The Role of Genetic Expression Profile (GEP) In the Management of Melanoma

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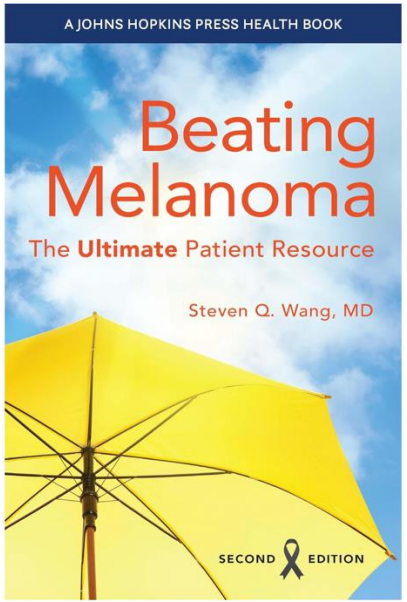
Disclosure.

BeatingMelanoma.com



SkylineDX

Topics

1. Why do we need the GEP test?
2. Current state of limitation & potentials.

AJCC staging for prognostic prediction

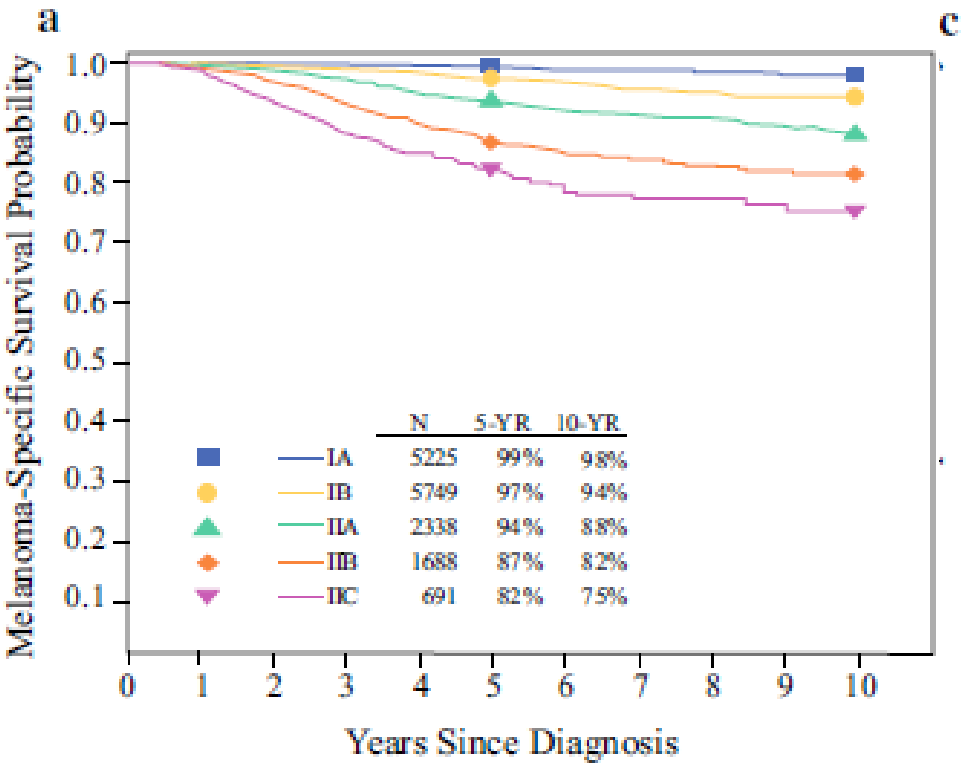
Latest 8th edition released in 2018

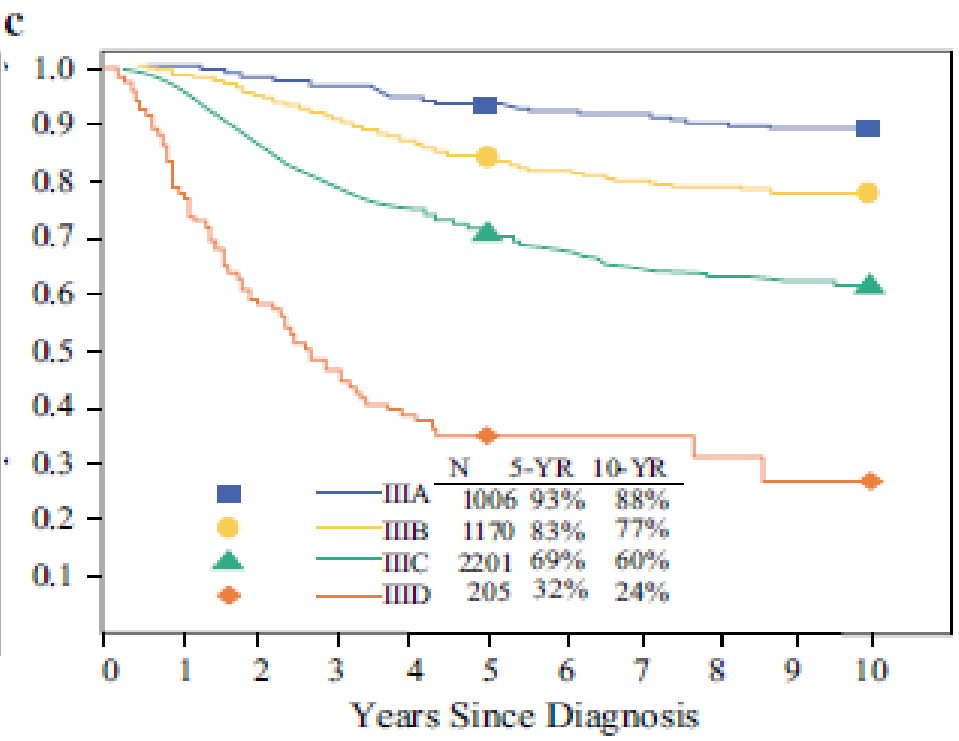
- Clinico-pathologic and outcomes data for 44,000 patients

- Key variables:
  - -Breslow depth (pathology)
  - -ulceration (pathology)
  - -SLN status (SLNB)
  - -Distant metastatic disease (imaging)

