



# Evaluating the effect of detection modalities in the Danish clinical follow-up program of cutaneous melanoma—a retrospective cohort study

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## Abstract

**Background** A rising incidence of cutaneous melanoma causes a high prevalence of patients eligible for clinical follow-up, which increases the burden on the resources in the health care system. The objectives of this study are to investigate the effect of the current surveillance program in terms of detecting recurrence or development of de novo cutaneous melanomas and evaluate the efficacy of the different detection modalities including self-skin examination, physical examination, and routine imaging.

**Methods** The study is designed as a retrospective cohort study. Patients with  $\geq 1$  follow-up visit(s) in the first 2 years after diagnosis of stage IB–IIIC disease in the melanoma surveillance program at Aarhus University Hospital in 2019 are included. Detection of recurrence rate by either physician-based examination, self-skin examination or routine imaging is compared.

**Results** Two-hundred and ninety-one patients were included and 26 recurrences/de novo cutaneous melanomas were identified. Physician-based exams detected 39.5%, self-skin examination detected 34.9%, and imaging detected 27.8% of the recurrences.

**Conclusions** Physician-based examination and self-skin examination are the most effective modalities to detect recurrences. Imaging modalities detected most recurrences when performed due to suspicion. The number needed to treat for stage IB was relatively high, which is why a prolonged interval between follow-up visits for this stage is advisable. The risk of recurrence is associated with disease stage which is why it is reasonable to base the follow-up program for melanoma patients on this parameter.

Level of evidence: Level II, Risk/Prognostic

**Keywords** Melanoma · Follow-up · Modalities · Cancer · Plastic surgery

## Introduction

The prevalence of cutaneous malignant melanoma is increasing and melanoma currently ranks number 17 of the most common cancers worldwide [1]. The incidence of cutaneous melanoma in Denmark has more than doubled over the past 25 years [2, 3]. The prognosis and risk of recurrence are largely dependent on tumor thickness, ulceration status, mitotic index, and lymph node involvement [4–12].

Detection of disease and recurrence at an early stage is therefore important [13, 14].

Follow-up schedules for patients with melanoma have been established in order to detect recurrences as well as de novo melanomas. The rising incidence of cutaneous melanoma and an increased life expectancy of the population has resulted in a large number of patients enrolled in clinical control programs for melanoma. This increases the burden on economic resources and time consumption in the health care system. Continuous surveillance of the quality and effectiveness of these follow-up programs is therefore crucial.

The Danish clinical control program for melanoma is based on the TNM classification and staging from the American Joint Commission on Cancer (AJCC) 8th edition [15]. Patients who have been diagnosed with melanoma are

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offered clinical examination of the skin and follow-up on relevant symptoms at each visit.

Stage IA patients are offered a single visit after 3 months, whereas stage IB and above are followed for 5 years either by a plastic surgeon or an oncologist.

Patients at intermediate-risk, including those with stage IB and IIA disease, are followed every 6 months. Patients at high-risk (stages IIB, IIC, and III) are followed every 3 months for the first 2 years after the diagnosis and every 6 months the following 3 years. For this group, clinical examinations are supplemented by a routine position emission tomography/computed tomography scan (PET/CT). PET/CT is performed at baseline and 6, 12, 24, and 36 months after surgical resection with curative intent.

A focused ultrasound (US) of the relevant lymph node basins is offered every 3 months during the complete follow-up period to all patients who have micro-metastasis in the loco-regional lymph nodes, unless a complete lymph node dissection has been performed. Patients with stage IV disease follow an individually arranged schedule.

After the last follow-up visit at the hospital, all patients with stage IB or higher are recommended an annual consultation with their general practitioner for an additional period of 5 years [15].

In recent years, surveillance strategies of melanoma have influenced the academic dialog in order to assess the most effective follow-up regime for patients with melanoma [14, 16–18]. However, evidence-based guidelines for surveillance of these patients are limited. Although diagnosis and treatment strategies of melanoma are widely accepted and aligned in the western world, discrepancy of the follow-up schedules after surgical treatment exists. The schedules vary in frequency of follow-up visits and the medical specialty performing the examinations as well as the use of routine imaging modalities and laboratory tests [19].

