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Prognostic significance of the CP-GEP assay combining clinicopathological factors and gene expression profiling in AJCC v8 stage I/II cutaneous melanoma patients

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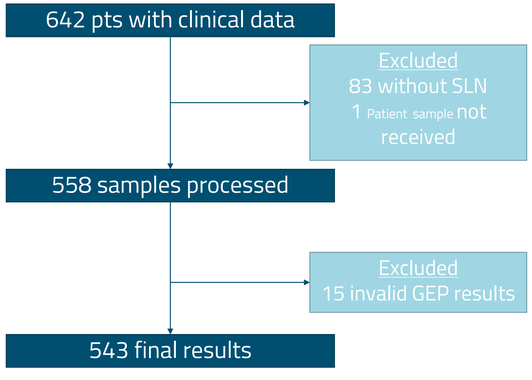
Background - AJCC v8 includes Breslow thickness and ulceration to subdivide stage I and II CM pts into risk groups. In light of the results from adjuvant therapy in stage II CM, it has been discussed that pts' **follow-up and treatment** should consider additional markers, namely **CP-GEP**, to further **refine the risk classification.**

Aim: to clinically validate the prognostic CP-GEP assay for stage I/II CMs combining Breslow, age and the expression of 8 genes SERPINE2, GDF15, ITGB3, CXCL8, LOXL4, TGFBR1, PLAT and MLANA.

Methods - all formalin-fixed paraffin-embedded primary melanomas **stage I/II CMs** with **negative sentinel lymph node** (SLN) diagnosed between 2000-2017 and archived in **Tuebingen** were included. Quantitative reverse transcription polymerase chain reaction of the **8 genes** was performed and combined with age and tumor thickness to define **CP-GEP low- vs. high-risk** groups.

Figure 1: Generation of the study cohort



CP-GEP is a **non-invasive** and **independent prognostic model** for risk of relapse in stage I/II melanoma. It **identifies SLN negative** patients with **high risk** of relapse. **CP-GEP** should be used for **complementing** AJCC classification and **therapeutic decisions.**

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Results

Table 1: Patients characteristics

Gender	Female	234 (43.1)
	Male	309 (56.9)
Age (years)	Median [IQR]	66 [54 - 74]
Breslow thickness (mm)	Median [IQR]	1.70 [1.20 - 2.80]
	Range	0.3-14.0
Ulceration	**Absent**	**408 (75.1)**
	Present	135 (24.9)
CP-GEP	Low-risk	232 (42.7%)
	High-risk	**311 (57.3%)**

Stages	IA	78 (14.4)
	IB	**223 (41.1)**
	IIA	**123 (22.7)**
	IIB	73 (13.4)
	IIC	46 (8.5)
T-categories	T1a	8 (1.5)
	T1b	70 (12.9)
	T2a	**223 (41.1)**
	T2b	35 (6.4)
	T3a	88 (16.2)
	T3b	52 (9.6)
	T4a	21 (3.9)
	T4b	46 (8.5)

Localization	Head/Neck	101 (18.6)
	Trunk	**197 (36.3)**
	Upper Extremities	58 (10.7)
	Lower Extremities	109 (20.1)
	Acral	78 (14.4)
Histologic type	**Superficial spreading**	**314 (57.8)**
	Nodular	66 (12.2)
	Lentigo maligna	43 (7.9)
	Acral lentiginous	72 (13.3)
	Other	48 (8.8%)

Figure 2: Kaplan-Meier survival curves for the whole collective according to CP-GEP risk subgroups

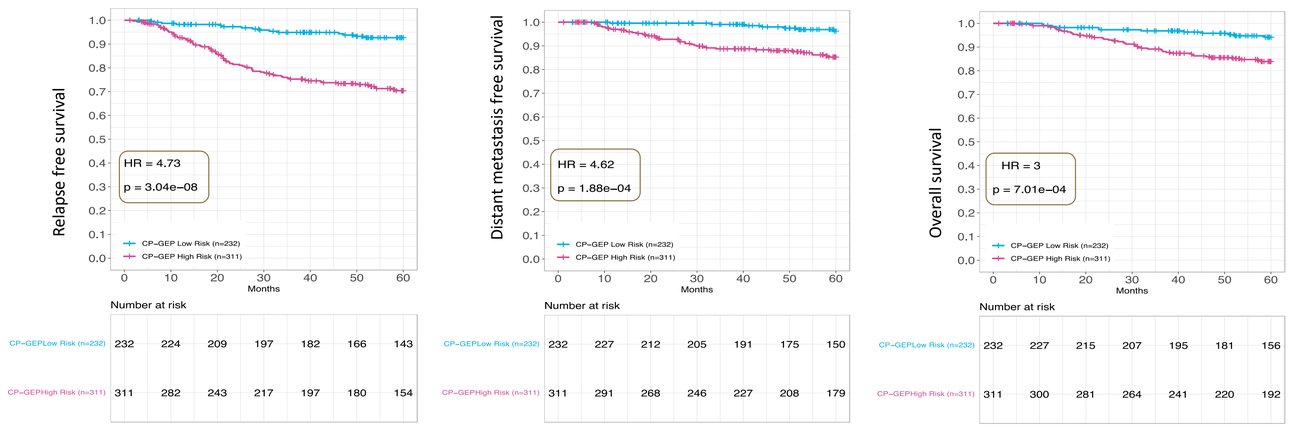

Table 2: 5-y survival rates according to CP-GEP risk sub-groups and AJCCv8 stage; RFS = relapse free survival, DMFS= distant metastasis free survival; OS= overall survival

	CP-GEP high	CP-GEP low	IA	IB	IIA	IIB	IIC	All
	N=311	N=232	N=78	N=223	N=123	N=73	N=46	N=543
5y RFS % (95% CI)	71 (65-76)	92 (87-95)	96 (85-99)	89 (83-92)	75 (65-82)	69 (57-79)	41 (25-55)	80 (76-83)
5y DMFS % (95% CI)	86 (81-90)	96 (92-98)	96 (84-99)	96 (92-98)	91 (84-96)	82 (69-90)	60 (42-74)	90 (87-93)
5y OS% (95% CI)	85 (80-89)	95 (91-97)	97 (90-99)	97 (93-98)	86 (77-91)	80 (68-88)	65 (48-78)	89 (86-92)

In **multivariate Cox regression analysis for RFS** including Breslow thickness, ulceration and age, **contribution of CP-GEP remained independently significant** (HR = 2.75, p = 0.0008) compared to age (HR 1.03; p < 0.0007), Breslow (HR 1.21; p < 0.0001) and ulceration (HR 1.37; p = 0.1694).