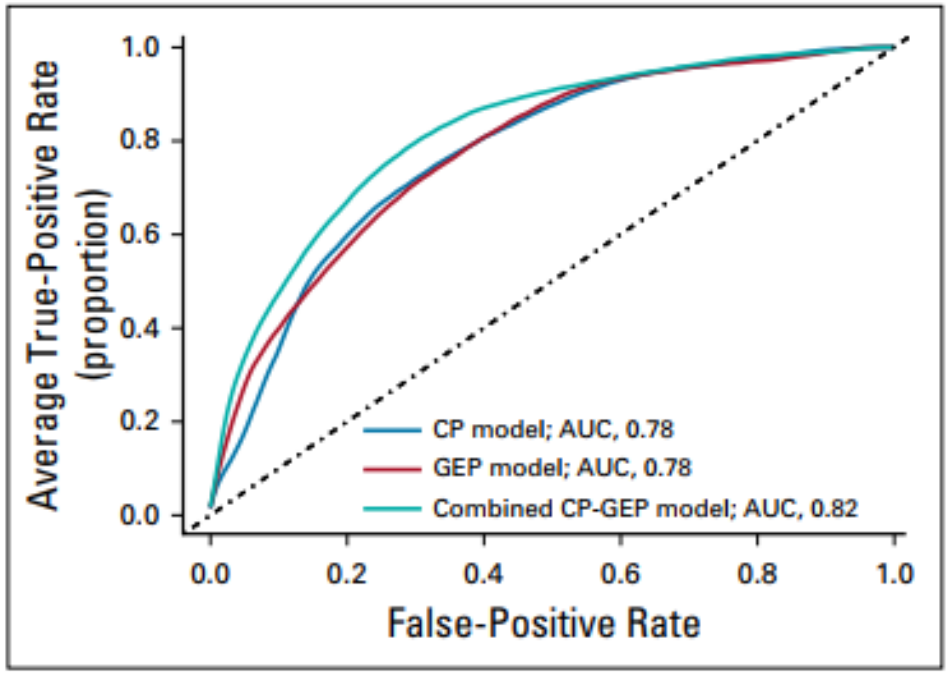
Integrating 31-Gene Expression Profiling With Clinicopathologic Features to Optimize Cutaneous Melanoma Sentinel Lymph Node Metastasis Prediction

Eric D. Whitman, MD[1]; Vadim P. Koshenkov, MD[2]; Brian R. Gastman, MD[3]; Deri Lewis, MD[4]; Eddy C. Hsueh, MD[5]; Ho Pak, MD[6]; Thomas P. Trezona, MD[7]; Robert S. Davidson, MD[8]; Michael McPhee, MD[9]; J. Michael Guenther, MD[10]; Paul Toomey, MD[11]; Franz O. Smith, MD[12]; Peter D. Beitsch, MD[13]; James M. Lewis, MD[14]; Andrew Ward, NP[14]; Shawn E. Young, MD[15]; Parth K. Shah, MD[15]; Ann P. Quick, PhD[16]; Brian J. Martin, PhD[16]; Olga Zolochevska, PhD[16]; Kyle R. Covington, PhD[16]; Federico A. Monzon, MD[16]; Matthew S. Goldberg, MD[16]; Robert W. Cook, PhD[16]; Martin D. Fleming, MD[17]; David M. Hyams, MD[18]; and John T. Vetto, MD[19]

Reduction rate	23.0[a]	32.1
Sensitivity	95.1	89.8
Pretest SLN positivity rate	10.9	8.0
PPV of ≥ 5% risk	14.4	10.6

EP
ual
SLN
vity

The 8-GEP + CP assay has also been developed to identify patients with low risk of SLN positivity



T Category	P	SY	SP	NPV (95% CI)	PPV
T1b	0.03	0.41	0.82	0.98 (0.95 to 1.00)	0.07
T2a	0.13	0.80	0.53	0.95 (0.91 to 0.98)	0.21
T2b	0.17	0.94	0.27	0.96 (0.91 to 1.00)	0.21

The 8-GEP + CP assay uses Breslow thickness and age, combined with 8-genes with a high/low risk cut-off.

However, this GEP test has not shown independent value from other clinical and pathologic factors, which is a critical development limitation.

Can either the 8-GEP + CP assay or the i31-GEP (SLNB) do better than 19:1 true:false negatives?

