

Indications for Digital Monitoring of Patients With Multiple Nevi: Recommendations from the International Dermoscopy Society

Teresa Russo¹, Vincenzo Piccolo¹, Elvira Moscarella¹, Philipp Tschandl², Harald Kittler², John Paoli³, Aimilios Lallas⁴, Ralph P. Braun⁵, Luc Thomas⁶, H. Peter Soyer⁷, Josep Malvehy⁸, Susana Puig⁸, Ashfaq Marghoob⁹, Alon Scope¹⁰, Andreas Blum¹¹, Allan C. Halpern⁹, Horacio Cabo¹², Scott Menzies¹³, Wilhelm Stolz¹⁴, Masaru Tanaka¹⁵, Harold Rabinovitz¹⁶, Rainer Hofmann-Wellenhof¹⁷, Renato Marchiori Bakos¹⁸, Iris Zalaudek¹⁹, Giovanni Pellacani²⁰, Ana Varela Veiga²¹, Laura Rosende Maceiras²¹, Cristina de las Heras-Sotos²¹, Giuseppe Argenziano¹

1 Dermatology Unit, University of Campania “Luigi Vanvitelli”, Naples, Italy

2 Department of Dermatology, Medical University of Vienna, Vienna, Austria

3 Department of Dermatology and Venereology, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

4 First Department of Dermatology, Aristotle University, Thessaloniki, Greece

5 Department of Dermatology, University Hospital Zürich, Zürich, Switzerland

6 Department of Dermatology, Lyon-1 University, and Cancer research center Lyon, Lyon, France

7 The University of Queensland Diamantina Institute, The University of Queensland, Dermatology Research Centre, Brisbane, Australia

8 Melanoma Unit, Dermatology Department, Hospital Clinic Barcelona, Universitat de Barcelona & IDIBAPS & CIBERER, Barcelona, Spain

9 Memorial Sloan Kettering Cancer Center, Hauppauge, New York, USA

10 The Kittner Skin Cancer Screening and Research Institute, Sheba Medical Center and Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel

11 Public, Private and Teaching Practice of Dermatology, Konstanz, Germany

12 Dermatology Institute of Medical Research, University of Buenos Aires, Buenos Aires, Argentina

13 Discipline of Dermatology, Sydney Medical School, The University of Sydney and Sydney Melanoma Diagnostic Centre, Royal Prince Alfred Hospital, Camperdown, NSW Australia

14 Department of Dermatology, Allergology, and Environmental Medicine Clinic Thalkirchen, Hospital Munich, Munich, Germany

15 Department of Dermatology, Tokyo Women’s Medical University Medical Center East, Japan

16 Department of Dermatology Medical College of Georgia, Augusta, United States

17 Department of Dermatology and Venereology, Medical University of Graz, Graz, Austria

18 Department of Dermatology, Hospital de Clinicas de Porto Alegre - Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil

19 Department of Dermatology, University of Trieste, Trieste, Italy

20 Department of Dermatology, University of Rome La Sapienza, Rome, Italy

21 Department of Dermatology, University Hospital Complex of Ferrol, A Coruña, Spain

Key words: dermoscopy, dermatoscopy, digital monitoring, multiple nevi, total body photography

Citation: Russo T, Piccolo V, Moscarella E, et al. Indications For Digital Monitoring Of Patients With Multiple Nevi: Recommendations From The International Dermoscopy Society. *Dermatol Pract Concept*. 2022;12(4):e2022182. DOI: <https://doi.org/10.5826/dpc.1204a182>

Accepted: January 13, 2022; **Published:** October 2022

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Funding: None.

Competing interests: None.

Authorship: All authors have contributed significantly to this publication.

Corresponding author: Vincenzo Piccolo, Dermatology Unit, University of Campania “Luigi Vanvitelli”, Naples, Italy.
E-mail: piccolo.vincenzo@gmail.com

ABSTRACT **Introduction:** In patients with multiple nevi, sequential imaging using total body skin photography (TBSP) coupled with digital dermoscopy (DD) documentation reduces unnecessary excisions and improves the early detection of melanoma. Correct patient selection is essential for optimizing the efficacy of this diagnostic approach.

