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Prognostic factors in distinct melanoma types

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Citation

Ipenburg, N. A. (2022, March 2). *Prognostic factors in distinct melanoma types*. Retrieved from <https://hdl.handle.net/1887/3277983>

Version: Publisher's Version

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CHAPTER 1

General introduction

EPIDEMIOLOGY

Cutaneous melanoma is a malignant tumor of melanocytes, the pigment producing cells residing in the skin. Melanomas also occur in other sites, such as the eye, meninges and mucosa. Over two hundred years ago, the first case of cutaneous melanoma was described.^{1,2} In recent decades, the incidence of melanoma has increased across the globe.³⁻⁵ In 2018, 6709 individuals were diagnosed with melanoma in the Netherlands and almost 800 died of the disease.⁶

Individual risk factors for developing melanoma encompass host factors and environmental factors. The most important environmental cause of melanoma is sun exposure. Ultraviolet radiation causes DNA damage. More than 90% of melanomas are attributed to sun exposure.⁷⁻⁹ Especially intermittent sun exposure, such as sunbathing, is associated with an increased melanoma risk.^{10,11} Individuals with large congenital nevi, dysplastic nevi or a high number of melanocytic nevi are at increased risk of developing melanoma.^{10,12-15} Other host factors that are associated with an increased melanoma risk are fair skin, red hair, old age, history of skin cancer, and a family history of melanoma.¹⁶⁻¹⁹

CLINICAL DIAGNOSIS AND DIAGNOSTIC EXCISIONAL BIOPSY

Melanoma most often presents as a new or changing pigmented skin lesion (Figure 1). Several aspects of the lesion are assessed by the dermatologist. Lesions that are different from the other pigmented lesions in the patient, also called ugly duckling sign, should raise suspicion for melanoma.²⁰ The ABCDE criteria (**A**symmetry, **B**order irregularity, **C**olor variation, **D**iameter > 6mm, **E**volving) are frequently used to evaluate suspicious pigmented lesions with the naked eye.²¹ Dermoscopy is essential in the clinical diagnosis of melanoma (Figure 2). It is more accurate than visual inspection alone.²² The clinical and dermoscopic appearance varies between melanoma subtypes. Superficial spreading melanoma, nodular melanoma, lentigo maligna melanoma, and acral lentiginous melanoma are the four main histological subtypes of melanoma.²¹ Nodular melanomas are in general more difficult to detect and have more aggressive characteristics.^{21,23}

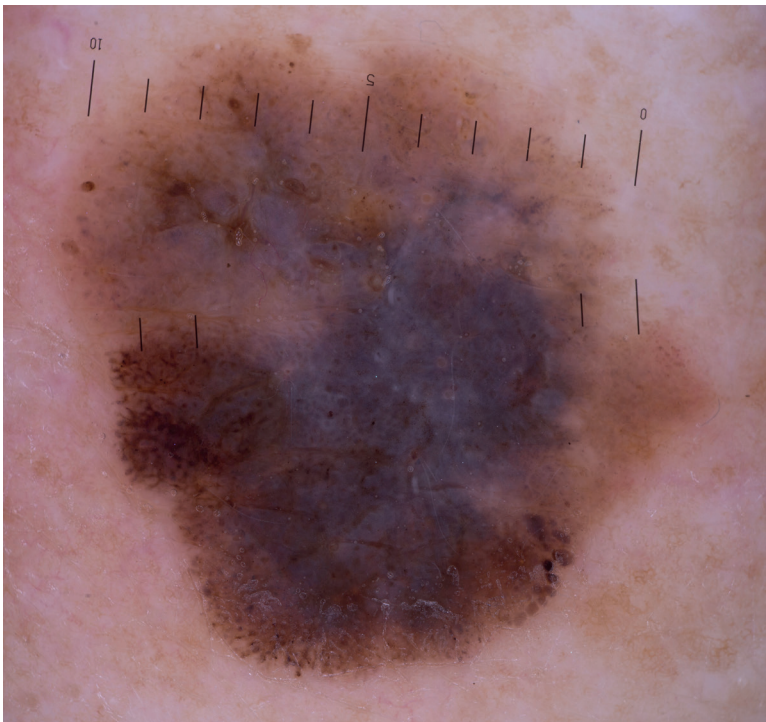
Excisional biopsy with narrow (1-3mm) margins is the recommended initial management for suspicious pigmented skin lesions.²⁴⁻²⁶ However, melanomas are frequently diagnosed by partial biopsy, such as punch, shave or incisional biopsy.²⁷ In Australia, more than 25% of all melanomas is diagnosed by partial biopsy.²⁸

Figure 1. Clinical picture of cutaneous melanoma.

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Figure 2. Dermoscopy of cutaneous melanoma.



Histopathological misdiagnosis is more common for melanocytic lesions assessed with partial than with excisional biopsy.²⁹ Partial biopsies are associated with several pitfalls. Sampling of only the benign part of the lesion might result in misdiagnosis. Partial biopsy of a melanocytic nevus may result in regenerative changes that overlap with the histological features of melanoma. This can lead to overdiagnosis of melanoma. Tumor implantation and inaccurate assessment of important pathological features, such as Breslow thickness, are other potential problems.^{28,29}

HISTOPATHOLOGY AND STAGING

Histopathological tumor characteristics are assessed by the (dermato)pathologist on the excisional biopsy specimen. These characteristics are essential in the staging process. All patients are staged using the American Joint Committee on Cancer/Union Internationale Contre le Cancer (AJCC/UICC) melanoma staging classification (Table 1 and 2).³⁰ Management decisions and prognostic information are derived from this classification.

The thickness of the primary melanoma is an important prognostic feature of a clinically localized melanoma.^{31–33} It was first described by Alexander Breslow in 1970 and is therefore also known as Breslow thickness.³⁴ Tumor thickness is measured from the top of the granular layer of the epidermis to the deepest malignant cells invading the dermis. Initially a cut off thickness of $\leq 0.75\text{mm}$ was used to define thin melanomas with a good prognosis. In the 6th and 7th editions of the AJCC melanoma staging classification, melanomas with a tumor thickness of $\leq 1.0\text{mm}$ were classified as thin.^{35,36} A recent study showed that 0.8mm is a clinically important cut-off.³⁷ This is reflected in the most recent 8th edition of the AJCC/UICC melanoma staging classification.³⁰

Ulceration has been part of the melanoma staging system for decades.^{30,35,36} Ulcerated tumors have a higher risk of disease recurrence and melanoma-related death.^{31,33,38} Although not part of the staging classification, the extent of ulceration is of prognostic significance. Extensively ulcerated melanomas have a worse outcome than minimally ulcerated tumors.³⁹