Test validation cases	8-GEP + CP	i31-GEP (SLNB)
T1b†-T2	187	763

Yousaf et al. had three T1a tumors

i31-GEP validated in 4-fold as many cases

8-GEP + CP		TN	FN
T1b-T2		177	10
Rat /1 1 ratio			

The 8-GEP + CP assay does worse than standard of care!!

i31-GEP (SLNB)	N	TN	FN
T1b-T2	763	154	5
Ratio: 154:5 = 30:1 ratio			

The i31-SLNB outperforms standard of care!!!

Whitman et al. *JCO PO* 2021; Mulder et al *BJD* 2020; Yousaf et al. *IJD* 2021; Johansson et al. *EJSO* 2021

What else could precision risk be used for? Different risk thresholds?

T-category	Risk threshold	Correctly identified as negative	Incorrectly identified as negative	Correctly identified negative SLNB reduced for every missed positive
T1b	5%	105	3	35:1 (vs. 19:1 standard)
T1b	6%	143	3	47:1 (vs. 16.7:1 standard)
T1b	7%	171	3	57:1 (vs. 14.3:1 standard)
T1b	8%	195	5	39:1 (vs 12.5:1 standard)
T1b	9%	215	10	21:1 (vs. 11.1:1 standard)
T1b	10%	223	13	17:1 (vs. 9:1 standard)

What if the risk threshold acceptable to you or your patients is different than 5%? What if it is 6%? 10%?

Binned approaches like the 8-GEP + CP do not allow for this.

Brief Report

ONLINE FIRST

April 27, 2022

Utility of a Model for Predicting the Risk of Sentinel Lymph Node Metastasis in Patients With Cutaneous Melanoma

Michael A. Marchetti, MD[1]; Stephen W. Dusza, DrPH, MPH[1]; Edmund K. Bartlett, MD[2]

» Author Affiliations

JAMA Dermatol. Published online April 27, 2022. doi:10.1001/jamadermatol.2022.0970

Utility of a Model for Predicting the Risk of Sentinel Lymph Node Metastasis in Patients With Cutaneous Melanoma

Table 2. Net Benefit and Relative Utility of the i31-GEP-SLNB Prediction Model Using a 5% Risk Threshold

	SLN biopsy		
T Category	Strategy 1: none[a]	Strategy 2: all[b]	Strategy 3: using i31-GEP SLNB model
Net benefit (95% CI)			
T1a-HR	0	−0.021 (−0.044 to 0.001)	−0.003 (−0.018 to 0.119)
T1b	0	0.005 (−0.019 to 0.030)	0.017 (−0.006 to 0.040)
T2a	0	0.069 (0.037 to 0.100)	0.070 (0.039 to 0.101)
T2b	0	0.081 (0.026 to 0.136)	0.083 (0.025 to 0.142)
Relative utility, % (95% CI)[c]			
T1a-HR	0	NA	NA
T1b	0	9 (0-64)	31 (0-69)
T2a	0	60 (46-73)	61 (48-74)
T2b	0	64 (38-89)	66 (46-85)

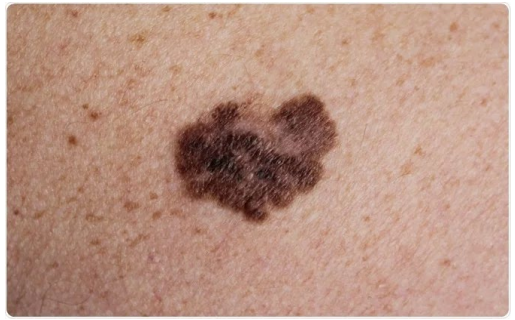
Abbreviations: SLN, sentinel lymph node; T1a-HR, T1a high-risk patients (mitotic index ≥2 mm^2; lymphovascular invasion, absence of tumor infiltrating lymphocytes, age <40 years, microsatellites, regression, or transected base).

[a] The SLN biopsy for none is equivalent to a strategy with 0% sensitivity and 100% specificity.

[b] The SLN biopsy for all is equivalent to a strategy with 100% sensitivity and 0% specificity.

[c] Relative utility is calculated by dividing the net benefit by the maximum achievable utility (prevalence) and ranges from 0% to 100%. In other words, relative utility is the maximum fraction of expected utility achieved by risk prediction compared with perfect prediction. Relative utility allows an assessment of the potential for improved performance with better prediction models.