Objectives: The purpose of the study was to identify, via expert consensus, the best indications for TBSP and DD follow-up.

Methods: This study was performed on behalf of the International Dermoscopy Society (IDS). We attained consensus by using an e-Delphi methodology. The panel of participants included international experts in dermoscopy. In each Delphi round, experts were asked to select from a list of indications for TBSP and DD.

Results: Expert consensus was attained after 3 rounds of Delphi. Participants considered a total nevus count of 60 or more nevi or the presence of a CDKN2A mutation sufficient to refer the patient for digital monitoring. Patients with more than 40 nevi were only considered an indication in case of personal history of melanoma or red hair and/or a MC1R mutation or history of organ transplantation.

Conclusions: Our recommendations support clinicians in choosing appropriate follow-up regimens for patients with multiple nevi and in applying the time-consuming procedure of sequential imaging more efficiently. Further studies and real-life data are needed to confirm the usefulness of this list of indications in clinical practice.

Introduction

A combined clinical and dermoscopic examination of melanocytic lesions allows for the recognition of most melanomas at a baseline visit [1-3]. In a patient with a single doubtful lesion, although only moderately atypical, the best approach is prompt excision and histopathologic examination. Conversely, in patients with multiple nevi, the approach of excising any atypical lesion appears neither reasonable nor cost-effective. In this scenario, sequential monitoring and imaging using total body skin photography (TBSP) coupled with digital dermoscopy (DD) documentation represents the best approach to minimize unnecessary excisions while maximizing early detection of melanoma (Figures 1 and 2). While DD is useful to evaluate morphologic changes of the individual monitored lesions, TBSP mostly helps in the recognition of new lesions or significant changes in lesions that were not previously documented dermoscopically [2-7].

It has been calculated that about 10% of melanomas are diagnosed over time in the context of clinically and dermoscopically inconspicuous tumors in patients with multiple and/or atypical nevi [1,2]. In a recent cohort study dealing with high-risk patients in a melanoma dermatology clinic, 60.8% of melanomas were found with the assistance of TBSP (31.6%) or sequential DD imaging (29.2%) [3].

Melanomas detected via sequential monitoring with TBSP and DD usually escape baseline detection because they neither display melanoma-specific criteria, nor substantially differ from the patients nevi [9]. This more frequently occurs in individuals with peculiar nevus phenotypes, such as familial melanoma patients [10]. However, TBSP and DD are time-consuming techniques, so appropriate indications are crucial for the method to be effective. Recently, a study by Haenssle et al on 688 patients concluded that patients with multiple nevi and additional risk factors for melanoma had the highest benefit from sequential DD imaging in terms of early melanoma detection over time [6,7]. Several additional studies deal with the relevant additional risk factors to be evaluated when referring a patient for digital monitoring, but there is some heterogeneity among them [11-14]. Since a consensus agreement is still lacking, we are trying to provide one.

Objectives

The purpose of this study was, therefore, to set up a list of indications for digital follow-up performed via TBSP coupled with DD through the selection of specific melanoma risk factors that may serve to better recognize patients who will benefit from this approach.