Allen and Spitz were the first to describe the poorer survival of patients having a primary melanoma with many mitoses.⁴⁰ Tumor mitotic rate has since been validated as an independent prognostic factor in numerous studies.^{41–46} It was incorporated in the 7th edition of the AJCC staging classification but has been removed as a staging parameter in the most recent staging system.^{30,36}

Table 1. TNM staging categories.³⁰

Tumor (T)	Tumor thickness	Ulceration
T1a	< 0.8mm	Without ulceration
T1b	< 0.8mm	With ulceration
	0.8 – 1.0mm	With or without ulceration
T2a	>1.0 – 2.0mm	Without ulceration
T2b	>1.0 – 2.0mm	With ulceration
T3a	>2.0 – 4.0mm	Without ulceration
T3b	>2.0 – 4.0mm	With ulceration
T4a	> 4.0mm	Without ulceration
T4b	> 4.0mm	With ulceration
Node (N)	No. of tumor involved regional lymph nodes	Type of metastasis*
N0	0	
N1a	1	Clinically occult
N1b	1	Clinically detected
N1c	0	In-transit, satellite and/or microsatellite metastasis
N2a	2-3	Clinically occult
N2b	2-3	Clinically detected
N2c	1	In-transit, satellite and/or microsatellite metastasis
N3a	≥ 4	Clinically occult
N3b	≥ 4	Clinically detected
N3c	≥ 2	In-transit, satellite and/or microsatellite metastasis
Metastasis (M)	Site	
M0	No distant metastasis	
M1a	Skin, soft tissue and/or nonregional lymph node	
M1b	Lung	
M1c	Non-CNS visceral sites	
M1d	CNS	

*Clinically occult lymph node metastases are detected by sentinel node biopsy and without clinical or radiographic evidence of regional lymph node metastasis. Clinically detected nodal metastases are identified by clinical, radiographic or ultrasound examination.

Table 2. AJCC clinical and pathological prognostic stage groups (8th edition).³⁰

	Clinical stage			Pathological stage			
	T	N	M	T	N	M	
IA	T1a	N0	M0	IA	T1a	N0	M0
					T1b	N0	M0
IB	T1b	N0	M0	IB	T2a	N0	M0
	T2a	N0	M0				
IIA	T2b	N0	M0	IIA	T2b	N0	M0
	T3a	N0	M0		T3a	N0	M0
IIB	T3b	N0	M0	IIB	T3b	N0	M0
	T4a	N0	M0		T4a	N0	M0
IIC	T4b	N0	M0	IIC	T4b	N0	M0
III	Any T	≥ N1	M0	IIIA	T1-T2a	N1a or N2a	M0
				IIIB	T1-T2a	N1b/c or N2b	M0
					T2b/T3a	N1a-N2b	M0
				IIIC	T1a-T3a	N2c or N3	M0
					T3b/T4a	≥ N1	M0
				T4b	N1a-N2c	M0	
IIID	T4b	N3	M0				
IV	Any T	Any N	M1	IV	Any T	Any N	M1

WIDE LOCAL EXCISION AND SENTINEL NODE BIOPSY

If an invasive primary cutaneous melanoma is diagnosed, wide local excision (WLE) of the lesion or biopsy site is indicated to reduce the risk of local recurrence. WLE surgical margins depend on tumor thickness.²⁴⁻²⁶ The recommended safety margins are 1cm for melanomas with tumor thickness < 2mm and 2cm for thicker melanomas.²⁴

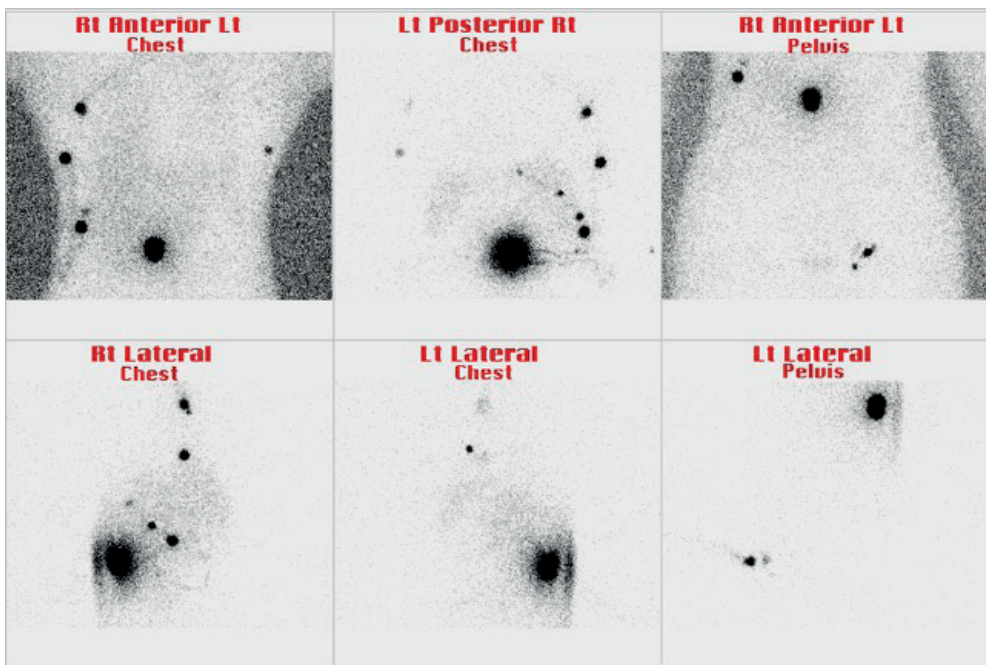
For many years, excision of the primary tumor was often combined with prophylactic regional lymph node dissection.⁴⁷ Since only 20% of the clinically localized melanoma patients has involved lymph nodes, many patients could not have any benefit from such a procedure. Prophylactic lymph node dissections were abandoned after studies showed that routine use of this procedure did not improve survival.⁴⁸⁻⁵¹

In 1992, the sentinel node (SN) concept was introduced by Morton and Cochran.⁵² A SN is defined as any node on a direct lymphatic drainage pathway from the primary tumor.⁵³ Multiple drainage pathways and thus multiple SNs can be present in one patient.⁵⁴⁻⁵⁷ Sentinel node biopsy (SNB) can establish the tumor-status of the entire regional lymph node field.^{58,59} Only patients with an involved SN underwent immediate removal of the remaining regional

lymph nodes, the so-called completion lymph-node dissection (CLND). Before the introduction of this procedure in melanoma, the term *sentinel node* was already mentioned in studies of penile cancer, parotid cancer, testis and omentum.⁶⁰⁻⁶⁴