Gershenwald, *CA Cancer J Clin* 2017

AJCC staging for prognostic prediction

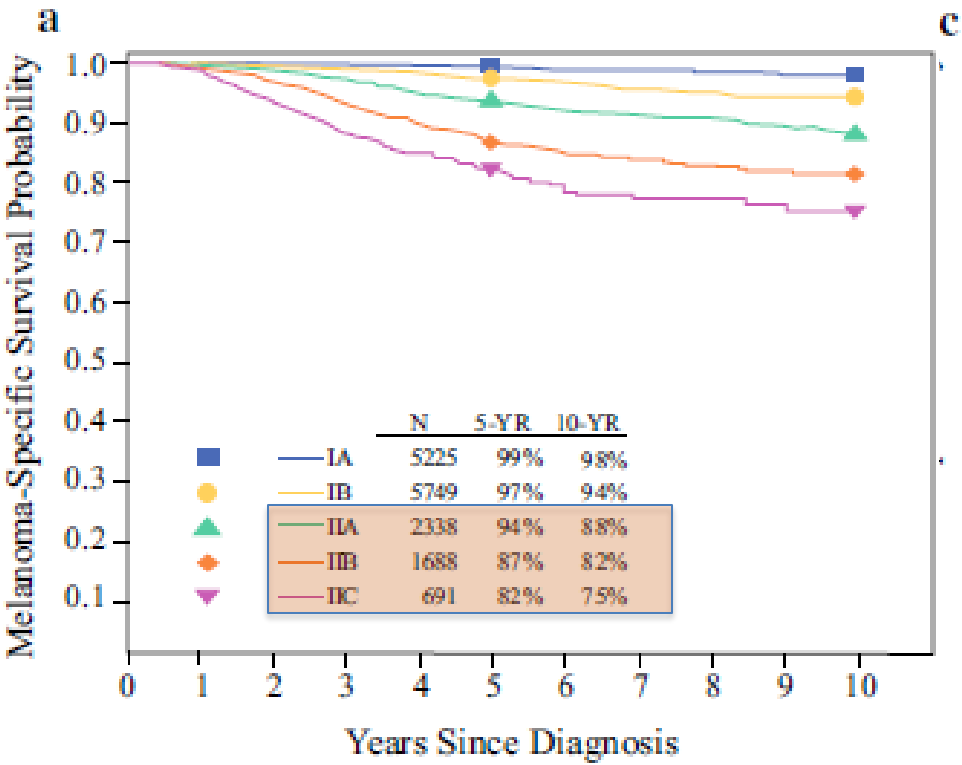


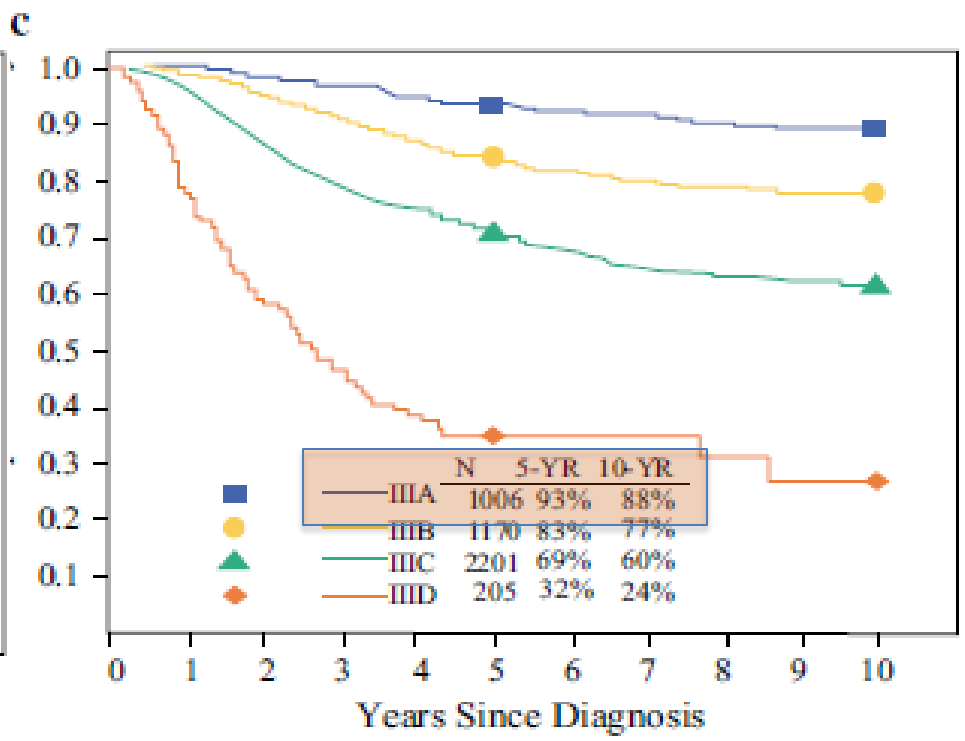


**Other factors not included
i.e., age, sex, anatomic site, pathologic factors, patient preferences etc.

Gershenwald, et al. CA Cancer J Clin. 2018

AJCC staging for prognostic prediction





**Other factors not included
i.e., age, sex, anatomic site, pathologic factors, patient preferences etc.

Gershenwald, et al. CA Cancer J Clin. 2018

AJCC Prognostic Limitations

1. Limitation in predicting survival outcome (IIIA >IIB/C)

Can we do better in aligning the staging system with survival outcome?

AJCC Prognostic Limitations

1. Limitation in predicting survival outcome (IIIA >IIB/C)
2. Metastatic disease & death from thin melanomas
   - 3-5% thin melanomas (T<1mm) develop metastatic disease[1]; represents 20-30% of melanoma deaths[2,3].

(T1a <0.8mm + no ulceration)
(T1b <0.8-1mm+ w/ or w/out ulceration)

(T2a 1-2mm + no ulceration)

(T2b 1-2mm + ulceration)

	N	5-YR	10-YR
IA	5225	99%	98%
IB	5749	97%	94%
IIA	2338	94%	88%
IIB	1688	87%	82%
IIC	691	82%	75%

Can we identify the 3-5% high risk, thin melanoma patients?

1. Gershenwald, *CA Cancer J Clin* 2017
2. Criscione, *JID* 2010;
3. Whiteman, *JID* 2015

AJCC Prognostic Limitations

1. Limitation in predicting survival outcome (IIIA >IIB/C)
2. Metastatic disease & death from thin melanomas
   - 3-5% thin melanomas develop metastatic disease[1]; represents 20-30% of melanoma deaths[2,3].
3. SLNB procedure:
   - >85% patients who undergo SLNB will have a negative results
   - False Negative rate between 5-21%
   - Surgical complication rate (6-11%) – infection & seroma

Can we identify which patients REALLY need the SLNB?

1. Gershenwald, *CA Cancer J Clin* 201
2. Criscione, *JID* 2010;
3. Whiteman, *JID* 2015

AJCC Prognostic Limitations

1. Limitation in predicting survival outcome (IIIA >IIB/C)
2. Metastatic disease & death from thin melanomas
   - 3-5% thin melanomas develop metastatic disease[1]; represents 20-30% of melanoma deaths[2,3].
3. SLNB procedure:
   - >85% patients who undergo SLNB will have a negative results
   - False Negative rate between 5-21%
   - Surgical complication rate (11%)
4. Adjuvant Treatment
   - Stage III; IIB/C

Can we identify which patients REALLY need the adjuvant?

1. Why do we need the GEP testing?

Can we do better in aligning the staging system with survival outcome?

Can we identify which patients REALLY need the SLNB?

Can we identify the 3-5% high risk, thin melanoma patients?

Can we identify which patients REALLY need the adjuvant?

2. Current State of Technology

Castle Biosciences (United States)
31-gene panel (31-GEP)

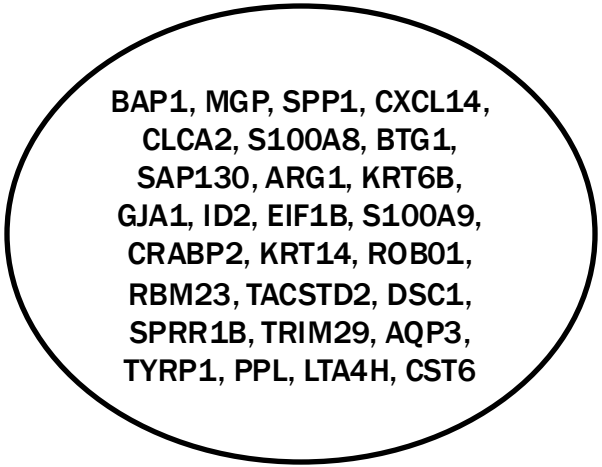
SkylineDx (Netherlands and United States)
8-gene panel (+ age, thickness) (CP-GEP)

NeraCare GmbH (Germany)
11-gene panel (11-GEP)

Consideration In Evaluating Data

- Quality of the studies: Internal vs. external generated study. Retrospective vs. Prospective data.
- Look beyond the overall cohort data (e.g., sensitivity, specificity, NPV, PPV etc). Look at the data for individual cohorts by stage (e.g., Stage I vs. II) or tumor thickness
- Understand for every patient we help, we may also be harming other patients. Sensitivity & NPV values matter.
- Will the test results change clinical management
- Cost

Discriminant genes…no overlap!