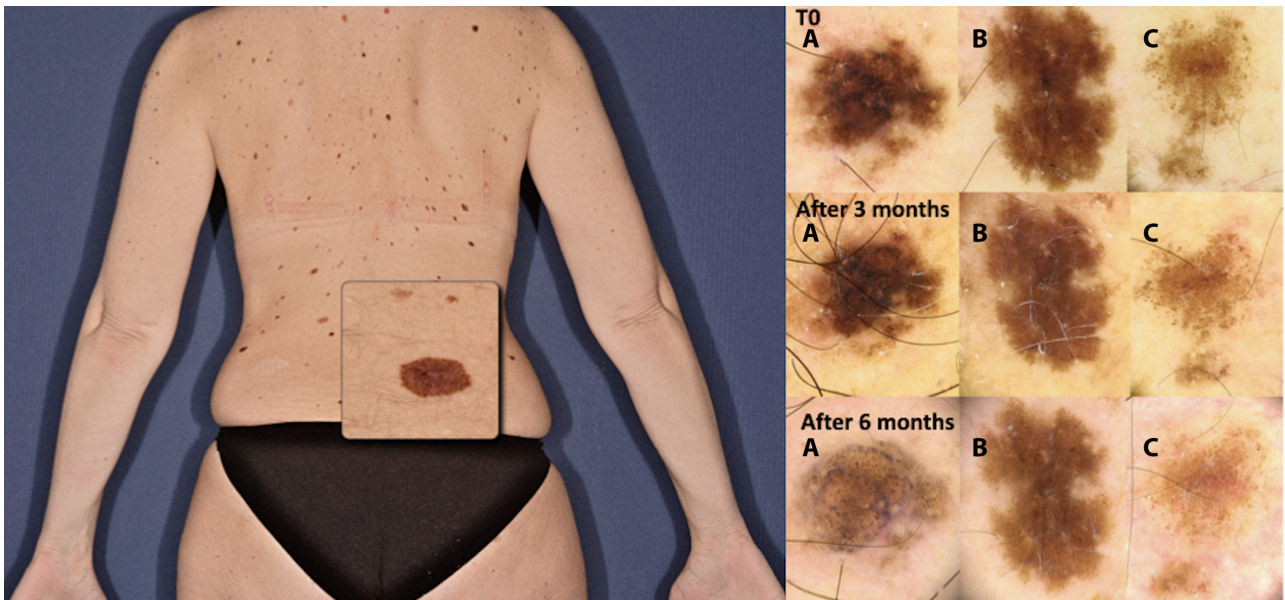


Figure 1. Patient with more than 60 nevi. Side by side comparison of 3 lesions (A, B, C) during follow-up. Note the increased regression structures over time of the first lesion (A) on the left, which was therefore excised and diagnosed as a melanoma in situ.