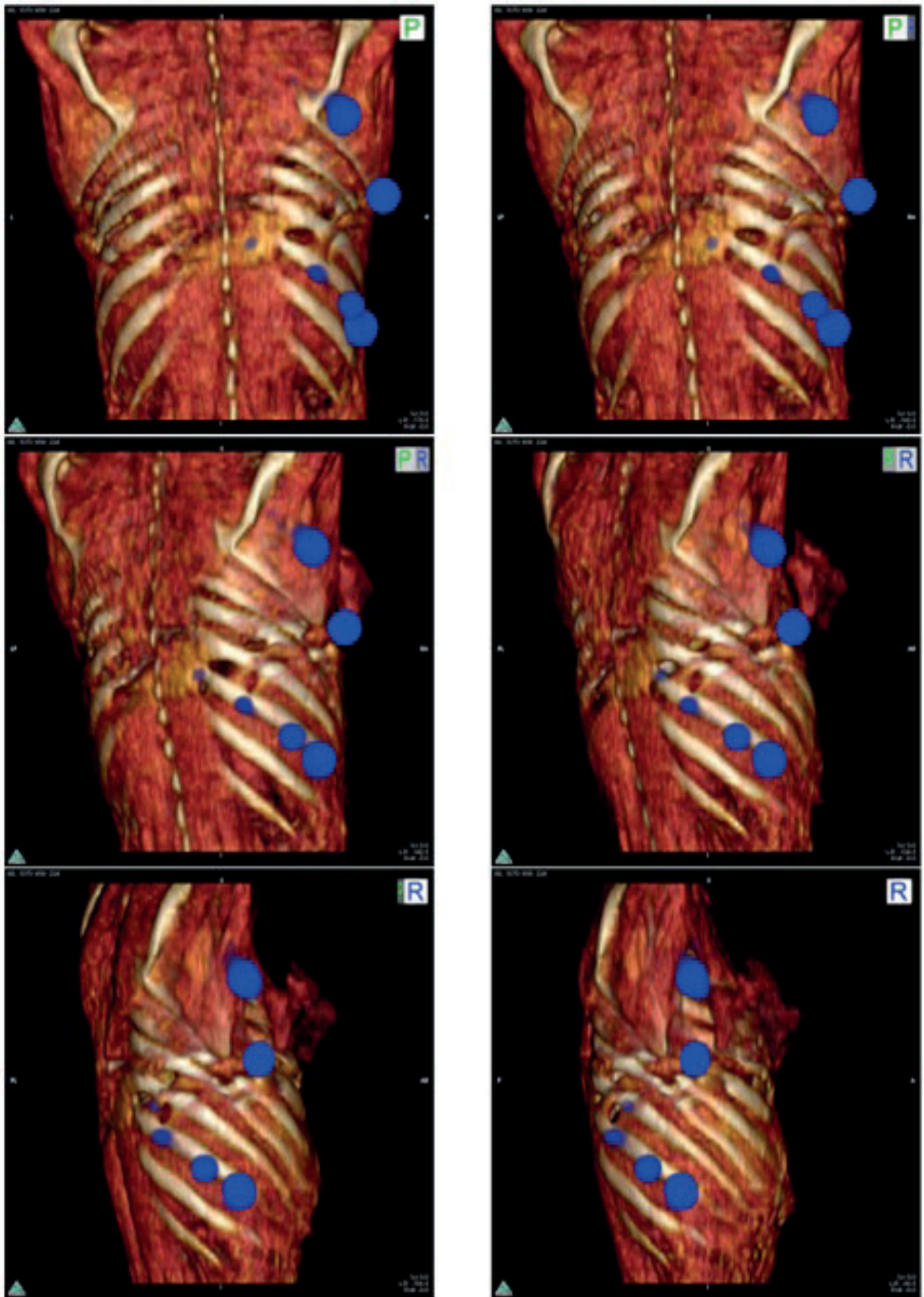
The nuclear medicine physician is of great importance in the identification of these SNs. Technetium-99m colloid is injected at the primary melanoma site. The tracer flows from the primary tumor through the afferent lymph vessel to the lymph nodes. Dynamic and static lymphoscintigraphy visualize the SNs (Figure 3).⁶⁵ Single photon emission computed tomography with integrated computerized tomography (SPECT/CT) is added to show the SNs exact anatomical location (Figure 4).⁶⁶⁻⁶⁹ Non-palpable metastases can be detected by ultrasound (US) after which fine needle biopsy is performed.

Figure 3. Lymphoscintigrams in a patient with a melanoma on the mid back show sentinel nodes in the axillae, on the right chest wall and in the left groin.



The surgeon uses a gamma ray detection probe to locate the SNs. Intra-operatively, patent blue dye is injected intradermally at the primary tumor site. The blue travels the same route as the radiopharmaceutical. The blue-stained afferent lymph vessel can also guide the surgeon to the SNs. Only these lymph nodes are removed and assessed for the presence or absence of metastases.

Figure 4. Single photon emission computed tomography with integrated computerized tomography (SPECT/CT) displays sentinel nodes of melanoma located on the chest.



Histopathological examination is performed on multiple sections stained with hematoxylin and eosin and immunohistochemical markers, such as S100, HMB45, MelanA and SOX10.^{70,71}

The SN status is the most important prognostic factor in patients with a clinically localized melanoma.^{58,72–75} Patients with a positive SN have a worse prognosis than SN-negative patients. The first Multicenter Selective Lymphadenectomy Trial (MSLT-I) proved the importance of this staging procedure and showed that patients who underwent SNB had fewer recurrences than patients who underwent WLE and nodal observation.⁵⁸ SNB combined with CLND also improved melanoma-specific survival (MSS) of patients with an intermediate-thickness melanoma (1.2 – 3.5mm) who had occult nodal metastases.⁵⁸ SN-positivity is rare (<5%) in melanomas < 0.8mm in thickness. Melanomas with a tumor thickness of 0.8 – 1.0 mm have a 8 to 12% change of having spread to a SN.^{76–79} Therefore, SNB is recommended for patients with a clinically localized melanoma that has a thickness ≥ 0.8 mm or if ulceration is present (T1b or higher).^{24,25} SNB seems reliable when performed after WLE, but concomitant WLE and SNB is preferred.⁸⁰

SPECIAL POPULATIONS

Elderly

Elderly people have the highest melanoma incidence and mortality.^{81–83} Between 1989 and 2015, the incidence in Dutch men aged ≥ 70 years has increased with more than 500%.⁸⁴ Compared to younger patients, primary melanomas of older patients are on average thicker, more often ulcerated and have more dermal mitoses.^{38,85,86} Nodular melanomas are also more frequent.^{86,87} While their melanomas are more aggressive, the SN-positivity rate is lower in these patients.^{38,88,89} Age-related lymphatic dysfunction might be an explanation for this inverse correlation.⁹⁰

Melanoma guidelines are also applicable to elderly patients.^{24,25} However, studies show substandard surgical treatment in this group of patients.^{87,91} Incisional biopsies and suboptimal excision margins are common.^{86,87,91} SNB is less frequently performed in older patients with clinically localized melanoma.^{86,91,92} Clinical decision-making in the elderly is complicated by several factors, of which frailty, medical comorbidities and reduced life-expectancy are examples.