Now, let's focus on prognosis

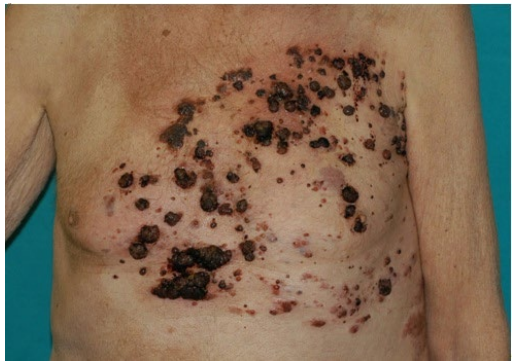


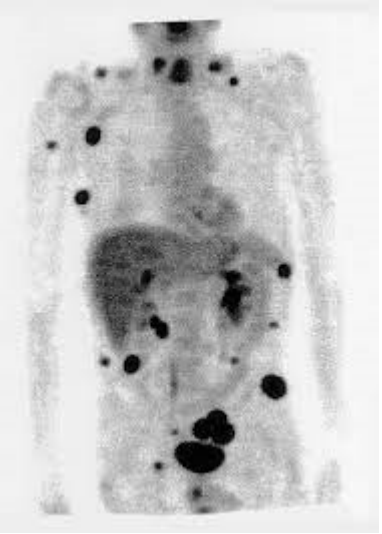
What's the risk for a positive SLN?

Traditionally, tumor thickness and ulceration are used to make this decision.

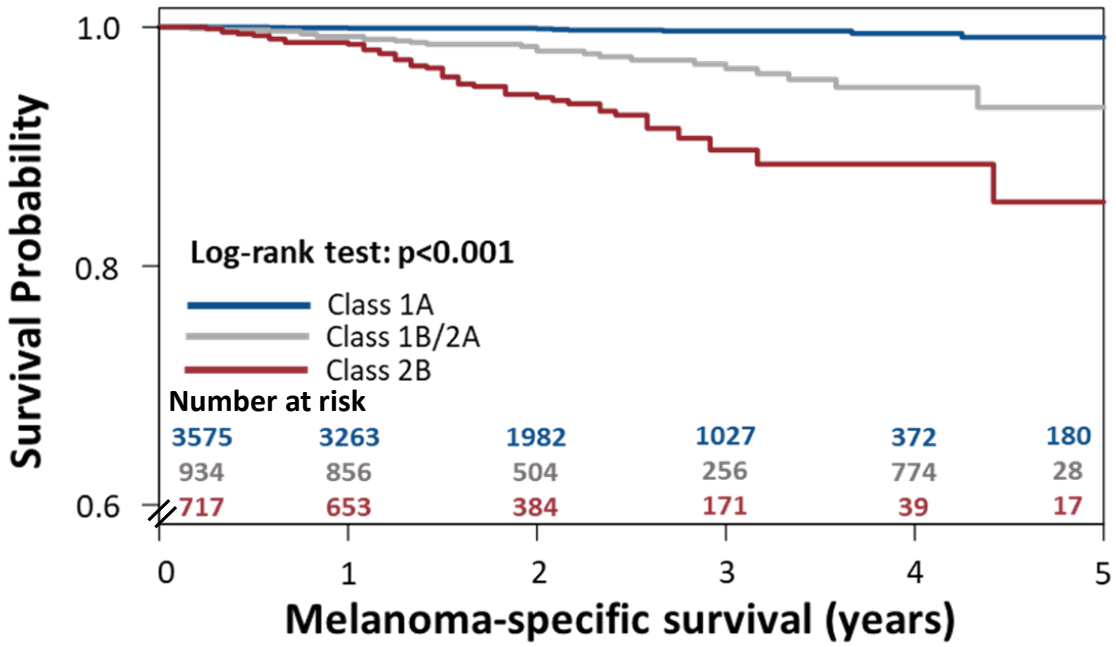
What's the risk of recurrence (follow up, imaging and referral decisions)?