This study examines how frequent either recurrence or a de novo melanoma is detected within the first 2 years of the Danish follow-up program for patients in the intermediate-risk or high-risk follow-up program. Furthermore, it assesses the effectiveness of the various modalities used to detect recurrence.

## Methods

### Study population and outcome

The study is based on retrospectively collected patient data. The cohort was defined by data from the Danish National Patient Registry (DNPR) identified by the BI-PORTAL of Region Midt. A total of 394 patients with cutaneous melanoma who had at least one follow-up visit at the Department of Plastic and Breast Surgery at Aarhus University Hospital

(AUH) in 2019 were identified. All were invited to participate in the study and 291 patients gave written consent and were included. Patients with disseminated melanoma (stage IV) or low-risk (stage IA) disease were excluded. Furthermore, patients who were seen at follow-up in 2019 but outside the first 2-year window of the follow-up program were also excluded from the study. Data were subsequently collected by manual review of medical records. Demographical data on age at the time of diagnosis and sex as well as information of tumor characteristics including Breslow thickness, histological ulceration, subtype of melanoma, site of primary tumor, lymph node status, residual tumor status after primary and secondary excision, and distant metastasis at the time of diagnosis was obtained.

Patients were staged based on TNM classification of cutaneous melanoma retrieved from the AJCC's 8th edition (2017). Additionally, it was noted if the patient had attended the optional melanoma group education program prior to their first control at 3 months post-surgery.

Recurrences and de novo melanomas diagnosed during the follow-up period were recorded. Furthermore, the diagnostic modalities used to detect recurrences or new melanomas were noted and classified as being either identified by the patient due to symptoms (e.g., changes in the skin, feeling of subcutaneous nodule, palpable changes in the lymph node basins, seizures, cough, or gastrointestinal symptoms), detected at physical examination performed by the physician (PE) or detected by routine imaging (PET/CT scans and lymph node US).

### Data management

All collected data were stored in the Research Electronic Data Capture (REDCap) database hosted by Region Midt—AUH [20, 21]. Data management and analysis was conducted in Stata v17 (StataCorp).

### Statistics

A descriptive statistical analysis was performed—normally distributed data are presented as mean with standard deviation (SD) and, for data lacking normal distribution, as interquartile range (IQR) with median.

Further statistical analysis was conducted using a Cox Proportional-Hazard regression model. The Cox regression was used to calculate the hazard ratio (HR) indicating the risk of recurrence or de novo melanoma of each stage of disease compared to stage IB. A multivariate model was applied to adjust for age, sex, primary tumor site, subtype, and adjuvant therapy status as these factors are known to affect tumor biology and risk of recurrence [6, 7, 10, 22]. A *p* value of 0.05 or less was used to denote statistical significance.

## Ethics

This study was approved by Region Midt (case no. 1–45–70–39–21) and the Board of Directors at Aarhus University Hospital. All patients included in the study gave their written, informed consent before data were collected from the medical records.

## Results

In total, 394 patients were eligible for inclusion in the study. Of these, 291 (74%) gave written consent to have their medical records reviewed and were included in the study. Baseline characteristics are presented in Table 1.

A total of 583 outpatient control visits were registered. Approximately half of these were patients with stage IB disease (Table 2). The proportion of findings suspect for recurrence (by either patient, physician or imaging) were highest among stage IIIA patients (37.3%) and lowest among patients in stage IB (14.5%).

Documented de novo melanoma or recurrences were identified in 26 patients which equals to 8.9% of the study population. Two patients were diagnosed with a non-melanoma skin cancer during a follow-up which is not included in the tables. No other types of malignant tumors (lung, breast, colorectal, etc.) were detected in the study population.

The number needed to treat (NNT) to find a case of recurrence was highest in stage IB and lowest in stage IIIC (Table 3).

The multivariate analysis adjusted for age, sex, primary tumor location, subtype, and adjuvant therapy showed a significantly increased risk of recurrence in stage IIB (HR 38.7, 95% CI (4.7–321.1),  $p=0.001$ ) and stage IIIB (HR 16.3, 95% CI (1.3–198.4),  $p=0.028$ ) when compared to stage IB (Table 4).