Children and adolescents

Pediatric melanoma is arbitrarily defined as melanoma diagnosed below the age of 20 years.²¹ It is the most common type of skin cancer in children and adolescents.⁹³ Pediatric melanoma is frequently associated with pre-existing conditions such as large congenital melanocytic nevi and xeroderma pigmentosum.⁹⁴ While within most age groups melanoma incidence has increased, a declining incidence of pediatric melanoma is observed.^{3,95-97}

Only 0.1% of the melanoma cases occur in children and adolescents. Due to the rarity, melanoma is often not considered in this age group.⁹³ The clinical features are also frequently atypical and do not follow the conventional ABCDE criteria.^{98,99} Modified ABCD criteria (**A**melanotic, **B**leeding or **B**ump, **C**olor uniformity, **D**e novo and any **D**iameter) have therefore been proposed.⁹⁹ Children and adolescents have been excluded from randomized controlled trials studying different aspects of melanoma management.^{33,58,100} Currently, adult melanoma guidelines are applied to pediatric melanoma patients. SNB is also performed in pediatric melanoma patients. Paradoxically, pediatric patients have a higher incidence of SN-metastasis but a more favorable survival rate than adults.^{38,101,102}

Familial melanoma

Approximately 10% of patients diagnosed with melanoma have a positive family history.^{103,104} Genes implicated in familial melanoma include cyclin-dependent kinase inhibitor 2A (*CDKN2A*), cyclin-dependent kinase inhibitor 4 (*CDK4*), BRCA1-associated protein-1 (*BAP1*), protection of telomeres 1 (*POT1*), telomerase reverse transcriptase (*TERT*), ACD shelterin complex subunit and telomerase recruitment factor (*ACD*), telomeric repeat-binding factor 2-interacting protein (*TERF2IP*) and microphthalmia-associated transcription factor (*MITF*).¹⁰⁴⁻¹⁰⁶ Genetic testing is recommended for patients who meet the criteria for familial melanoma, which are defined as the occurrence of three or more melanomas in multiple members of a family, at least two of which are diagnosed in first-degree relatives.¹⁰⁷ Clinical genetic consultation is also advised when two first degree relatives are diagnosed with melanoma, families in which melanoma and pancreatic cancer are diagnosed, patients with three or more melanomas, patients with melanoma diagnosed before the age of 18 years, patients with multiple *BAP1*-deficient melanocytic nevi and patients with a combination of melanoma and pancreatic cancer or uveal melanoma.¹⁰⁷ Patients with hereditary breast and ovarian cancer syndrome (*BRCA1* and *BRCA2*), Li-Fraumeni syndrome (*TP53*), xeroderma pigmentosum, and PTEN hamartoma tumor syndromes (*PTEN*) are also at increased risk of developing melanoma.¹⁰⁵ Germline mutations in *CDKN2A* are found in about 20-40% of

melanoma families.^{108,109} In the Netherlands, the most prevalent *CDKN2A* germline mutation is the p16-Leiden mutation (c.225-243del19). This specific founder mutation probably originated from an endogamous population.^{110,111} The high penetrance gene *CDKN2A* encodes two different tumor suppressor proteins: p16INK4A (p16) and p14ARF (p14). These patients have a life-time melanoma risk of about 70% and frequently at a young age.^{104,105,112} *CDKN2A* mutation carriers also have an increased risk of developing pancreatic cancer, head and neck tumors, and lung cancer.¹¹³ Recent studies on survival of *CDKN2A* germline mutation carriers with melanoma showed conflicting results.^{114–116} In a Swedish cohort, these melanoma patients had a worse survival than sporadic melanoma patients.^{114,115} However, an Italian group found no survival difference.¹¹⁶

AREAS OF UNCERTAINTY

Clinically localized melanoma has been extensively studied. However, several clinical questions are still unanswered.

SNB has become a routine staging procedure in patients with clinically localized melanoma. However, SNB may be less attractive in some categories. SNB is sometimes omitted in patients with advanced age, substantial comorbidities or if SNB is likely to be technically challenging. Instead of SNB, preoperative lymphoscintigraphy followed by focused US of the identified SNs is performed at each follow-up visits. It is unknown whether focused US of the lymph nodes is an acceptable alternative for SNB in these special populations.

Due to the rarity of melanoma in children and adolescents, little is known on prognostic factors in these young patients. In adult melanoma patients, tumor mitotic rate is one of the strongest predictors of survival. Previous studies showed that tumor mitotic rate is lower in pediatric melanomas than in other age groups. However, the prognostic significance of mitotic rate in clinically localized pediatric melanoma is uncertain.

The biology of melanoma in familial melanoma patients carrying the *CDKN2A* germline mutation seems to be more aggressive. As mentioned, previous studies showed conflicting results regarding a survival difference between *CDKN2A* mutation carriers and sporadic melanoma patients. The frequency of SN-positivity and its prognostic significance are also uncertain.

Individual prognostic factors can be combined into a prognostic model enabling personalized follow-up and treatment of individual patients. The European Organisation for Research

and Treatment of Cancer (EORTC) built a prognostic model and nomogram for recurrence and melanoma-specific mortality in SN-negative melanoma patients. Currently, it is not known how applicable and accurate this prognostic model is to other populations. External validation is essential to ensure the applicability to other melanoma populations.

AIM AND OUTLINE OF THIS THESIS

This thesis describes prognostic factors and management of special melanoma populations.

Chapter two describes patients who underwent lymphoscintigraphy but did not undergo SNB because of advanced age and/or comorbidities. Instead, they were monitored with focused US of their SNs at each follow-up visit. Survival outcomes of this group were compared to patients who did undergo SNB. The aim of this study was to assess whether lymphoscintigraphy with focused US follow-up of SNs is a reasonable management alternative to SNB in patients who are elderly and/or have substantial comorbidities.