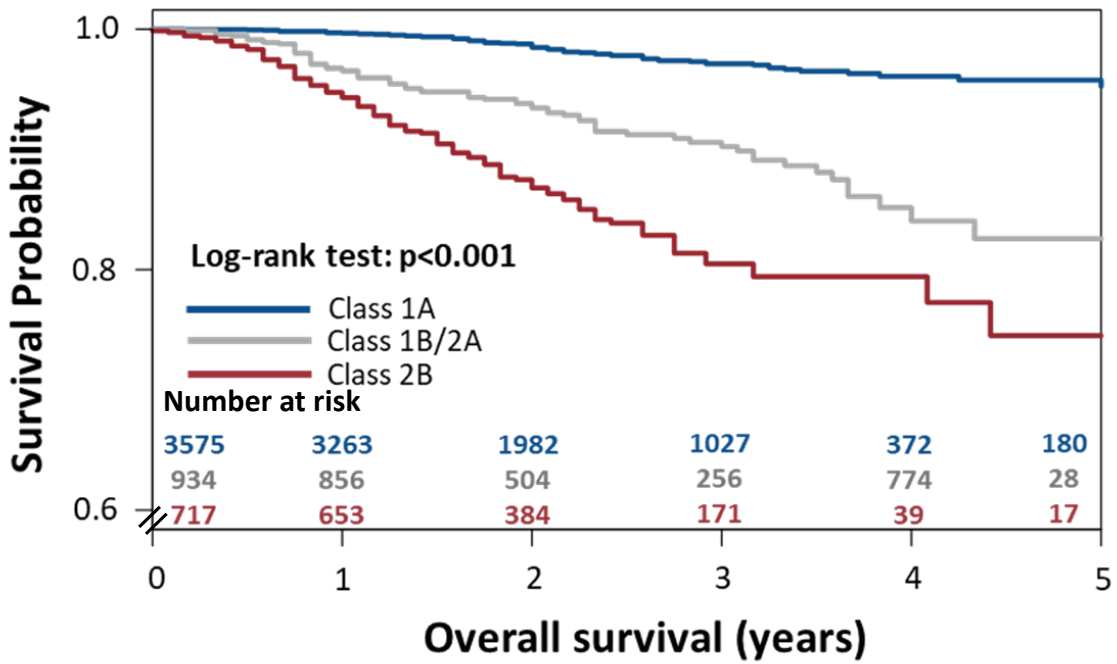
Traditionally, tumor thickness, ulceration, and SLN status are used to make this decision





NCI/SEER cohort of unselected prospectively tested patients confirms previously reported risk stratification for patients with Stage I-III cutaneous melanoma (n=5,226)





The separation of Class 1A, Class 1B/2A, and Class 2B MSS and OS risk in 31-GEP tested patients within the SEER registry mirrors the risk separation in previously reported studies[1,2]

Kurley et al. Presented at EADO, April 21-23, 2022, [1]Gastman et al. *JAAD* 2019, [2]Hsueh et al. *JCO Precis Oncol* 2021

Patients tested with the 31-GEP had higher survival than untested patients at three years

	3-year MSS (95% CI)	Deaths, % (n/N)
31-GEP Tested	97.7% (97.0-98.4%)	1.6% (58/3621)
Matched Untested	96.6% (96.2-97.1%)	2.2% (238/10863)
Hazard ratio‡	0.73 (0.54-0.97)	P=0.028
	3-year OS (95% CI)	**Deaths, % (n/N)**
31-GEP Tested	93.1% (92.0-94.2%)	4.8% (174/3621)
Matched Untested	91.2% (90.4-91.9%)	6.1% (658/10863)
Hazard ratio‡	0.79 (0.67-0.93)	P=0.006

‡Hazard ratio (HR) was computed using the matched untested patients as reference for 31-GEP tested cohort.

DecisionDx-Melanoma Shows Similar or Better Performance When Compared to other Standard of Care Prognostic Tests

MSLT-1 Study[1]:

1. What is the impact of a traditional risk-stratification test (i.e.SLN biopsy)?
   - **MSLT-1 found that SLN biopsy had no impact on 10-year MSS**
   - **DecisionDx-Melanoma had a statistically significant absolute MSS benefit at 3 years over those not tested (p<0.05)**

Tumor size	P-value	10-yr MSS
Thin (<1.2mm)	Not reported	Not impacted
Intermediate (1.2-3.5mm)	not significant (p=.18)	Not impacted
Thick (>3.5)	not significant (p=.56)	Not impacted

Other NCI/SEER collaborative studies[2]

2. How significant is the absolute benefit?
   - NCI/SEER collaborated with OncotypeDx-Breast (ODX) on a similar analysis for use in guiding management decisions in breast cancer.
   - Patients who were tested with OncotypeDx-Breast had improved breast cancer specific-survival (BCSS) compared to untested patients (p<0.05)