31-GEP

CP-GEP
(Merlin Assay)

11 GEP

31-GEP validation studies (10+)

Development and Internal Validation Retrospective Cohorts (2015-2017)

Clin Cancer Res. 2015 Jan 1;21(1):175-83. doi: 10.1158/1078-0432.CCR-13-3316.

Development of a prognostic genetic signature to predict the metastatic risk associated with cutaneous melanoma.

Gerami P[1], Cook RW[2], Wilkinson J[3], Russell MC[4], Dhillon N[5], Amaria RN[6], Gonzalez R[6], Lyle S[7], Johnson CE[2], Oelschlager KM[2], Jackson GL[8], Greisinger AJ[9], Maetzold D[2], Delman KA[4], Lawson DH[4], Stone JF[3].

J Am Acad Dermatol. 2017 May;76(5):818-825.e3. doi: 10.1016/j.jaad.2016.11.051. Epub 2017 Jan 19.

Identification of high-risk cutaneous melanoma tumors is improved when combining the online American Joint Committee on Cancer Individualized Melanoma Patient Outcome Prediction Tool with a 31-gene expression profile-based classification.

Ferris LK[1], Farberg AS[2], Middlebrook B[3], Johnson CE[3], Lassen N[3], Oelschlager KM[3], Maetzold DJ[3], Cook RW[3], Rigel DS[4], Gerami P[5].

J Am Acad Dermatol. 2015 May;72(5):780-5.e3. doi: 10.1016/j.jaad.2015.01.009. Epub 2015 Mar 3.

Gene expression profiling for molecular staging of cutaneous melanoma in patients undergoing sentinel lymph node biopsy.

Gerami P[1], Cook RW[2], Russell MC[3], Wilkinson J[4], Amaria RN[5], Gonzalez R[6], Lyle S[7], Jackson GL[8], Greisinger AJ[9], Johnson CE[2], Oelschlager KM[2], Stone JF[4], Maetzold DJ[2], Ferris LK[10], Wayne JD[11], Cooper C[12], Obregon R[12], Delman KA[3], Lawson D[3].

Internal + External Validation Retrospective Cohorts (2018)

J Am Acad Dermatol. 2018 Aug 3. pii: S0190-9622(18)32328-4. doi: 10.1016/j.jaad.2018.07.028. [Epub ahead of print]

Identification of patients at risk for metastasis using a prognostic 31-gene expression profile in subpopulations of melanoma patients with favorable outcomes by standard criteria.

Gastman BR[1], Gerami P[2], Kurley SJ[3], Cook RW[4], Leachman S[5], Vetto JT[6].

External Validation Retrospective Cohorts (2018)

BMC Cancer. 2018 Feb 5;18(1):130. doi: 10.1186/s12885-018-4016-3.

Performance of a prognostic 31-gene expression profile in an independent cohort of 523 cutaneous melanoma patients.

Zager JS[1], Gastman BR[2], Leachman S[3], Gonzalez RC[4], Fleming MD[5], Ferris LK[6], Ho J[7], Miller AR[8], Cook RW[9], Covington KR[9], Meldi-Plasseraud K[9], Middlebrook B[9], Kaminester LH[10], Greisinger A[11], Estrada SI[12], Pariser DM[13,14], Cranmer LD[15], Messina JL[16], Vetto JT[17], Wayne JD[18,19,20], Delman KA[21], Lawson DH[22], Gerami P[23,24].

Dermatol Surg. 2018 Jul 9. doi: 10.1097/DSS.0000000000001588. [Epub ahead of print]

Estimation of Prognosis in Invasive Cutaneous Melanoma: An Independent Study of the Accuracy of a Gene Expression Profile Test.

Greenhaw BN[1,2], Zitelli JA[2], Brodland DG[2].

External Validation Retrospective/Prospective Cohorts (2019)

Future Oncol. 2019 Apr;15(11):1207-1217. doi: 10.2217/fon-2018-0912. Epub 2019 Jan 29.

Guidance of sentinel lymph node biopsy decisions in patients with T1-T2 melanoma using gene expression profiling.

Vetto JT[1], Hsueh EC[2], Gastman BR[3], Dillon LD[4], Monzon FA[5], Cook RW[6], Keller J[2], Huang X[6], Fleming A[6], Hewgley P[6], Gerami P[7,8,9], Leachman S[10], Wayne JD[7,8,11], Berger AC[12], Fleming MD[6].

More Studies Since 2019

External Validation Prospective Cohorts (2017-2019)

Cancer Med. 2019 May;8(5):2205-2212. doi: 10.1002/cam4.2128. Epub 2019 Apr 5.

Prospective validation of the prognostic 31-gene expression profiling test in primary cutaneous melanoma.

Keller J[1], Schwartz TL[1], Lizalek JM[1], Chang ES[1], Patel AD[1], Hurley MY[2], Hsueh EC[1].

J Hematol Oncol. 2017 Aug 29;10(1):152. doi: 10.1186/s13045-017-0520-1.

Interim analysis of survival in a prospective, multi-center registry cohort of cutaneous melanoma tested with a prognostic 31-gene expression profile test.

Hsueh EC[1], DeBloom JR[2], Lee J[3], Sussman JJ[4], Covington KR[5], Middlebrook B[5], Johnson C[5], Cook RW[6], Slingluff CL Jr[7], McMasters KM[8].

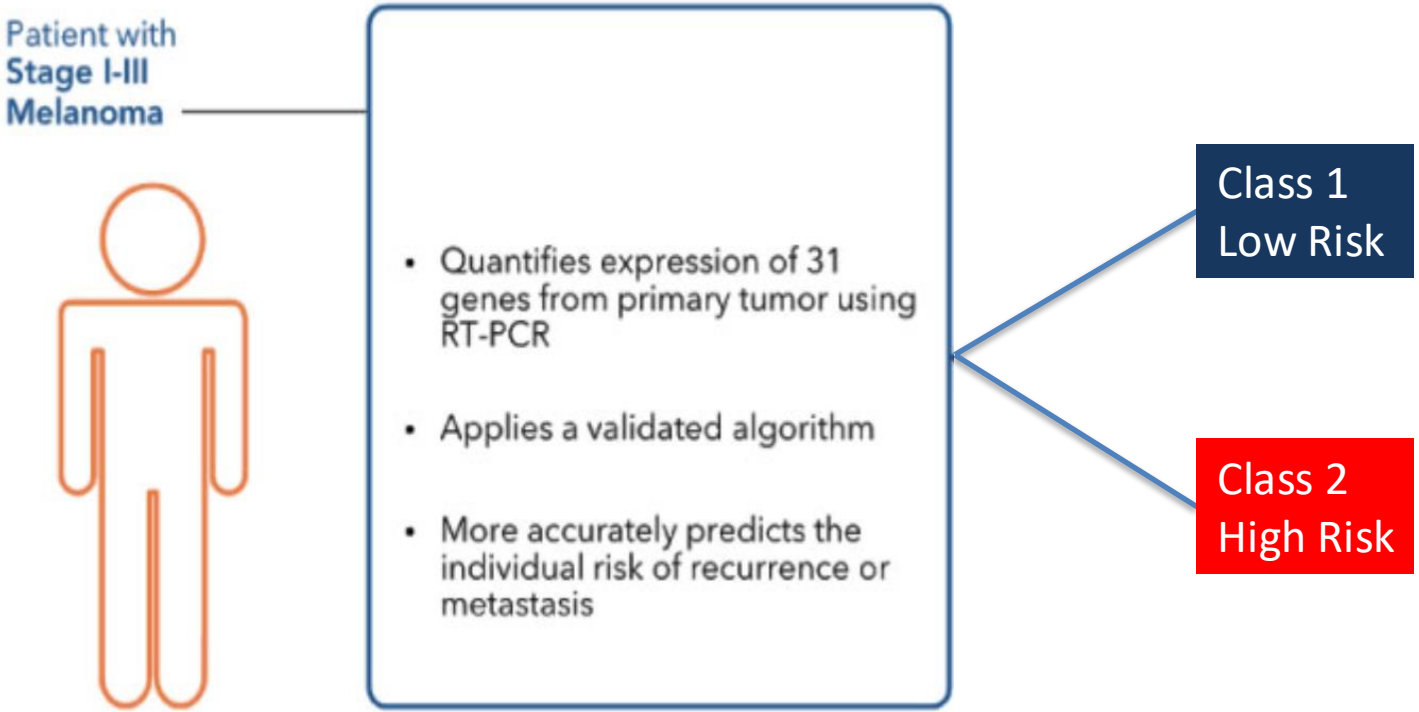
J Eur Acad Dermatol Venereol. 2019 May;33(5):857-862. doi: 10.1111/jdv.15454. Epub 2019 Feb 28.