Chapter three concerns a cohort study of patients with clinically localized melanoma in whom the intended SNB was canceled after preoperative lymphoscintigraphy. Demographics and melanoma characteristics of this group were compared to patients in whom SNB was performed. The study in chapter three sought to determine if lymphoscintigraphy with focused US follow-up of SNs is an acceptable alternative for patients in whom a SNB procedure is likely to be challenging.

Chapter four describes children and adolescents diagnosed with melanoma. The aim of the study was to assess the prognostic value of tumor mitotic rate in these young patients.

Chapter five compares the characteristics and survival of *CDKN2A* mutation carriers with sporadic melanoma patients. This study aimed to assess whether presence of a pathogenic *CDKN2A* germline mutation was associated with survival in melanoma patients.

Chapter six reports the characteristics and outcome of hereditary melanoma patients carrying germline *CDKN2A* mutations who underwent SNB. The goal of this study was to assess the frequency and predictive value of SN-positivity in *CDKN2A* mutation carriers.

Chapter seven describes the external validation of a prognostic model, including Breslow thickness, ulceration and primary tumor site, to predict survival of patients with SN-negative melanoma. The secondary aim of the study was to assess whether the prognostic model could be improved by adding other prognostic factors.

REFERENCES

1. Bodenham DC. A study of 650 observed malignant melanomas in the South-West region. *Ann R Coll Surg Engl.* 1968;43(4):218-239.
2. Home E. *Observations on Cancer, Case VIII.*; 1805.
3. Paulson KG, Gupta D, Kim TS, et al. Age-specific incidence of melanoma in the United States. *JAMA Dermatol.* 2020;156(1):57.
4. Arnold M, Holterhues C, Hollestein LM, et al. Trends in incidence and predictions of cutaneous melanoma across Europe up to 2015. *J Eur Acad Dermatol Venereol.* 2014;28(9):1170-1178.
5. Whiteman DC, Green AC, Olsen CM. The growing burden of invasive melanoma: Projections of incidence rates and numbers of new cases in six susceptible populations through 2031. *J Invest Dermatol.* 2016;136(6):1161-1171.
6. Integraal Kankercentrum Nederland. Cijfers over kanker. Accessed March 18, 2020. <https://www.cijfersoverkanker.nl>.
7. Berwick M, Buller DB, Cust A, et al. Melanoma epidemiology and prevention. *Cancer Treat Res.* 2016;167(6):17-49.
8. Armstrong BK, Kricger A. How much melanoma is caused by sun exposure? *Melanoma Res.* 1993;3(6):395-401.
9. Parkin DM, Mesher D, Sasieni P. 13. Cancers attributable to solar (ultraviolet) radiation exposure in the UK in 2010. *Br J Cancer.* 2011;105 Suppl:S66-9.
10. Gandini S, Sera F, Cattaruzza MS, et al. Meta-analysis of risk factors for cutaneous melanoma: II. Sun exposure. *Eur J Cancer.* 2005;41(1):45-60.
11. Nelemans PJ, Rampen FHJ, Ruiter DJ, Verbeek ALM. An addition to the controversy on sunlight exposure and melanoma risk: A meta-analytical approach. *J Clin Epidemiol.* 1995;48(11):1331-1342.
12. Bataille V, de Vries E. Melanoma-part 1: epidemiology, risk factors, and prevention. *BMJ.* 2008;337:a2249-a2249.
13. Bauer J, Garbe C. Acquired melanocytic nevi as risk factor for melanoma development. A comprehensive review of epidemiological data. *Pigment Cell Res.* 2003;16(3):297-306.
14. Garbe C, Krüger S, Orfanos CE, et al. Associated factors in the prevalence of more than 50 common melanocytic nevi, atypical melanocytic nevi, and actinic lentiginos: Multicenter case-control study of the central malignant melanoma registry of the German dermatological society. *J Invest Dermatol.* 1994;102(5):700-705.
15. Grob JJ, Gouvernet J, Aymar D, et al. Count of benign melanocytic nevi as a major indicator of risk for nonfamilial nodular and superficial spreading melanoma. *Cancer.* 1990;66(2):387-395.
16. Tucker MA, Goldstein AM. Melanoma etiology: Where are we? *Oncogene.* 2003;22(20):3042-3052.
17. Bliss JM, Ford D, Swerdlow AJ, et al. Risk of cutaneous melanoma associated with pigmentation characteristics and freckling: systematic overview of 10 case-control studies. The International Melanoma Analysis Group (IMAGE). *Int J Cancer.* 1995;62(4):367-376.
18. van der Leest RJT, Flohil SC, Arends LR, de Vries E, Nijsten T. Risk of subsequent cutaneous malignancy in patients with prior melanoma: A systematic review and meta-analysis. *J Eur Acad Dermatol Venereol.* 2015;29(6):1053-1062.
19. van der Leest RJT, Hollestein LM, Liu L, Nijsten T, de Vries E. Risks of different skin tumour combinations after a first melanoma, squamous cell carcinoma and basal cell carcinoma in Dutch population-based cohorts: 1989-2009. *J Eur Acad Dermatol Venereol.* 2018;32(3):382-389.