Despite representing only 10% of the study population, stage IIB patients accounted for the majority of the recurrences by constituting approximately one-third of all recurrences (38.7%).

In general, recurrences were predominantly detected within the regional lymph nodes followed by distant metastasis. Local recurrence was only found in one case and in patient with stage IIC.

Detection modality used for each incidence of recurrence is presented in Table 5. Imaging modalities account for routine imaging and imaging conducted as extra tests. Recurrences in the regional lymph node were somewhat equal detected by either patient, by physician or by imaging. Overall, recurrences and de novo primary melanomas were detected by the patient in 34.9% of the cases while physicians detected 39.5%.

**Table 1** Baseline characteristics of melanoma population, AUH, 2019

Baseline characteristics	
Characteristic	( <i>n</i> =291)
Sex (%)	
Male	149 (51.2)
Female	142 (48.8)
Median age (IQR)	63.5 (52.0–75.0)
Median Breslow thickness, mm (IQR)	1.42 (0.72–2.12)
Tumor subtype (%)	
Superficial spreading	231 (79.4%)
Nodular	37 (13.1%)
Acral lentiginous	4 (1.4%)
Lentigo maligna	4 (1.4%)
Desmoplastic	2 (0.7%)
Spitzoid	1 (0.3%)
Not otherwise specified (NOS)	11 (3.8%)
Tumor site (%)	
Head and neck	38 (1.3%)
Trunk	130 (44.7%)
Upper extremity	46 (15.8%)
Lower extremity	77 (26.5%)
Ulceration (%)	
Present	66 (22.8%)
Absent	218 (75.4%)
Unknown	5 (1.7%)
Sentinel node biopsy (%)	
Yes	268 (92.1%)
No	23 (7.9%)
Sentinel node location (%)	
Neck	35 (1.3%)
Axil	146 (54.7%)
Inguinal	96 (36.0%)
Extra regional	13 (4.9%)
Fossa cubiti	2 (0.7%)
T classification (%)	
1a	1 (0.3%)
1b	78 (26.9%)
2a	102 (35.2%)
2b	19 (6.5%)
3a	38 (13.1%)
3b	27 (9.3%)
4a	9 (3.1%)
4b	17 (5.8%)
Stage (%)	
IB	162 (55.7%)
IIA	36 (12.4%)
IIB	30 (10.3%)
IIC	10 (3.4%)
IIIA	17 (5.8%)
IIIB	18 (6.2%)
IIIC	16 (5.5%)

**Table 2** Outpatient controls and recurrence detection in relation to disease stage

	Stage IB	Stage IIA	Stage IIB	Stage IIC	Stage IIIA	Stage IIIB	Stage IIIC
Outpatient control visits	276	69	77	30	51	40	40
Recurrence suspected at visit (%)	40 (14.5)	18 (26.1)	24 (31.2)	8 (26.6)	19 (37.3)	11 (28.0)	9 (22.5)
Recurrence confirmed	1	2	10	2	3	2	6
Male	1	1	9	-	3	2	6
Female	-	1	1	2	-	-	-
Controls per confirmed recurrence	276:1	34.5:1	7:1	15:1	17:1	20:1	6.7:1
Recurrence proportion of all controls	0.36%	2.9%	13%	6.7%	5.9%	5%	15%

**Table 3** Outpatient visits and detection of recurrence

Total outpatient visits	(n = 583)			
No. of suspected recurrences (%)	129 (22.1)			
Total recurrences	(n = 26)			
Sex	Patients (%)	HR	95% CI	<i>p</i> value
Male	22 (84.6)	Reference	-	-
Female	4 (15.4)	0.25	0.07–0.90	0.03
Stage	Recurrence(s)	Numbers needed to treat (NNT)*		
IB	1	276		
IIA	2	34.5		
IIB	10	7		
IIC	2	15		
IIIA	3	17		
IIIB	2	20		
IIIC	6	6.7		

\*Numbers needed to treat to find one recurrence

**Table 4** Multivariate analysis of recurrence risk by overall stage

	Hazard ratio*	95% confidence interval	<i>p</i> value
Overall stage			
IB	Reference	Reference	-
IIA	7.9	0.8–78.8	0.080
IIB	38.7	4.7–321.1	0.001
IIC	8	0.6–99.4	0.100
IIIA	5.2	0.2–41.5	0.190
IIIB	16.3	1.3–198.4	0.028
IIIC	8.7	0.9–83.3	0.061

\*Multivariate analysis adjusted for age, sex, primary tumor location, tumor subtype, adjuvant therapy

With respect to the total amount of routine scans conducted, 10.6% of PET/CT and 4% of the lymph node US detected recurrence.