	3 yr MSS
31-GEP Tested	97.7%
Matched Untested	96.6%
Absolute Mortality Difference	**1.1% (p<0.05)**

DecisionDx-Melanoma showed absolute MSS mortality difference of 1.1% at 3 years over those not tested

	3 yr BCSS
ODX Tested	99.6%
Matched Untested	99.1%
Absolute Mortality Difference	**0.50% (p<0.05)**

ODX showed absolute BCSS mortality difference of 0.5% at 3 years over those not tested

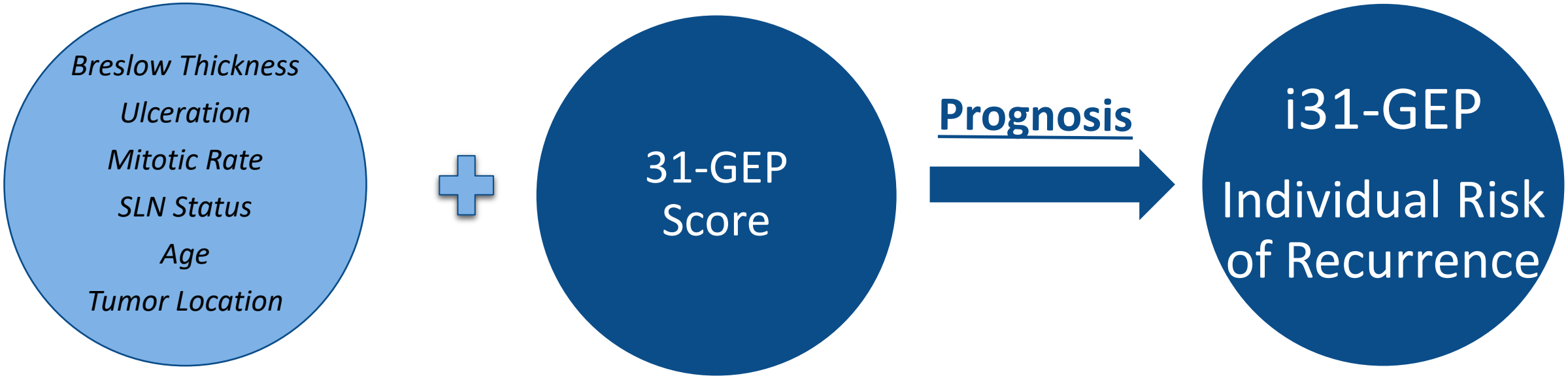
1. Morton et al *N Engl J Med* 2014;370:599-609 2. Zhang et al *Breast Cancer Res Treat*. 2020 April; 180(2): 491-501.