20. Grob JJ. The “ugly duckling” sign: Identification of the common characteristics of nevi in an individual as a basis for melanoma screening. *Arch Dermatol*. 1998;134(1):103-a-104.
21. Garbe C, Amaral T, Peris K, et al. European consensus-based interdisciplinary guideline for melanoma. Part 1: Diagnostics – Update 2019. *Eur J Cancer*. 2020;126:141-158.
22. Dinnes J, Deeks JJ, Chuchu N, et al. Dermoscopy, with and without visual inspection, for diagnosing melanoma in adults. *Cochrane Database Syst Rev*. 2018;12:CD011902.
23. Dessinioti C, Dimou N, Geller AC, et al. Distinct clinicopathological and prognostic features of thin nodular primary melanomas: An international study from 17 centers. *J Natl Cancer Inst*. 2019;111(12):1314-1322.
24. Garbe C, Amaral T, Peris K, et al. European consensus-based interdisciplinary guideline for melanoma. Part 2: Treatment – Update 2019. *Eur J Cancer*. 2020;126:159-177.
25. Swetter SM, Tsao H, Bichakjian CK, et al. Guidelines of care for the management of primary cutaneous melanoma. *J Am Acad Dermatol*. 2019;80(1):208-250.
26. Veerbeek L, Kruit WHJ, de Wilt JHW, Mooi WJ, Bergman W, Multidisciplinaire richtlijnwerkgroep melanoom. [Revision of the national guideline ‘Melanoma’]. *Ned Tijdschr Geneeskd*. 2013;157(12):A6136.
27. Kelly JW, Henderson M a, Thursfield VJ, Slavin J, Ainslie J, Giles GG. The management of primary cutaneous melanoma in Victoria in 1996 and 2000. *Med J Aust*. 2007;187(9):511-514.
28. Luk PP, Vilain R, Crainic O, McCarthy SW, Thompson JF, Scolyer RA. Punch biopsy of melanoma causing tumour cell implantation: Another peril of utilising partial biopsies for melanocytic tumours. *Australas J Dermatol*. 2015;(November 2014):227-231.
29. Ng JC, Swain S, Dowling JP, Wolfe R, Simpson P, Kelly JW. The impact of partial biopsy on histopathologic diagnosis of cutaneous melanoma: Experience of an Australian tertiary referral service. *Arch Dermatol*. 2010;146(3):234-239.
30. Gershenwald JE, Scolyer RA, Hess KR, et al. Melanoma staging: Evidence-based changes in the American Joint Committee on Cancer eighth edition cancer staging manual. *CA Cancer J Clin*. 2017;67(6):472-492.
31. Balch CM, Soong SJ, Gershenwald JE, et al. Prognostic factors analysis of 17,600 melanoma patients: validation of the American Joint Committee on Cancer melanoma staging system. *J Clin Oncol*. 2001;19(16):3622-3634.
32. Balch CM, Soong S, Ross MI, et al. Long-term results of a multi-institutional randomized trial comparing prognostic factors and surgical results for intermediate thickness melanomas (1.0 to 4.0 mm). Intergroup Melanoma Surgical Trial. *Ann Surg Oncol*. 2000;7(2):87-97.
33. Faries MB, Thompson JF, Cochran AJ, et al. Completion dissection or observation for sentinel-node metastasis in melanoma. *N Engl J Med*. 2017;376(23):2211-2222.
34. Breslow A. Thickness, cross-sectional areas and depth of invasion in the prognosis of cutaneous melanoma. *Ann Surg*. 1970;172(5):902-908.
35. Balch CM, Buzaid AC, Soong S, et al. Final version of the American Joint Committee on Cancer staging system for cutaneous melanoma. *J Clin Oncol*. 2001;19(16):3635-3648.
36. Balch CM, Gershenwald JE, Soong SJ, et al. Final version of 2009 AJCC melanoma staging and classification. *J Clin Oncol*. 2009;27(36):6199-6206.
37. Lo SN, Scolyer RA, Thompson JF. Long-term survival of patients with thin (T1) cutaneous melanomas: A Breslow thickness cut point of 0.8 mm separates higher-risk and lower-risk tumors. *Ann Surg Oncol*. 2018;25(4):894-902.

38. Balch CM, Soong S, Gershenwald JE, et al. Age as a prognostic factor in patients with localized melanoma and regional metastases. *Ann Surg Oncol*. 2013;20(12):3961-3968.
39. In 't Hout FEM, Haydu LE, Murali R, Bonenkamp JJ, Thompson JF, Scolyer RA. Prognostic importance of the extent of ulceration in patients with clinically localized cutaneous melanoma. *Ann Surg*. 2012;255(6):1165-1170.
40. Allen AC, Spitz S. Malignant melanoma. A clinicopathological analysis of the criteria for diagnosis and prognosis. *Cancer*. 1953;6(1):1-45.
41. Azzola MF, Shaw HM, Thompson JF, et al. Tumor mitotic rate is a more powerful prognostic indicator than ulceration in patients with primary cutaneous melanoma: An analysis of 3661 patients from a single center. *Cancer*. 2003;97(6):1488-1498.
42. Francken AB, Shaw HM, Thompson JF, et al. The prognostic importance of tumor mitotic rate confirmed in 1317 patients with primary cutaneous melanoma and long follow-up. *Ann Surg Oncol*. 2004;11(4):426-433.
43. Thompson JF, Soong S-J, Balch CM, et al. Prognostic significance of mitotic rate in localized primary cutaneous melanoma: An analysis of patients in the multi-institutional American Joint Committee on Cancer melanoma staging database. *J Clin Oncol*. 2011;29(16):2199-2205.
44. Wat H, Senthilselvan A, Salopek TG. A retrospective, multicenter analysis of the predictive value of mitotic rate for sentinel lymph node (SLN) positivity in thin melanomas. *J Am Acad Dermatol*. 2016;74(1):94-101.
45. Mandalà M, Galli F, Cattaneo L, et al. Mitotic rate correlates with sentinel lymph node status and outcome in cutaneous melanoma greater than 1 millimeter in thickness: A multi-institutional study of 1524 cases. *J Am Acad Dermatol*. 2017;76(2):264-273.e2.
46. Barnhill RL, Katzen J, Spatz A, Fine J, Berwick M. The importance of mitotic rate as a prognostic factor for localized cutaneous melanoma. *J Cutan Pathol*. 2005;32(4):268-273.
47. Neuhaus SJ, Clark MA, Thomas JM. Dr. Herbert Lumley Snow, MD, MRCS (1847-1930): The original champion of elective lymph node dissection in melanoma. *Ann Surg Oncol*. 2004;11(9):875-878.
48. Veronesi U, Adamus J, Bandiera DC, et al. Delayed regional lymph node dissection in stage I melanoma of the skin of the lower extremities. *Cancer*. 1982;49(11):2420-2430.
49. Cascinelli N, Morabito A, Santinami M, MacKie R, Belli F. Immediate or delayed dissection of regional nodes in patients with melanoma of the trunk: A randomised trial. *The Lancet*. 1998;351(9105):793-796.
50. Balch CM, Soong S-J, Bartolucci AA, et al. Efficacy of an elective regional lymph node dissection of 1 to 4 mm thick melanomas for patients 60 years of age and younger. *Ann Surg*. 1996;224(3):255-266.
51. Sim FH, Taylor WF, Pritchard DJ, Soule EH. Lymphadenectomy in the management of stage I malignant melanoma: A prospective randomized study. *Mayo Clin Proc*. 1986;61(9):697-705.
52. Morton DL. Technical details of intraoperative lymphatic mapping for early stage melanoma. *Arch Surg*. 1992;127(4):392.
53. Nieweg OE, Tanis PJ, Kroon BB. The definition of a sentinel node. *Ann Surg Oncol*. 2001;8(6):538-541.
54. Ribero S, Osella-Abate S, Pasquali S, et al. Prognostic role of multiple lymphatic basin drainage in sentinel lymph node-negative trunk melanoma patients: A multicenter study from the Italian melanoma intergroup. *Ann Surg Oncol*. 2016;23(5):1708-1715.