The majority of the recurrences found by imaging were detected by the additional tests conducted due to suspicion rather than routine imaging (Table 6).

The number of extra tests (lymph node US, PET/CT, biopsies, other scans, etc.) was recorded for all controls with suspicion of recurrence.

A total of 114 extra tests were performed in the 129 cases of suspicion of recurrence. Overall, an average of 0.9 extra tests were conducted for each suspicion of recurrence (Table 2). Excisional biopsy was the most frequent modality used for extra testing ( $n = 33$ ), followed by US ( $n = 29$ ) and PET/CT scans ( $n = 7$ ) (Table 7).

Information of attendance in the group education on ABCDE principles of nevi and self-examination was obtained for roughly half of the patients (45.7%) and the attendance rate was 57%

## Discussion

This study addresses the effectiveness of the current follow-up program concerning detection of recurrence in patients with cutaneous melanoma. The frequency of recurrence was assessed based upon disease stage and detection modality. With regard to demographics and tumor characteristics, our

**Table 5** Recurrence by site and detection modality

Recurrence site	Local (n=2)	Regional lymph node(n=21)	Distant (n=14)	De novo (n=6)	%
<b>Detection modality</b>					
Patient-detected	1	6	5	3	34.9
Physician-detected	1	8	5	3	39.5
Imaging-detected					27.8%
PET/CT	-	4	5	-	20.9
Lymph node US	-	3	-	-	6.9

Recurrences or de novo melanomas are registered > 1 time if detected by multiple detection modalities

**Table 6** Routine and additional visits/scans and recurrence

	Total	Suspicious findings (%)	Confirmed recurrence (%)	NNT
Routine visit	522	79 (15.1)	12 (2.3)	43.5
Acute visit	63	51 (81.0)	15 (23.8)	4.2
<b>Routine scans</b>				
Ultrasound	75	7 (9.3)	3 (4.0)	25
PET/CT	94	32 (34.0)	10 (10.6)	9.4
<b>Additional scans</b>				
Ultrasound	29	29 (100)	9 (31.0)	3.2
PET/CT	7	7 (100)	6 (85.7)	1.7

Effectiveness of routine imaging versus imaging due to suspicion

study population was comparable to those of larger studies in the western world [23, 24].

In general, we registered few recurrences, only 26 which represent 8.9% of the total number of patients in this cohort. This is low compared to rates of recurrence in other large published cohort studies that found recurrence rates to be 27–30% [25–27]. This is probably due to the limited follow-up period of 2 years where other studies followed their patients for 8–18 years [25, 27]. The follow-up was chosen to be 2 years, since prior studies have proved most recurrences to occur within this period [28].

**Table 7** Additional diagnostic test(s) per suspicion of recurrence

Stage								Total
	IB	IIA	IIB	IIC	IIIA	IIIB	IIIC	
No. of additional testing	28	12	31	7	15	10	11	114
Additional tests per suspicion	0.7	0.7	1.3	0.9	0.8	0.9	0.8	0.9
<b>Modality</b>								
Excisional biopsy	17	3	3	4	4	1	1	33
Core needle biopsy	2	-	6	-	2	1	2	13
Ultrasound	4	6	9	-	4	3	3	29
PET/CT scan	-	2	3	-	1	1	-	7
Other*	5	1	10	3	4	4	5	32

\*Punch biopsies, fine needle aspiration, CT, magnetic resonance imaging (MRI), colonoscopy, and others

Despite representing 10.3% of the study population, stage IIB patients accounted for the majority of the recurrences by constituting approximately one-third of all recurrences (38.7%).

This finding is in part consistent with other comparable studies, but our study differs in having few recurrences in stage IIC [25–27]. Compared to other studies, we would have suspected stage IIB and IIC to mimic each other in terms of recurrence rates [25–27].