31-Gene Expression Profile Testing and outcomes prognostication

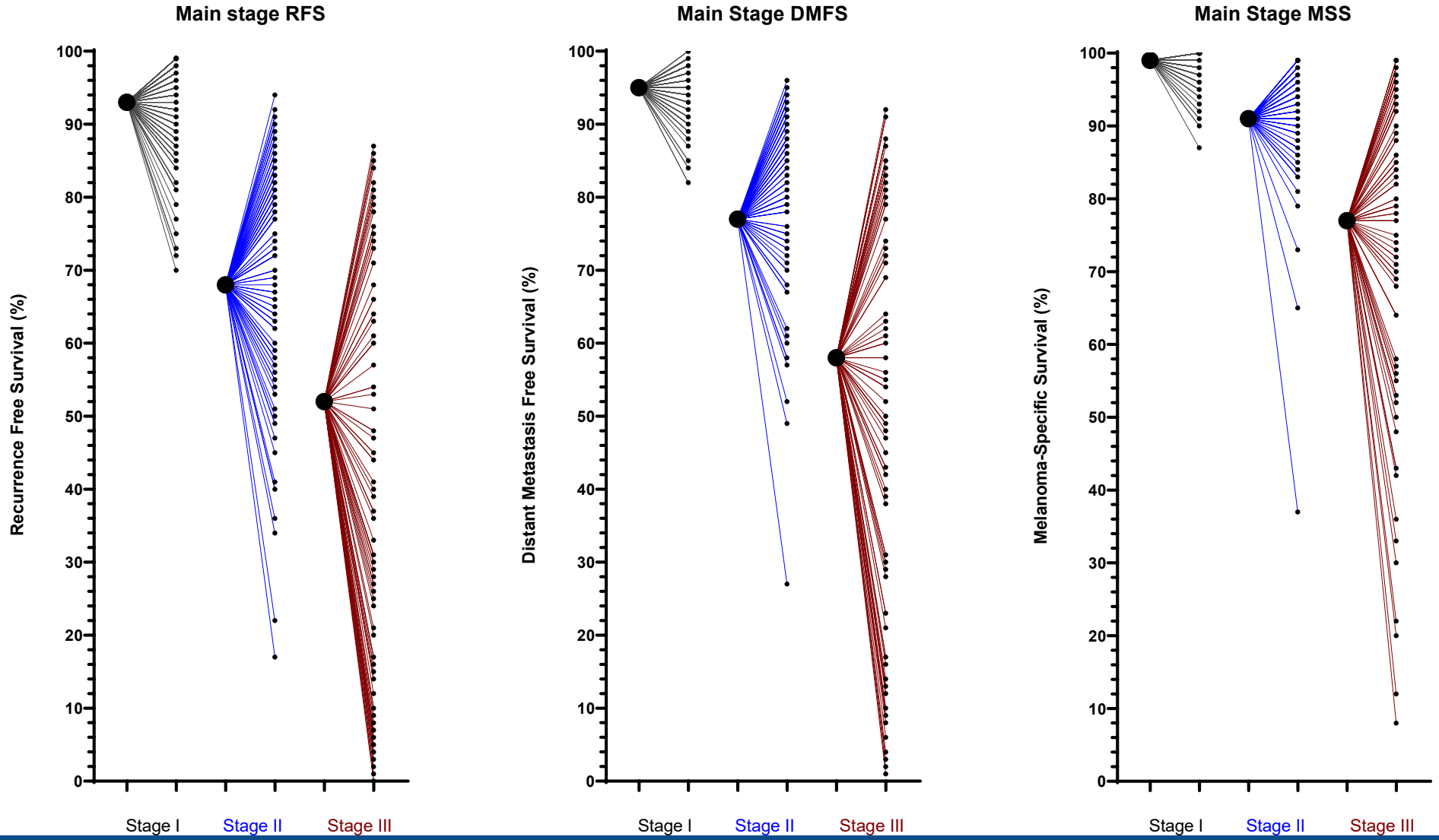
Can we get more even MORE PRECISE???

Added precision for outcomes assessment:

Integrating the 31-GEP score with clinicopathologic factors in a validated AI driven algorithm for precise, personalized risk and survival outcomes prediction