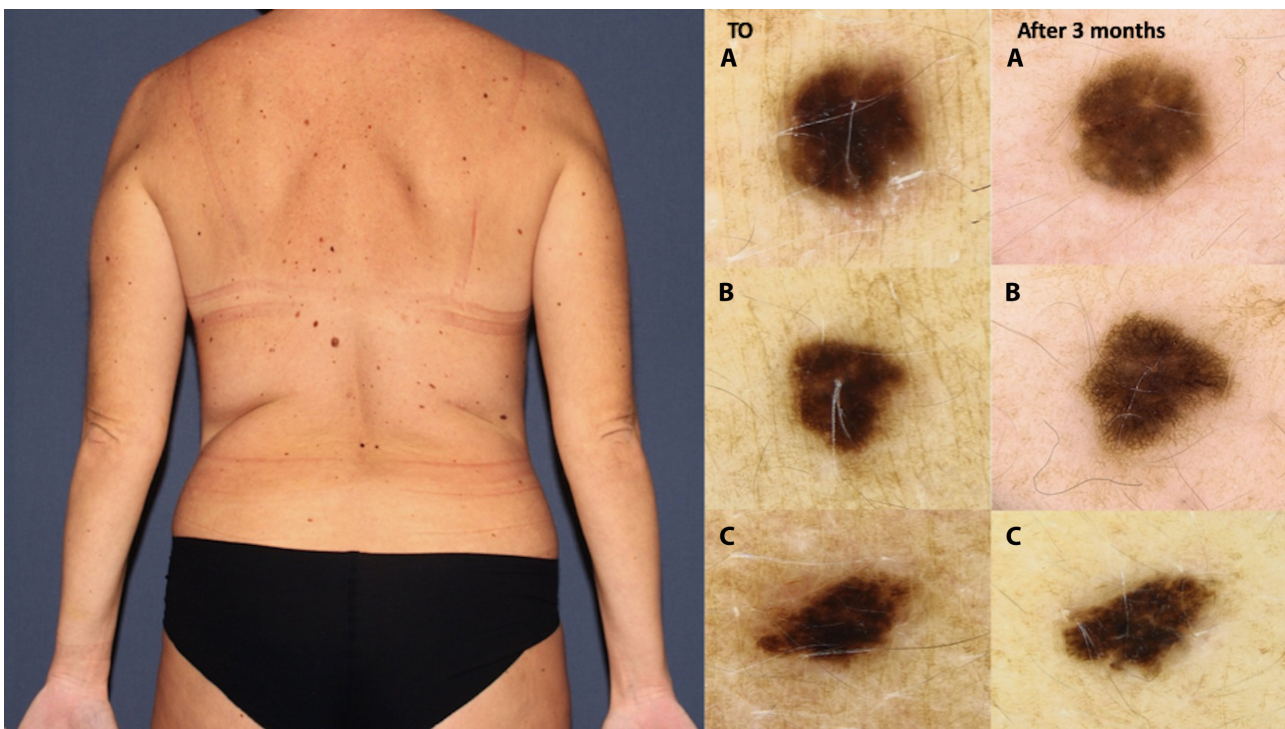


Figure 2. Patient with more than 40 nevi and previous melanoma. Lesion C showed remarkable change in the lesion after 3 months of follow-up and was therefore excised and confirmed to be a melanoma in situ, while lesion A and B did not show significant modifications.

Methods

This study was performed on behalf of the International Dermoscopy Society (IDS), with consensus obtained through the e-Delphi methodology [15]. Participants were recruited among the executive board members of the IDS who were specifically asked by email invitation for their consent to take part in the study. Only those who accepted to join the project

received the SurveyMonkey (<https://www.surveymonkey.com/>) link and password for taking part in the survey.

The study consisted of two steps: (I) identification of major risk factors for melanoma in patients with multiple nevi according to the most relevant meta-analyses and studies; and (II) selection of indications for TBSP and DD after a three-round questionnaire proposed to a panel of international experts in dermoscopy. During each round, participants were

given a 4-week period to complete the survey and reminders were sent to non-responders on days 7, 14 and 21. The three rounds were conducted over a 6-month period and the final list of indications was obtained and completed within 8 months. The aforementioned criteria for the enrolment of patients for digital monitoring programs were finally drawn up with the collaboration of expert members of the IDS, who contributed to the study with their answers, advice and feedback.

Step 1: Identification of Risk Factors for Melanoma in Patients With Multiple Nevi

The questions for the survey were obtained after a literature search of relevant meta-analyses and studies about major melanoma risk factors. The presence of multiple nevi was considered the basic requirement for patient enrolment in a digital monitoring program using TBSP coupled with DD. The number and type of nevi needed to reach the cut-off point were discussed in the second step. The lower size limit to consider the nevus eligible to be counted has been conventionally established at 2 mm. The proposed questions were associated with their background studies and their relative levels of evidence assigned based on

the Oxford 2011 Levels of Evidence [16]. Melanoma risk factors were expressed in terms of relative risk (RR) and odds ratio (OR) with the exception of CDKN2A mutation [17-21], for which we considered the ratio between lifetime risk of melanoma in patients with the mutation and lifetime risk in the general population (Table 1). Variables increasing the melanoma risk at least 3 times were considered as major risk factors; variables increasing the risk between 2 and 3 times were considered as intermediate risk factors; and variables increasing the risk by less than 2 times were considered as minor risk factors [22].

Step 2: Selection of Indications for TBSP and DD After a Three-round Questionnaire Proposed to a Panel of International Experts in Dermoscopy

Participants were first asked if a given risk factor, in combination with the presence of multiple nevi, is relevant enough to justify inclusion in the list of indications. The questions were uploaded in two different blinded Delphi rounds on the SurveyMonkey platform and were proposed to the experts who were included for the 1st round survey. They were asked to judge their agreement for each sentence using the 5-point

Table 1. Risk factors for cutaneous melanomas and their relative risks (modified from Chen et al [4]).