Early outcome of a 31-gene expression profile test in 86 AJCC stage IB-II melanoma patients. A prospective multicentre cohort study.

Podlipnik S[1], Carrera C[1], Boada A[2], Richarz NA[2], López-Estebaranz JL[3], Pinedo-Moraleda F[3], Elosua-González M[3], Martín-González MM[4], Carrillo-Gijón R[4], Redondo P[5], Moreno E[5], Malvehy J[1], Puig S[1].

31-GEP Risk Stratification

(Old Classification System)



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Identification of patients at risk for metastasis using a prognostic 31-gene expression profile in subpopulations of melanoma patients with favorable outcomes by standard criteria.

Gastman BR[1], Gerami P[2], Kurley SJ[3], Cook RW[4], Leachman S[5], Vetto JT[6].

OBJECTIVE: To assess risk prediction by a 31-GEP test within three American Joint Committee on Cancer low-risk CM populations: sentinel lymph node (SLN)-negative, stage I-IIA, or thin (≤1mm, T1) tumors.

METHODS: Three previous validation studies provided a non-overlapping cohort of 690 patients with 31-GEP results, staging information, and survival outcomes. Kaplan-Meier and Cox regression analysis were performed.

RESULTS: Results included the identification of 70% of SLN-negative patients who metastasized as Class 2; reduced recurrence-free survival for patients with thin tumors and Class 2B biology compared to Class 1A biology ($p<0.0001$); and, determination of the 31-GEP test as an independent predictor of risk compared to traditional staging factors in stage I-IIA patients.

LIMITATIONS: Diagnoses spanned multiple versions of pathologic staging criteria.

CONCLUSIONS: The 31-GEP test identifies high-risk patients who are likely to recur or die from melanoma within low-risk groups with SLN negative disease, stage I-IIA, and thin tumor CM subpopulations.

N.B. Mixed internal/external validation cohort

Gastman et al JAAD 2018

JAMA Dermatology | Original Investigation

Performance of Gene Expression Profile Tests for Prognosis in Patients With Localized Cutaneous Melanoma

A Systematic Review and Meta-analysis

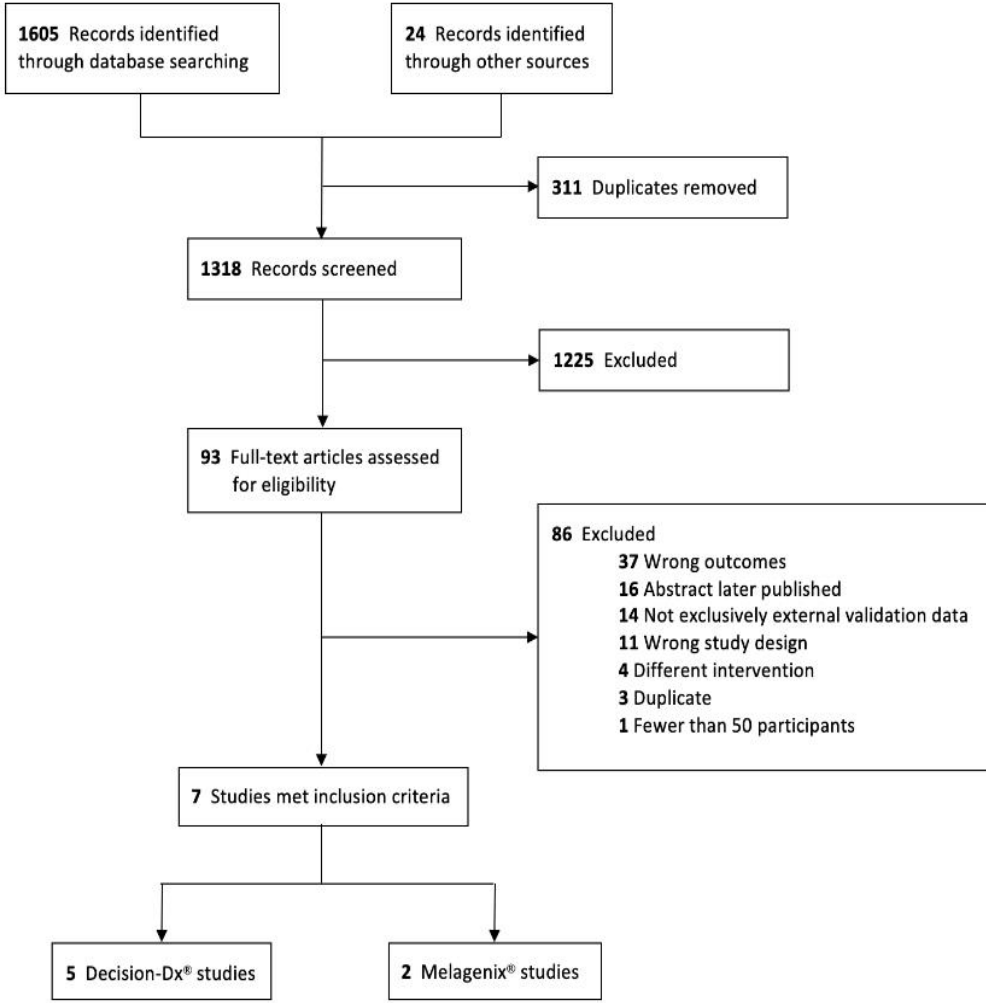
Michael A. Marchetti, MD; Daniel G. Coit, MD; Stephen W. Dusza, DrPH; Ashley Yu; LaToya McLean, MS; Yinin Hu, MD; Japbani K. Nanda, BS; Konstantina Matsoukas, MLIS; Silvia E. Mancebo, MD; Edmund K. Bartlett, MD

Our primary goals:

- stage-specific performance
- external validation studies only

Our primary limitation:

- could not report hazard ratios



Marchetti MA et al. JAMA Dermatology 2020

Stage I Results – *31-GEP*

4 studies, 623 patients

- 21 = recurrence, 6 (29%) had high-risk GEP
- 602 = no recurrence, 541 (90%) had low-risk GEP