55. Porter GA, Ross MI, Berman RS, Lee JE, Mansfield PF, Gershenwald JE. Significance of multiple nodal basin drainage in truncal melanoma patients undergoing sentinel lymph node biopsy. *Ann Surg Oncol.* 2000;7(4):256-261.
56. Federico AC, Chagpar AB, Ross MI, et al. Effect of multiple-nodal basin drainage on cutaneous melanoma. *Arch Surg.* 2008;143(7):632-637.
57. Ahmadzadehfar H, Hinz T, Wierzbicki A, et al. Significance of multiple nodal basin drainage in patients with truncal melanoma. *QJ Nucl Med Mol Imaging* 2016;60(3):274-279.
58. Morton DL, Thompson JF, Cochran AJ, et al. Final trial report of sentinel-node biopsy versus nodal observation in melanoma. *N Engl J Med.* 2014;370(7):599-609.
59. Thompson JF, McCarthy WH, Bosch CMJ, et al. Sentinel lymph node status as an indicator of the presence of metastatic melanoma in regional lymph nodes. *Melanoma Res.* 1995;5(4):255-260.
60. Cabanas RM. An approach for the treatment of penile carcinoma. *Cancer.* 1977;39(2):456-466.
61. Sayegh E, Brooks T, Sacher E, Busch F. Lymphangiography of the retroperitoneal lymph nodes through the inguinal route. *J Urol.* 1966;95(1):102-107.
62. Gould EA, Winship T, Philbin PH, Kerr HH. Observations on a "sentinel node" in cancer of the parotid. *Cancer.* 1960;13(1):77-78.
63. Braithwaite LR. The flow of lymph from the ileocaecal angle, and its possible bearing on the cause of duodenal and gastric ulcer. *Br J Surg.* 1923;11(41):7-26.
64. Nieweg OE, Uren RF, Thompson JF. The history of sentinel lymph node biopsy. *Cancer J.* 2015;21(1):3-6.
65. Uren RF, Howman-Giles R, Chung D, Thompson JF. Guidelines for lymphoscintigraphy and F18 FDG PET scans in melanoma. *J Surg Oncol.* 2011;104(4):405-419.
66. Vermeeren L, Valdés Olmos RA, Klop WMC, et al. SPECT/CT for sentinel lymph node mapping in head and neck melanoma. *Head Neck.* 2011;33(1):1-6.
67. Vermeeren L, van der Ploeg IMC, Olmos RAV, et al. SPECT/CT for preoperative sentinel node localization. *J Surg Oncol.* 2010;101(2):184-190.
68. van der Ploeg IMC, Valdés Olmos RA, Kroon BBR, et al. The yield of SPECT/CT for anatomical lymphatic mapping in patients with melanoma. *Ann Surg Oncol.* 2009;16(6):1537-1542.
69. van der Ploeg IMC, Nieweg OE, Kroon BBR, et al. The yield of SPECT/CT for anatomical lymphatic mapping in patients with breast cancer. *Eur J Nucl Med Mol Imaging.* 2009;36(6):903-909.
70. Rawson R V., Scolyer RA. From Breslow to BRAF and immunotherapy: Evolving concepts in melanoma pathogenesis and disease progression and their implications for changing management over the last 50 years. *Hum Pathol.* 2020;95:149-160.
71. Scolyer RA, Murali R, McCarthy SW, Thompson JF. Pathologic examination of sentinel lymph nodes from melanoma patients. *Semin Diagn Pathol.* 2008;25(2):100-111.
72. Cascinelli N, Belli F, Santinami M, et al. Sentinel lymph node biopsy in cutaneous melanoma: the WHO melanoma program experience. *Ann Surg Oncol.* 2000;7(6):469-474.
73. Thompson JF, Scolyer RA, Kefford RF. Cutaneous melanoma. *The Lancet.* 2005;365(9460):687-701.
74. Morton DL, Thompson JF, Essner R, et al. Validation of the accuracy of intraoperative lymphatic mapping and sentinel lymphadenectomy for early-stage melanoma. *Ann Surg.* 1999;230(4):453.
75. Gershenwald JE, Thompson W, Mansfield PF, et al. Multi-institutional melanoma lymphatic mapping experience: The prognostic value of sentinel lymph node status in 612 stage I or II melanoma patients. *J Clin Oncol.* 1999;17(3):976-976.

76. Murali R, Haydu LE, Quinn MJ, et al. Sentinel lymph node biopsy in patients with thin primary cutaneous melanoma. *Ann Surg.* 2012;255(1):128-133.
77. Andtbacka RHI, Gershenwald JE. Role of sentinel lymph node biopsy in patients with thin melanoma. *J Natl Compr Canc Netw.* 2009;7(3):308-317.
78. Cordeiro E, Gervais M-K, Shah PS, Look Hong NJ, Wright FC. Sentinel lymph node biopsy in thin cutaneous melanoma: A systematic review and meta-analysis. *Ann Surg Oncol.* 2016;23(13):4178-4188.
79. Han D, Zager JS, Shyr Y, et al. Clinicopathologic predictors of sentinel lymph node metastasis in thin melanoma. *J Clin Oncol.* 2013;31(35):4387-4393.
80. Gannon CJ, Rousseau DL, Ross MI, et al. Accuracy of lymphatic mapping and sentinel lymph node biopsy after previous wide local excision in patients with primary melanoma. *Cancer.* 2006;107(11):2647-2652.
81. Tsai S, Balch C, Lange J. Epidemiology and treatment of melanoma in elderly patients. *Nat Rev Clin Oncol.* 2010;7(3):148-152.
82. Garcovich S, Colloca G, Sollena P, et al. Skin cancer epidemics in the elderly as an emerging issue in geriatric oncology. *Aging Dis.* 2017;8(5):643-661.
83. Kruijff S, Bastiaannet E, Francken AB, Schaapveld M, van der Aa M, Hoekstra HJ. Breslow thickness in the Netherlands: A population-based study of 40 880 patients comparing young and elderly patients. *Br J Cancer.* 2012;107(3):570-574.
84. Schuurman MS, Hollestein LM, Bastiaannet E, et al. Melanoma in older patients: Declining gap in survival between younger and older patients with melanoma. *Acta Oncol.* 2020;59(1):4-12.
85. Lasithiotakis K, Leiter U, Meier F, et al. Age and gender are significant independent predictors of survival in primary cutaneous melanoma. *Cancer.* 2008;112(8):1795-1804.
86. Ciocan D, Barbe C, Aubin F, et al. Distinctive features of melanoma and its management in elderly patients: A population-based study in France. *JAMA Dermatol.* 2013;149(10):1150-1157.
87. Rees MJ, Liao H, Spillane J, et al. Melanoma in the very elderly, management in patients 85 years of age and over. *J Geriatr Oncol.* 2018;9(5):488-493.
88. Chao C, Martin RCG, Ross MI, et al. Correlation between prognostic factors and increasing age in melanoma. *Ann Surg Oncol.* 2004;11(3):259-264.
89. Cavanaugh-Hussey MW, Mu EW, Kang S, Balch CM, Wang T. Older age is associated with a higher incidence of melanoma death but a lower incidence of sentinel lymph node metastasis in the SEER databases (2003-2011). *Ann Surg Oncol.* 2015;22(7):2120-2126.
90. Conway WC, Faries MB, Nicholl MB, et al. Age-related lymphatic dysfunction in melanoma patients. *Ann Surg Oncol.* 2009;16(6):1548-1552.
91. Rees MJ, Liao H, Spillane J, et al. Localized melanoma in older patients, the impact of increasing age and comorbid medical conditions. *Eur J Surg Oncol.* 2016; 42(9):1359-1366.
92. Sabel MS, Kozminski D, Griffith K, Chang AE, Johnson TM, Wong S. Sentinel lymph node biopsy use among melanoma patients 75 years of age and older. *Ann Surg Oncol.* 2015;22(7):2112-2119.
93. de Vries E, Steliarova-Foucher E, Spatz A, Ardanaz E, Eggermont AMM, Coebergh JWW. Skin cancer incidence and survival in European children and adolescents (1978-1997). Report from the Automated Childhood Cancer Information System project. *Eur J Cancer.* 2006;42(13):2170-2182.
94. Pappo AS. Melanoma in children and adolescents. *Eur J Cancer.* 2003;39(18):2651-2661.
95. Campbell LB, Kreicher KL, Gittleman HR, Strodtbeck K, Barnholtz-Sloan J, Bordeaux JS. Melanoma incidence in children and adolescents: Decreasing trends in the united states. *J Pediatr.* 2015;166(6):1505-1513.