Characteristic	Risk factor for cutaneous melanoma	Summary statistics (RR, OR)
Common nevi (total number)	16-40	1.47
	41-60	2.24
	61-80	3.26
	81-100	4.74
	101-120	6.89
Atypical nevi (total number)	1	1.45
	2	2.10
	3	3.03
	4	4.39
	5	6.36
Eye color	blue	1.47
	green	1.61
	hazel	1.52
Hair color	red	3.64
	blond	1.96
	light brown	1.62
Family history of melanoma	positive	1.74
Personal history of non-melanoma skin cancer	positive	2.74
Genetic factors	CDKN2A mutation	10 ^a
Sun exposure	strong history of sunburn	2.03
	ever use of tanning booth	2.06
Organ transplant history	positive	2.38

RR = relative risk; OR = odds ratio.

^a For CDKN2A, the risk is based on the ratio between the lifetime risk of melanoma in patients with the mutation and the lifetime risk of melanoma in the general population.

Likert Scale for Surveys (1: strongly agree, 2: agree; 3: neither agree nor disagree; 4: disagree; 5: strongly disagree) [23].

Each parameter was admitted to the 2nd round questionnaire of the consensus procedure if at least 65% of the experts rated it 1 or 2 according to the Likert Scale for Surveys [23]. The questions of the 2nd round were formulated based on the 1st one and, again, participants were asked to answer using the 5-point scale. Finally, in the last round, participants were asked to confirm or refute the list of indications obtained as a result of the first two rounds.

Results

First Round

Of the executive board members of the IDS invited by email, all (N = 27) confirmed their participation and received the link to answer the round 1 questionnaire anonymously. Of them, 25 completed the questionnaire. More than 90% of experts agreed (32%, N = 8) or strongly agreed (64%, N = 16) on the necessity to establish selection criteria for patients with multiple nevi who need digital monitoring. For 92% (N = 23) of participants, the total number of nevi was considered relevant to select these patients.

Table 1 shows the most common risk factors for melanoma and their relative risks. The great majority agreed (88%, N = 22) that significant risk factors for melanoma were those having a RR (relative risk) > 2. Moreover, 92% (N = 23) of participants agreed that patients with multiple nevi and at least one additional risk factor for melanoma could have a higher cumulative risk for melanoma than patients with only one risk factor, thus making them more eligible for long-term digital monitoring.

Participants were asked to propose other factors that should be considered as indication for digital monitoring. Two of 25 participants proposed the anxiety of patients with multiple nevi as a criterion for digital monitoring. Therefore, this criterion was added for the second round of questions. In the open answers, some participants underlined the necessity to avoid digital monitoring in the following clinical scenarios: (i) in children before puberty, even if multiple nevi were present; (ii) in patients with complex health conditions that can render the examination difficult; (iii) in the context of nodular lesions, especially if rapidly changing.

Second Round

The 2nd round questionnaire was sent to the 25 members who completed the first one, with 23 completing the round. At first, this round had the purpose to establish the number and type of nevi needed as cut-off for the definition of a patient with multiple nevi; secondly, the additional criteria

for selecting patients suitable for digital monitoring were established.

Fifteen (65%) experts agreed on the definition of a common nevus being a macular or papular symmetrical lesion, smaller than 6 mm in diameter, uniform in color, with well-defined borders and regular overall architecture in dermoscopy. Consequently, an atypical nevus was defined as a flat or slightly raised lesion usually larger than 6 mm, with ill-defined borders, irregular pigmentation, and a mixed pattern dermoscopically.

Given the RR of 3.26 of developing melanoma in patients with 61-80 common nevi [24], 70% (N = 16) of responders agreed to establish the threshold of at least 60 common nevi to select patients requiring digital monitoring, in the absence of additional risk factors. The experts showed their consensus to reduce the threshold to 40 common nevi (RR 2.24) if the patient had additional melanoma risk factors because of a higher cumulative risk of melanoma. However, the experts did not agree on establishing a cut-off number of atypical nevi as an indication for TBSP and DD if this was the only melanoma risk factor of the patient.