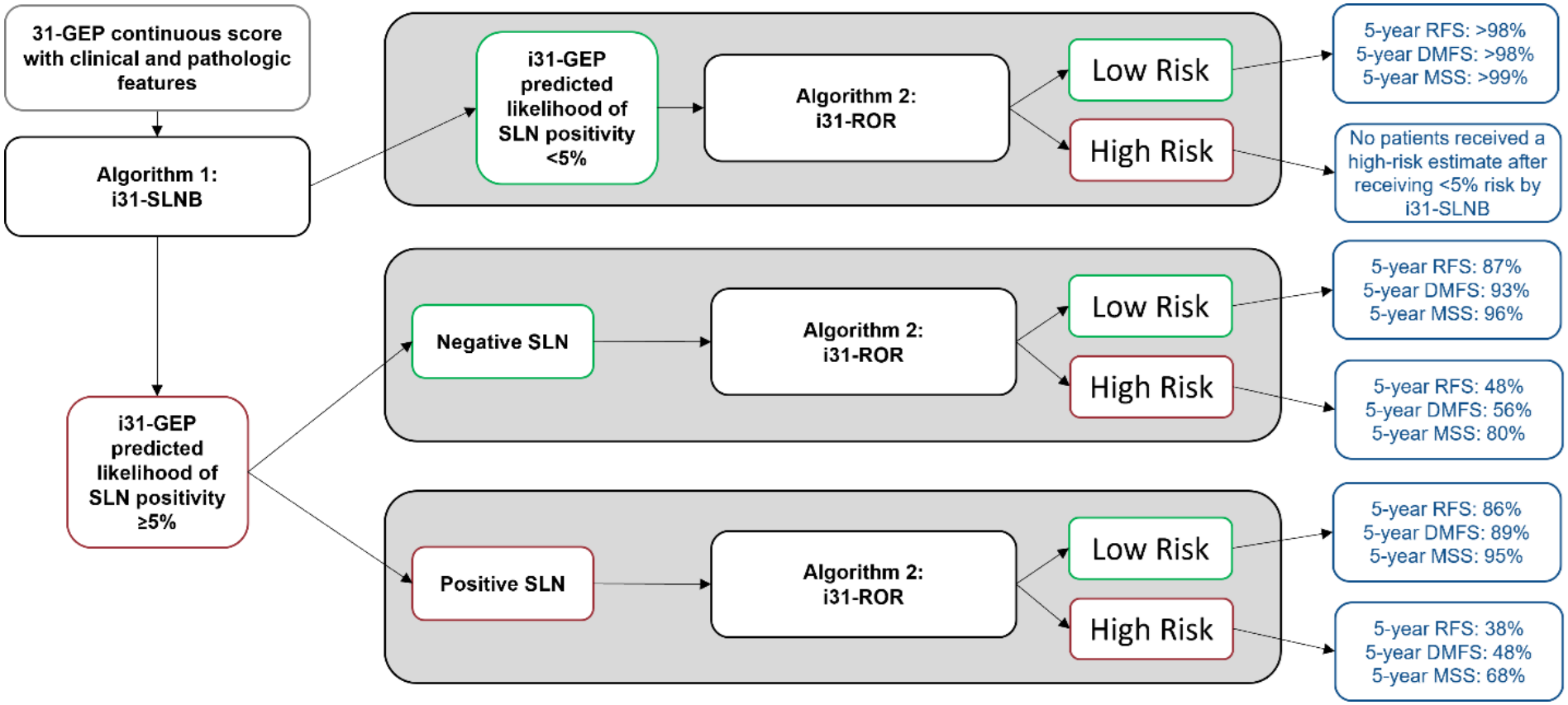


The i31-ROR allows for patient/clinician discussion about acceptable risk before management changes.



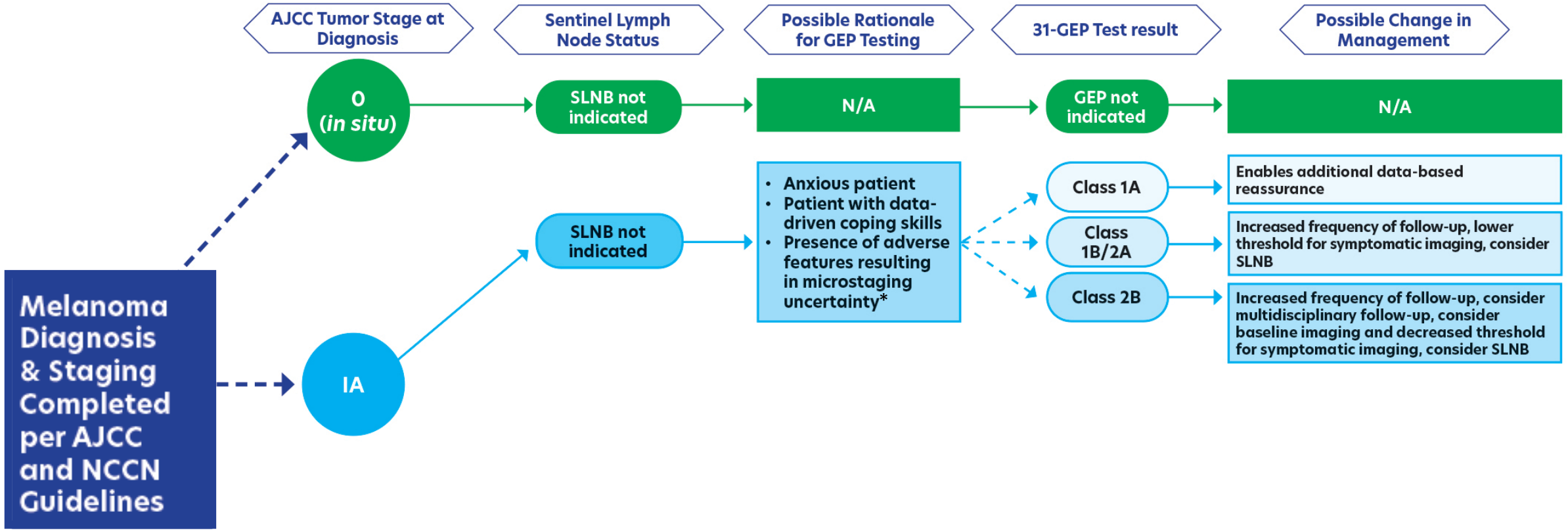
Jarell et al. *JAAD* in press

Combining the i31-SLNB and i31-ROR for a more comprehensive prognostic approach



How should I use the 31-GEP in the clinic?