96. Barr RD, Ries LAG, Lewis DR, et al. Incidence and incidence trends of the most frequent cancers in adolescent and young adult Americans, including “nonmalignant/noninvasive” tumors. *Cancer*. 2016;122(7):1000-1008.
97. Siegel DA, King J, Tai E, Buchanan N, Ajani UA, Li J. Cancer incidence rates and trends among children and adolescents in the United States, 2001-2009. *Pediatrics*. 2014;134(4):e945-55.
98. Ferrari A, Bono A, Baldi M, et al. Does melanoma behave differently in younger children than in adults? A retrospective study of 33 cases of childhood melanoma from a single institution. *Pediatrics*. 2005;115(3):649-654.
99. Cordoro KM, Gupta D, Frieden IJ, McCalmont T, Kashani-Sabet M. Pediatric melanoma: Results of a large cohort study and proposal for modified ABCD detection criteria for children. *J Am Acad Dermatol*. 2013;68(6):913-925.
100. Thomas JM, Newton-Bishop J, A'Hern R, et al. Excision margins in high-risk malignant melanoma. *N Engl J Med*. 2004;350(8):757-766.
101. Lorimer PD, White RL, Walsh K, et al. Pediatric and adolescent melanoma: A national cancer data base update. *Ann Surg Oncol*. 2016;23(12):4058-4066.
102. Livestro DP, Kaine EM, Michaelson JS, et al. Melanoma in the young: Differences and similarities with adult melanoma: A case-matched controlled analysis. *Cancer*. 2007;110(3):614-624.
103. Kibbi N, Kluger H, Choi JN. Melanoma: Clinical Presentations. In: *Cancer Treatment and Research*. Vol 167. Kluwer Academic Publishers; 2016:107-129.
104. Read J, Wadt KAW, Hayward NK. Melanoma genetics. *J Med Genet*. 2016;53(1):1-14.
105. Ransohoff KJ, Jaju PD, Tang JY, Carbone M, Leachman S, Sarin KY. Familial skin cancer syndromes Increased melanoma risk. *J Am Acad Dermatol*. 2016;74(3):423-434.
106. Potjer TP, Bollen S, Grimbergen AJEM, et al. Multigene panel sequencing of established and candidate melanoma susceptibility genes in a large cohort of Dutch non-CDKN2A/CDK4 melanoma families. *Int J Cancer*. 2019;144(10):2453-2464.
107. Halk AB, Potjer TP, Kukutsch NA, Vasen HFA, Hes FJ, van Doorn R. Surveillance for familial melanoma: Recommendations from a national centre of expertise. *Br J Dermatol*. 2019;181(3):594-596.
108. Goldstein AM, Chan M, Harland M, et al. Features associated with germline CDKN2A mutations: a GenoMEL study of melanoma-prone families from three continents. *J Med Genet*. 2006;44(2):99-106.
109. Kefford RF, Newton Bishop JA, Bergman W, Tucker MA. Counseling and DNA testing for individuals perceived to be genetically predisposed to melanoma: a consensus statement of the Melanoma Genetics Consortium. *J Clin Oncol*. 1999;17(10):3245-3251.
110. Bergman W, Gruis NA, Frants RR. The Dutch FAMMM family material: Clinical and genetic data. *Cytogenet Cell Genet*. 1992;59(2-3):161-164.
111. Gruis NA, van der Velden PA, Sandkuijl LA, et al. Homozygotes for CDKN2 (p16) germline mutation in Dutch familial melanoma kindreds. *Nat Genet*. 1995;10(3):351-353.
112. Helgadóttir H, Höiom V, Tuominen R, et al. Germline CDKN2A mutation status and survival in familial melanoma cases. *J Natl Cancer Inst*. 2016;108(11).
113. Potjer TP, Kranenburg HE, Bergman W, et al. Prospective risk of cancer and the influence of tobacco use in carriers of the p16-Leiden germline variant. *Eur J Hum Genet*. 2015;23(5):711-714.
114. Helgadóttir H, Höiom V, Tuominen R, et al. Germline CDKN2A Mutation Status and Survival in Familial Melanoma Cases. *J Natl Cancer Inst*. 2016;108(11):djw135.

115. Helgadottir H, Tuominen R, Olsson H, Hansson J, Höiom V. Cancer risks and survival in patients with multiple primary melanomas: Association with family history of melanoma and germline CDKN2A mutation status. *J Am Acad Dermatol.* 2017;77(5):893-901.
116. Dalmaso B, Pastorino L, Ciccarese G, et al. CDKN2A germline mutations are not associated with poor survival in an Italian cohort of melanoma patients. *J Am Acad Dermatol.* 2019;80(5):1263-1271.