For the other melanoma risk factors, we asked whether the anxiety (as suggested by 2 experts) could be an indication for TBSP and DD. Only 52% (N = 12) of participants considered it a relevant risk factor in patients with multiple nevi. This criterion was therefore excluded from the final list of indications.

Nineteen (83%) experts agreed on considering a personal history of melanoma coupled with more than 40 nevi as an indication for TBSP and DD. They also agreed to enlist patients for digital monitoring if they had more than 40 nevi and red hair, with (65%, N = 15) or without a MC1R mutation (74%, N = 17). Organ transplant recipients with at least 40 nevi were also judged suitable for digital monitoring (65%, N = 15). Finally, almost all members agreed (91.3%, N = 21) on considering digital monitoring to be useful in patients with a CDKN2A mutation (familial melanoma) even in patients with less than 40 nevi.

In the open final discussion of this round, with almost total agreement among the experts, it emerged that even in absence of referring relative risk data, other rarer identified melanoma-predisposing mutations different from CDKN2A and MC1R variants (ie BAP-1, CDK-4, and MIT-F) should not be ignored independently from the nevus count.

There was no agreement on indicating digital monitoring in patients with few atypical nevi or with less than 40 nevi. Personal history of non-melanocytic skin cancer, sunbed exposure or sunburns were not considered as valid criteria to select a patient for TBSP and DD even when associated with the presence of more than 40 nevi.

Third Round

The results of the second round allowed us to propose the following five indications for digital monitoring in the third round:

1. Patients with more than 60 melanocytic nevi.
2. Patients with a *CDKN2A* mutation or other rarer high-risk melanoma genetic variants.
3. Patients with more than 40 melanocytic nevi and a personal history of melanoma.
4. Patients with more than 40 melanocytic nevi and red hair and/or a MC1R mutation
5. Patients with more than 40 melanocytic nevi and a history of organ transplantation.

This final list (Table 2) was proposed by mail to the 25 members of the first Delphi round, clarifying that the strategy of silent consensus would be used (i.e. no answer would be interpreted as a positive response). Ultimately, 17 members (68%) confirmed their consensus to this list of criteria, while the remaining participants expressed their silent consensus.

Conclusions

In the last decade, many studies focused on digital monitoring of patients with multiple nevi, with special emphasis on the duration and scheduling of follow-up visits, the type and number of lesions to be digitally documented, and the type of changes that should lead to a biopsy [3-5]. However, no sufficient and exhaustive data have been reported about the indications for patient enrolment to digital monitoring. Being aware of the costs and duration of the TBSP and DD procedure, our aim was to more precisely identify the patient categories that can benefit from this diagnostic approach [24].

A high total number of nevi is clearly the basic condition to include a patient in a digital monitoring program. The participants considered a total nevus count of at least 60 (RR >3) sufficient to refer the patient for digital monitoring. This was based on a meta-analysis published by Gandini et al in 2005 that confirmed such patients' propensity to develop melanoma [25,26]. In detail, the higher the number of common nevi, the higher the RR for melanoma, which was estimated

to be 2.24 for a number of common nevi ranging from 41-60 nevi and 3.26 for 61-80 nevi. Thus, patients with more than 40 nevi (with a RR between 2 and 3) were considered to deserve this follow-up procedure only if presenting with additional risk factors, namely: a personal history of melanoma, red hair with or without a MC1R variant associated to melanoma risk or a history of organ transplantation [25,26].

In the same meta-analysis by Gandini et al, patients with two atypical nevi showed a RR of 2.10 [25,26]. Therefore, we asked participants if patients with multiple nevi (more than 40) and at least 2 atypical nevi should be enrolled for digital monitoring. This criterion probably did not reach a consensus because it is very frequent that a patient with more than 60 nevi also exhibits some atypical ones.