Stage I Patients (n=623)

	Recurrence	No Recurrence
Class II	6 (1%)	61 (10%)
Class I	15 (2%)	541 (87%)

6/(6+15)= 29%

541/(541+61)= 90%

Sensitivity: 29%

Specificity: 90%

Marchetti MA et al. JAMA Dermatology 2020

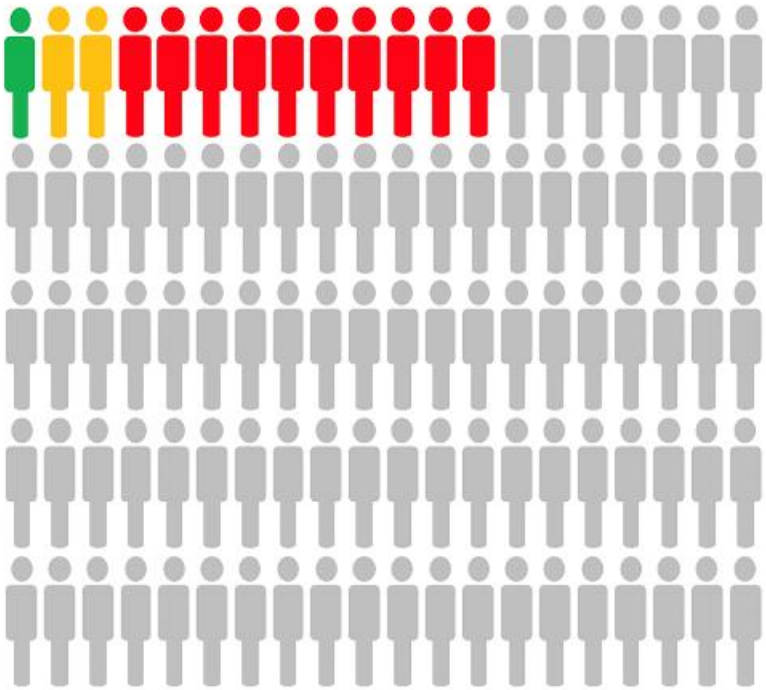
Definition

1. Sensitivity refers to a test's ability to designate an individual with disease as positive.
2. Specificity of a test is its ability to designate an individual who does not have a disease as negative.

Example:

If 100 patients known to have a disease were tested, and 43 test positive, then the test has 43% sensitivity. If 100 patients with no disease are tested and 96 return a completely negative result, then the test has 96% specificity

Stage I Results – *31-GEP*



1 **Benefited**
Patients correctly told they were high risk

2 Patients incorrectly told they were low risk

Sensitivity 29%

87 Patients correctly told they were low risk

10 Patients incorrectly told they were high risk

Specificity 90%

Harmed

Stage 1:
T1a-< 0.8 no ulcer
T1b-0.8 to 1
T2a: 1-2; no ulcer

Bottom line:

99% underwent 31-GEP test without benefit†

Marchetti MA et al. JAMA Derm 2020

Clinical scenario:

38 y.o. woman
Stage I Melanoma
Breslow 0.5mm
Right arm

AJCC Staging

Excision 1cm margin
No SLNB procedure
No imaging

Clinical scenario:

Sensitivity 29% - correctly id 1/3 patients with true dz, missed 2/3 patients

How good is a test that miss 2/3 of the true dz?

Specificity 90% -correctly id 90% patients w/o true dz, falsely id 10% as having dz

For every 1 patient we save out of 100, we have to send 10 patients for SLNB & possible long term imaging who really don't need it.

38 y.o. woman
Stage I Melanoma
Breslow 0.5mm
Right arm

AJCC Staging

Excision 1cm margin
No SLNB procedure
No imaging

31-GEP

Excision 1cm margin
SLNB procedure??
Imaging ??

Stage II Results – *31-GEP*

4 studies, 212 patients

- 72 = recurrence, 59 (82%) had high-risk GEP
- 140 = no recurrence, 62 (44%) had low-risk GEP

Stage II Patients (n=212)

	Recurrence	No Recurrence
Class II	59 (28%)	78 (37%)
Class I	13 (6%)	62 (29%)

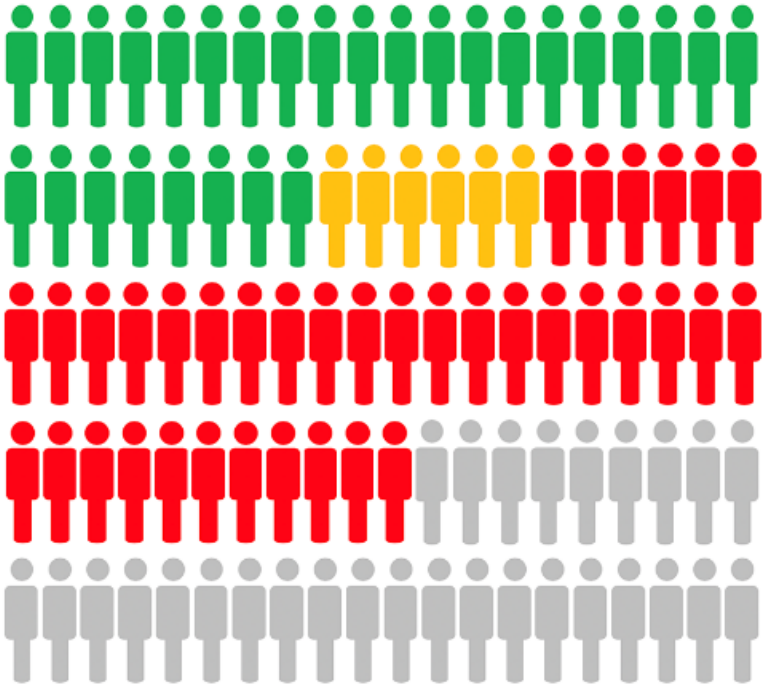
59/(59+13)=82%

62/(62+78)=44%

Sensitivity: 82% **Specificity: 44%**

Marchetti MA et al. JAMA Derm 2020

Stage II Results – *31-GEP*



28 **Benefited**
Patients correctly told they were high risk

6 Patients incorrectly told they were low risk

Sensitivity 82%

29 Patients correctly told they were low risk

37 Patients incorrectly told they were high risk

Specificity 44%

Harmed

Stage 2:
T2b (>1mm/ no ulceration) to T4b (>4mm)

Marchetti MA et al. JAMA Derm 2020

Clinical scenario:

38 y.o. woman
Stage II Melanoma
Breslow 1.3mm
Right arm

AJCC Staging

Excision 1cm margin
Yes SLNB procedure
No imaging

Clinical scenario:

Sensitivity 82% - correctly id 82% patients with true dz, missed 18% patients

How good is this test? If the test is negative, will you forgo SLNB?

Specificity 44% -correctly id 44% patients w/o true dz, falsely id 56% as having dz

For every 28 patient we save out of 100, we have to send 37 patients for adjuvant or long term imaging who really don't need it.