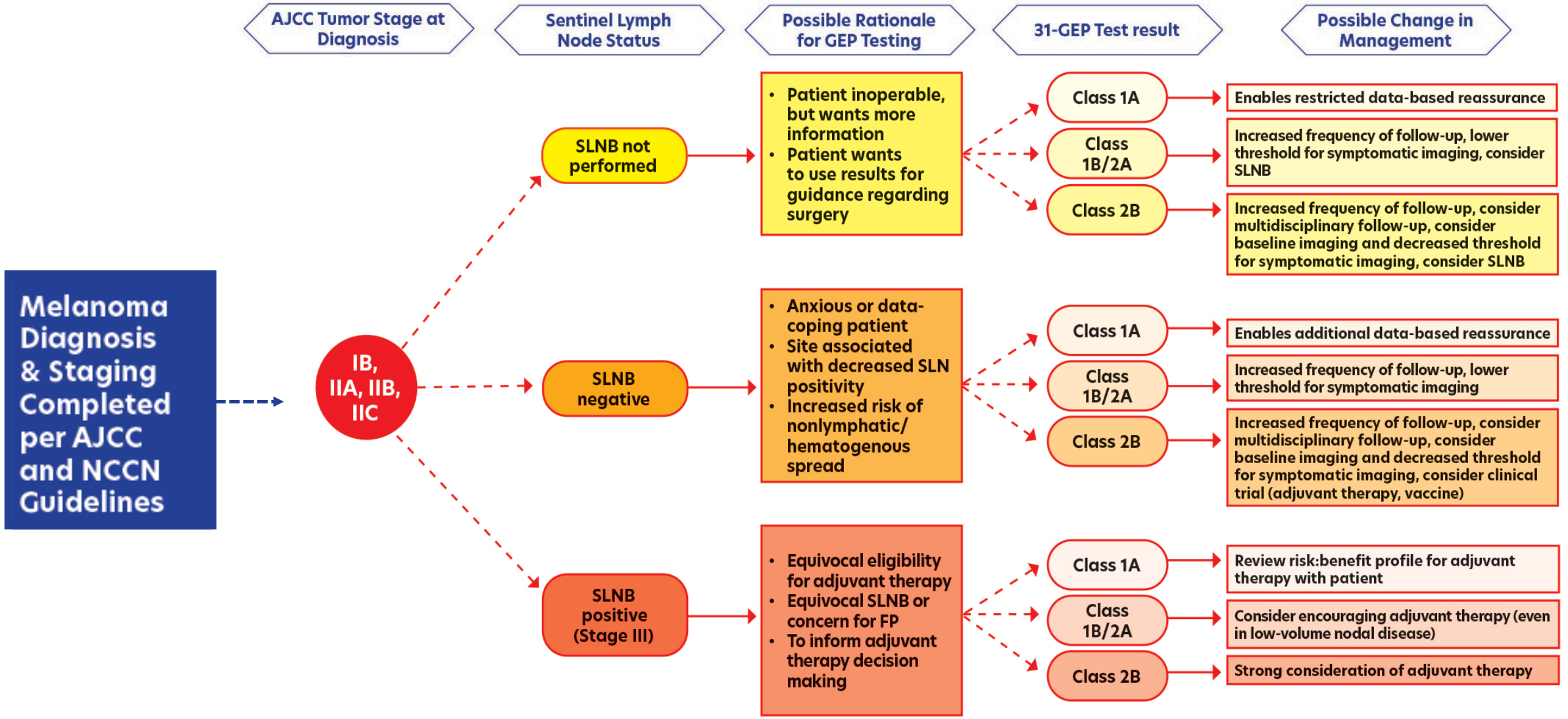
Integrating AJCC Staging & Gene Expression Profiling: Stage IA



*Adverse features resulting in uncertain microstaging include:

- Biopsies with a transected base
- Mitotic rate >1/mm^2
- Lymphovascular invasion

Integrating AJCC Staging & Gene Expression Profiling: Stages IB-IIC



Kwatra SG et al. *JCAD* 2020

Thank you

Aaron.Farberg@gmail.com