In 2015, Chen et al found a stable 2- to 3-fold increased risk depending on the number of previous melanomas, in both patients with familial melanoma and those with sporadic melanoma(s) [27]. For instance, in patients with a single previous melanoma, the risk for a second melanoma was 2.5 for patients with familial melanoma and 2.3 in patients with a sporadic melanoma. In 2019, Lallas et al in a prospective study in a cohort of 977 patients showed 8% cumulative risk of second primary melanoma, thus highlighting the value of TBSP and DD in this group of patients [28]. According to these findings, the personal history of melanoma (both in familial melanoma and in sporadic melanoma) was judged as a very effective criterion to better select patients for digital monitoring, as also suggested by Haenssle et al [6,7].

In 2010, Wheless et al reported a RR of 2.74 for developing melanoma in patients with a history of NMSC, compared to controls with no prior NMSC [29]. This group of patients, even when having multiple nevi, was not considered eligible for digital monitoring. Given the high prevalence of NMSC, this criterion could potentially increase the number of patients referred for this special follow-up procedure too much, without a real benefit in finding more melanomas over time.

In contrast, almost all participants agreed on including the red hair phenotype in the final list of indications. In a meta-analysis on phenotypic risk factors for cutaneous melanoma, the red hair phenotype was the only phenotypic aspect found to have a RR greater than 3 (3.64) for melanoma development, while all the other clinical features showed a

Table 2. List of indications for digital monitoring in patient with multiple nevi.

Indications for digital monitoring in patients with multiple nevi.
I. Patients with more than 60 melanocytic nevi.
II. Patients with a <i>CDKN2A</i> mutation or other rarer high-risk melanoma genetic variants.
III. Patients with more than 40 melanocytic nevi and a personal history of melanoma.
IV. Patients with more than 40 melanocytic nevi and red hair and/or a MC1R mutation
V. Patients with more than 40 melanocytic nevi and a history of organ transplantation.

RR below 2 [5,25,26]. Particularly, different studies, as that of Duffy et al confirmed the importance of the association of a MC1R genotype and the presence of multiple nevi in contributing synergically to increase the individual's melanoma risk [30-32].

A RR for melanoma of 2.03 was found in a meta-analysis by Gandini et al in case of strong sunburn history [33]. Similarly, a large case-control study from the Nurses Health Study published in 2006 found an OR of 2.06 for "ever" versus "never" usage of tanning booths [34]. Despite this risk, the IDS members did not consider patients with a strong history of sunburn or ever use of tanning booths to be qualified for digital monitoring if they had less than 60 nevi.

Concerning the potentially increased risk of melanoma after organ transplantation, the standardized incidence ratio for melanoma was reported to be 2.38 in this population, indicating a substantially increased risk [5,35,36]. Although other immune deficiencies increase the melanoma risk, their RRs are not well calculated yet. Thus, participants reached the consensus to refer patients with a history of organ transplantation to digital monitoring if they have more than 40 nevi.

The only exception to the rule of multiple nevi was made for patients with a known CDKN2A variant. CDKN2A variant carriers have at least a 10-fold risk of melanoma compared to people not carrying the mutation. Moreover, patients with CDKN2A often have more than 50 melanocytic nevi [17-21]. Due to this high risk, participants considered this category of patients deserving digital monitoring independently from the total nevus count.

In the final open discussion, with almost total agreement among the experts, an indication emerged to also consider patients with other rarer melanoma-predisposing mutations different from CDKN2A and MC1R variants (ie CDK-4, BAP-1, MITE, POT1, ACD, TERF2IP and TERT), even if for them the exact relative risk still remains unknown. These rarer patients have multiple nevi and an increased the risk of melanoma, therefore they were considered an exception independent from the nevus count [37-40].

In conclusion, this study suggests a list of indications for digital monitoring of patients at high risk for melanoma. This list could be a guide to help in selecting patients who could benefit the most from this time-consuming procedure. However, these criteria should always be integrated with the physicians experience in order to include also those exceptions that may escape using them strictly. Further studies and real-life data are needed to confirm the usefulness of this list of indications in clinical practice.

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