38 y.o. woman
Stage II Melanoma
Breslow 1.3mm
Right arm

AJCC Staging

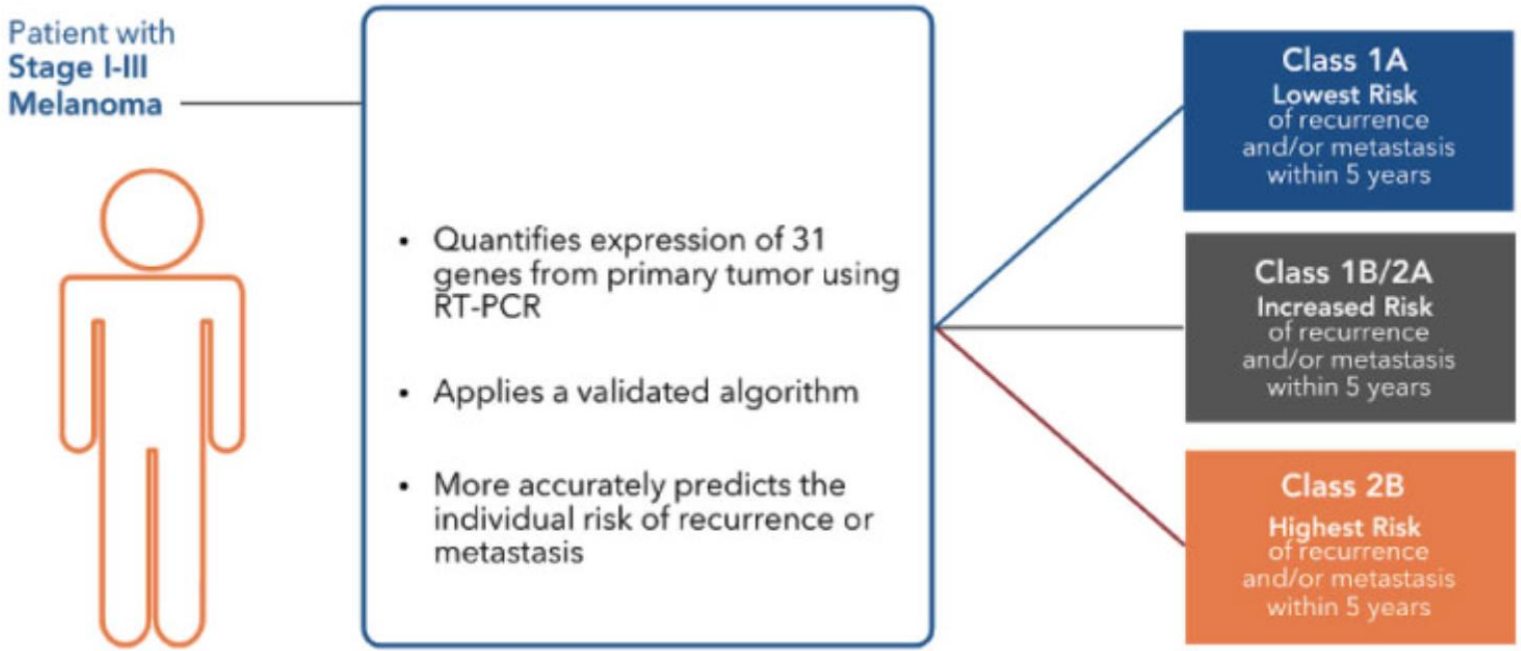
Excision 1cm margin
Yes SLNB procedure
No imaging

31-GEP

Excision 1cm margin
Yes SLNB procedure
Imaging or adjuvant ?

Revised 31-GEP + Clinicopathologic data

(Current Classification System)



Clinicopathologic info: age, Breslow, ulceration, and LN status

31-Gene Expression Profile Testing in Cutaneous Melanoma and Survival Outcomes in a Population-Based Analysis: A SEER Collaboration

PURPOSE The DecisionDx-Melanoma 31-gene expression profile (31-GEP) test is validated to classify cutaneous malignant melanoma (CM) patient risk of recurrence, metastasis, or death as low (class 1A), intermediate (class 1B/2A), or high (class 2B). This study aimed to examine the effect of 31-GEP testing on survival outcomes and confirm the prognostic ability of the 31-GEP at the population level.

METHODS Patients with stage I-III CM with a clinical 31-GEP result between 2016 and 2018 were linked to data from 17 SEER registries (n = 4,687) following registries' operation procedures for linkages. Melanoma-specific survival (MSS) and overall survival (OS) differences by 31-GEP risk category were examined using Kaplan-Meier analysis and the log-rank test. Crude and adjusted hazard ratios (HRs) were calculated using Cox regression model to evaluate variables associated with survival. 31-GEP tested patients were propensity score–matched to a cohort of non–31-GEP tested patients from the SEER database. Robustness of the effect of 31-GEP testing was assessed using resampling.

RESULTS Patients with a 31-GEP class 1A result had higher 3-year MSS and OS than patients with a class 1B/2A or class 2B result (MSS: 99.7% *v* 97.1% *v* 89.6%, $P < .001$; OS: 96.6% *v* 90.2% *v* 79.4%, $P < .001$). A class 2B result was an independent predictor of MSS (HR, 7.00; 95% CI, 2.70 to 18.00) and OS (HR, 2.39; 95% CI, 1.54 to 3.70). 31-GEP testing was associated with a 29% lower MSS mortality (HR, 0.71; 95% CI, 0.53 to 0.94) and 17% lower overall mortality (HR, 0.83; 95% CI, 0.70 to 0.99) relative to untested patients.

CONCLUSION In a population-based, clinically tested melanoma cohort, the 31-GEP stratified patients by their risk of dying from melanoma.

Bailey et al. JCO Precis Oncol 2023

TABLE 3. Survival Outcomes of Patients Tested With the 31-Gene Expression Profile Versus Not Tested After Matching for Socioeconomic, Demographic, and Pathologic Features

Group[a]	3-Year MSS, % (95% CI)	Deaths, % (n/N)
31-GEP tested (n = 3,258)	97.4 (96.6 to 98.2)	1.7 (57/3,258)
Matched untested (n = 9,774)	96.1 (95.5 to 96.6)	2.5 (242/9,774)
HR		0.71 (0.53 to 0.94)

Group	3-Year OS (95% CI)	Deaths, % (n/N)
31-GEP tested (n = 3,258)	92.4 (91.1 to 93.6)	5.2 (170/3,258)
Matched untested (n = 9,774)	90.9 (90.1 to 91.7)	6.2 (610/9,774)
HR		0.83 (0.70 to 0.99)

Abbreviations: 31-GEP, 31-gene expression profile; HR, hazard ratio; MSS, melanoma-specific survival; OS, overall survival.
[a]HR was computed using untested patients as the reference for 31-GEP testing. An HR <1.0 demonstrates improved survival in 31-GEP tested patients. Diagnosis and 31-GEP test date 2016-2018.

29% lower MSS mortality:
1-0.71=29%

Absolute Difference:
2.5-1.7 = 0.8%

17% lower OS mortality
1-0.83= 17%

Absolute Difference:
6.2-5.2 = 1%

CP-GEP

- **Model: age + thickness + RNA expressions of 8 genes (i.e., MLANA, GDF15, CXCL8, LOXL4, TGFBR1, ITGB3, PLAT & SERPINE2)**
- **Goal: identify MM patients who have a low risk for nodal metastasis and may forgo the SLNB**

- ***Reason:*** *SLNB procedure:*
  >85% patients who undergo SLNB will have a negative results
  False Negative rate between 5-21%
  Surgical complication rate (6-11%). Infection & seroma.

Bellomo et al 2020

CP-GEP

	Discovery	Retrospective		
	Bellomo et al (2020)	**Mulder et al (2020) EU**	**Yousaf et al (2021) USA**	**Johansson et al (2021) EU**
	T1-T3 N= 754	T1-T3 N=175	T1-T3 N= 193	T1-T3 N= 358
Prevalence	17.0%	26.9%	20.7%	10.6%
Sensitivity **95% CI**	90.0%	91.5% (80.1-96.6)	90.0% (76.3-97.2)	92.1% (78.6-98.3)
Specificity **95% CI**	49%	29.7% (22.5-38.1)	39.9% (32.1-48.1)	25.9% (21.2-31.1)
PPV **95% CI**	27%	32.3% (25.0-40.7)	28.1% (20.5-36.8)	12.9% (9.1-17.4)
NPV **95% CI**	96%	90.5% (77.9-96.2)	93.3% (81.7-98.6)	96.5% (90.1-99.3)
SLNB-RR	42%	24%	33.7%	24%

Definition

1. Sensitivity refers to a test's ability to designate an individual with disease as positive.
2. Specificity of a test is its ability to designate an individual who does not have a disease as negative.
3. Negative predictive value (NPV): proportion of negative results in a test that are true negative results. (If a test subject has a negative screening test, what is the probability that the subject really does not have the disease).

    -It is highly dependent on the prevalence of the disease. % of people in a population (group) has the disease.

    -does not take into account the sensitivity of the test

Example:

If there were 100 subjects whose screening test was negative, and 90 of these subjects were in fact free of disease. The NPV of the test was 90/100 = 90%.

Utility: identify MM patients who have a low risk for nodal metastasis and may forgo the SLNB

NPV 96%: out of 100 pts tested negative, and 96 pts REALLY do not have nodal mets.
4 will have nodal mets.

Q: will you use this test on your patient and forgo SLNB if the test is negative?

	Bellomo et al (2020)	Mulder et al (2020) EU	Yousaf et al (2021) USA	Johansson et al (2021) EU
NPV **95% CI**	96%	90.5% (77.9-96.2)	93.3% (81.7-98.6)	96.5% (90.1-99.3)

Utility: identify MM patients who have a low risk for nodal metastasis and may forgo the SLNB

NPV 96%: out of 100 pts tested negative, and 96 pts REALLY do not have nodal mets. 4 will have nodal mets and the test would missed it.

Q: will you use this test on your patient and forgo SLNB?

Sensitivity 90%: Out of 100 pts with nodal mets, the screening test identified 90 pts, And, the test missed 10 patients.

Q: will you use this test on your patient and forgo SLNB?

Ideal Test Need Both:
High Sensitivity
High NPV

	Bellomo et al (2020)	Mulder et al (2020) EU	Yousaf et al (2021) USA	Johansson et al (2021) EU
Sensitivity 95% CI	90.0%	91.5% (80.1-96.6)	90.0% (76.3-97.2)	92.1% (78.6-98.3)
NPV 95% CI	96%	90.5% (77.9-96.2)	93.3% (81.7-98.6)	96.5% (90.1-99.3)

CP-GEP

Discovery Study:

- N=754 (2004-2018; all received SLNB)

T Category	P	SY	SP	NPV (95% CI)	PPV	ACC	bACC	SLNb RR (95% CI)	ER
T1b	0.03	0.41	0.82	0.98 (0.95 to 1.00)	0.07	0.80	0.61	0.80 (0.74 to 0.86)	0.02
T2a	0.13	0.80	0.53	0.95 (0.91 to 0.98)	0.21	0.56	0.66	0.48 (0.42 to 0.54)	0.03
T2b	0.17	0.94	0.27	0.96 (0.91 to 1.00)	0.21	0.38	0.66	0.24 (0.14 to 0.34)	0.01
T3a	0.31	0.99	0.12	0.98 (0.95 to 1.00)	0.33	0.38	0.55	0.08 (0.03 to 0.12)	0.00
T3b	0.43	1.00	0.07	1.00 (0.97 to 1.00)	0.45	0.47	0.54	0.04 (0.00 to 0.09)	0.00

T1b sen 41%: test identified 41 out of 100 patients, but missed 59 patients w/ nodal dz.
T2a sen 80%: test identified 80 out of 100 patients, but missed 20 patients w/ nodal dz.

Bellomo et al 2020

Clinical evaluation of the clinicopathologic and gene expression profile (CP-GEP) in patients with melanoma eligible for sentinel lymph node biopsy: A multicenter prospective Dutch study

ABSTRACT

Sentinel lymph node biopsy (SLNB) is recommended for patients with >pT1b cutaneous melanoma, and should be considered and discussed with patients diagnosed with pT1b cutaneous melanoma for the purpose of staging, prognostication and determining eligibility for adjuvant therapy. Previously, the clinicopathologic and gene expression profile (CP-GEP, Merlin Assay®) model was developed to identify patients who can forgo SLNB because of a low risk for sentinel node metastasis. The aim of this study was to evaluate the clinical use and implementation of the CP-GEP model in a prospective multicenter study in the Netherlands. Both test performance and feasibility for clinical implementation were assessed in 260 patients with T1-T4 melanoma. The CP-GEP model demonstrated an overall negative predictive value of 96.7% and positive predictive value of 23.7%, with a potential SLNB reduction rate of 42.2% in patients with T1-T3 melanoma. With a median time of 16 days from initiation to return of test results, there was sufficient time left before the SLNB was performed. Based on these outcomes, the model may support clinical decision-making to identify patients who can forgo SLNB in clinical practice.

4 melanoma centers, prospective clinical trial in Netherlands

Stassen et al. Europ J. Surg Onc 2023

Table 3

Predictive utility of Merlin Assay for the individual T-stages.

	T1-T4 (n = 222)	T1 (n = 62)	T2 (n = 100)	T3 (n = 44)	T4 (n = 16)
Sensitivity (95% CI)	91.4% (76.9–98.2)	0% (0–70.8)	100% (78.2–100.0)	100% (71.5–100)	100% (54.2–100.0)
Specificity (95% CI)	45.8% (38.6–53.2)	83.1% (71.0–91.6)	38.8% (28.4–50.0)	6.06% (0.74–20.2)	0% (0.0–30.9)
PPV (95% CI)	23.7% (16.8–31.8)	0% (0–30.9)	22.4% (13.1–34.2)	26.2% (13.9–42.0)	37.5% (15.2–64.6)
NPV (95% CI)	96.7% (90.6–99.3)	94.2% (84.1–98.8)	100% (89.4–100)	100% (15.8–100)	N.A.
SLNB RR (95% CI)	39.2% (32.7–45.9)	83.9% (72.3–92.0)	33.0% (23.9–43.1)	4.5% (0.6–15.5)	0 (0–20.6)

List of abbreviations: PPV; positive predictive value, NPV; negative predictive value, SLNB RR; sentinel lymph node biopsy reduction rate, CI; confidence interval.

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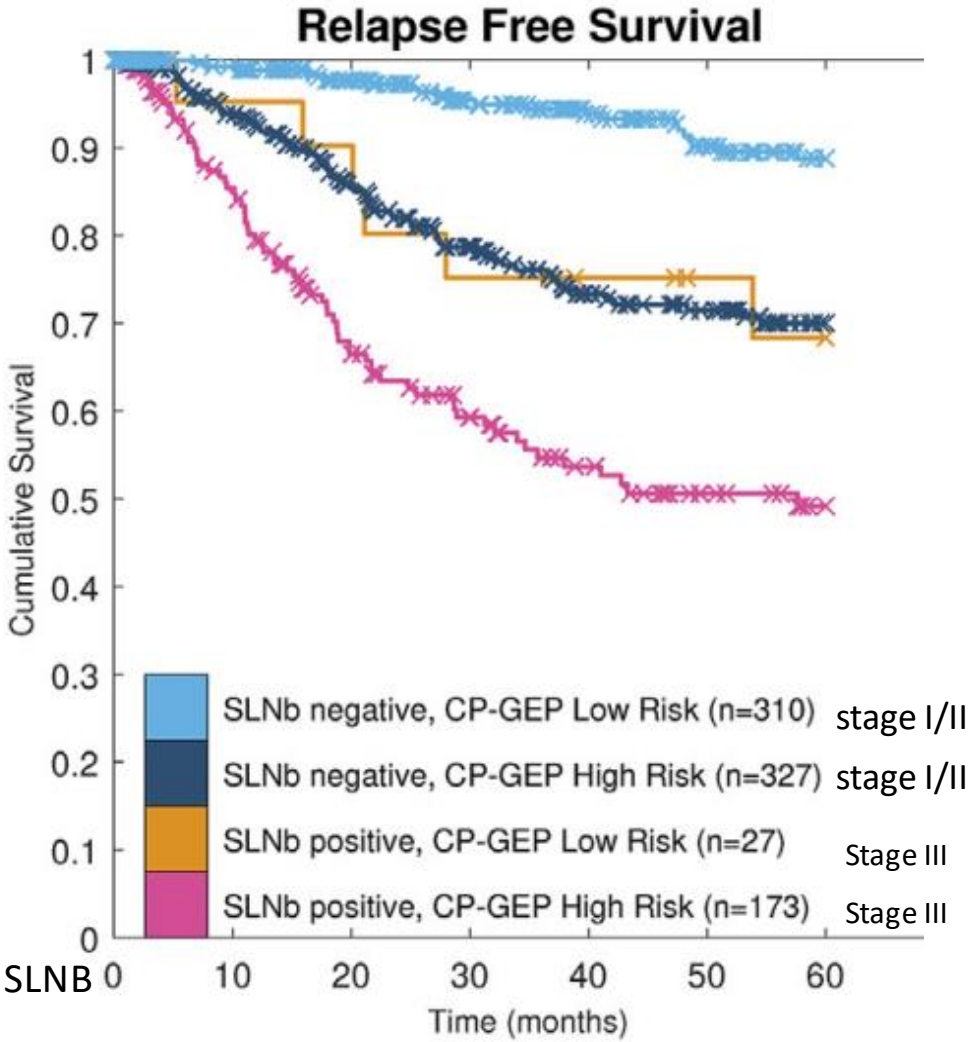
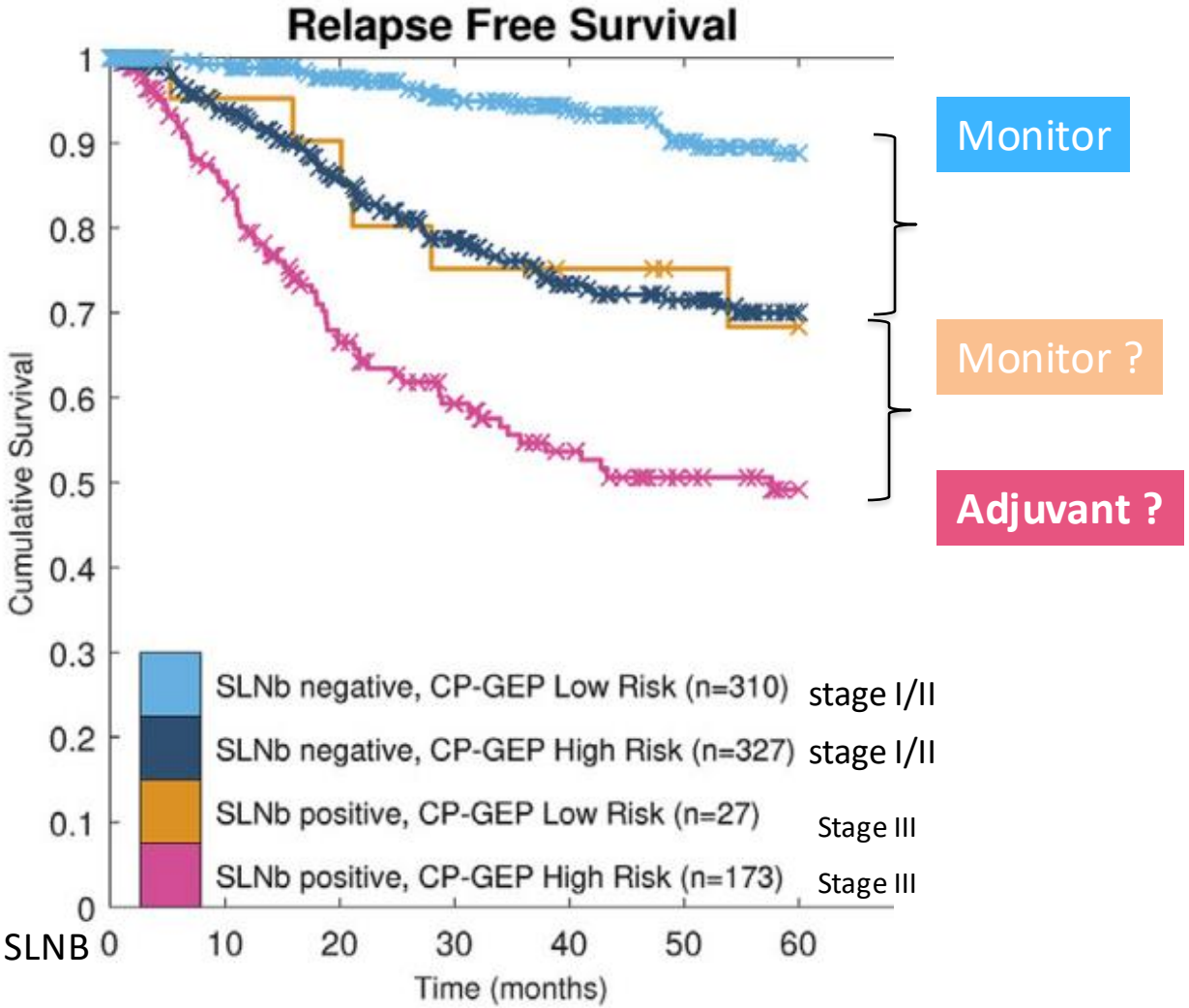
CP-GEP



831 patients treated with SLNB

Eggermont AMM et al. Eur J Canc

CP-GEP



831 patients treated with SLNB

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Consensus Statement

July 29, 2020

Prognostic Gene Expression Profiling in Cutaneous Melanoma

Identifying the Knowledge Gaps and Assessing the Clinical Benefit

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Key Findings

- Optimistic about the future use of GEP to improve risk stratification
- Current utility is limited by test performance in patients with stage I disease (70% patients)
- Significant challenges to perform clinical trials incorporating GEP testing w/ SLNB and adjuvant therapy
- Avoid routine use of GEP test to direct patient management
- More data is needed to support using GEP testing to inform recommendation regarding SLNB, Intensity of follow up, imaging surveillance and adjuvant therapy

Routine use of prognostic GEP testing not advocated by NCCN or AAD guidelines

Consideration In Evaluating Data

- Quality of the studies: Internal vs. external generated study. Retrospective vs. Prospective data.
- Look beyond the overall cohort data (e.g., sensitivity, specificity, NPV, PPV etc). Look at the data for individual cohorts by stage (e.g., Stage I vs. II) or tumor thickness
- Understand for every patient we help, we may also be harming other patients. Sensitivity & NPV values matter.
- Will the test results change clinical management
- Cost

Summary

1. Why do we need GEP testing?
2. Current state of the technology
   - Limitation & Potentials

Q&A

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