Recurrences in our study were predominantly detected in the regional lymph nodes (50%) followed by distant metastasis (28.2%). Local recurrence was only found in one case, this in stage IIC (3.8%). This largely ties in with previous findings [25]. However, Lee et al. found the recurrence rate for stage IIA and IIB to be highest for local recurrence and for stage IIC to be primarily systemic [27, 29]. It is noticeable that our study does not detect a higher amount with local recurrence in the lower disease stages as IB–IIB. Compared to other studies, we would suspect more recurrences in the regional lymph nodes and as distant metastasis for stage IIC [25, 27, 29].

When recurrence or a de novo melanoma is suspected, extra tests are required. We found the most frequent extra test performed in stage IB to be invasive excision biopsies with benign pathology (n=17). The value of extra tests with negative outcome must be carefully considered as this can

be associated with negative implications for the patient and may increase the use of economic resources.

The number needed to treat (NNT), defined as the amount of outpatient controls needed before identifying one case of recurrence, was highest in stage IB, decreasing significantly with higher stages of disease. Patients with stage IIB disease had NNT comparable to those in stage IIC disease, which is supported by pre-existing evidence, noting that stages IIB and IIC have a poorer prognosis than stage IIIA [25, 30].

As such, we anticipated stage IIC patients to resemble stage IIB patients in terms of recurrence pattern. However, the lower frequency of recurrence among stage IIC and thereby higher NNT is probably overestimated in our population due to the small proportion of this particular patient group in the total dataset.

The high NNT in stage IB may warrant a change in the follow-up program with a reduction of the frequency of follow-up visits for this large fraction of the patient population. However, a high frequency in follow-up visits among stages IIB and IIC should be maintained as they are at higher risk of developing recurrence. Additional studies are needed to validate whether a reduction in follow-up visits among stage IB patients is feasible and safe.

The effect of SSE in our study showed to be somewhat equal to the effectiveness of physician physical examination in detecting recurrences. A few other studies have assessed the efficacy of each surveillance modality in terms of detecting recurrence or de novo melanomas. Several studies suggest self-skin examination (SSE) as effective to detect early recurrence of melanoma, which may reduce the risk of advanced disease [26, 29, 31, 32]. This is consistent with our findings, where patient self-skin examination–detected recurrences accounted for 34.9%. Prior research has shown that nearly up to two-thirds of early recurrences could be detected by self-examination performed by the patient [29]. In general, the practice of SSE is believed to be high among survivors of cutaneous melanoma [33].

Physician-based examination is probably more likely to be systematic and thorough than self-examination performed by the patient. However, in prior studies, SSE proved to be more efficient than physician-based examination to detect recurrences [25, 27, 29]. However, documentation of SSE and the efficacy of SSE as a detection modality are complex, especially when reviewed retrospectively. The frequency of SSE-based disease detection and reporting in the medical charts may be dependent on the manner in which questions are asked and how it is documented in the medical journal [34].

Our study population was offered group education on SSE of melanomas and disease detection prior to their first clinical control 3 months after surgery. Attendance rate in the group education could be suggested

as a reasonable indicator of whether patients practice sufficient SSE or not. However, information of attendance to the group education program was only obtained for 45.7% of the study population of which the rate was 57%. We believe the proportion of patients who practice SSE is likely to be higher. Other studies support a high prevalence of SSE practice in melanoma patients—up to 85–88% among melanoma survivors [33]. Another previous study showed that individuals who perceive themselves at higher risk of developing melanoma are more likely to perform SSE [35].

In this study, imaging modalities (PET/CT and lymph node US) were found to be the least effective modality to detect recurrence when used as routine imaging. Imaging primarily confirmed recurrence in the regional lymph nodes and the distant metastasis in cases where there was a clinical suspicion. Furthermore, PET/CT detected more recurrences than US in the lymph nodes when used as routine imaging. These findings are in line with a previous study that primarily used CT scans as routine imaging. Out of 42 image-detected recurrences, the authors reported only one case detected by ultrasound of the regional lymph node basins [27].

A meta-analysis from 2012 reviewed 74 studies evaluating the effectiveness of the different imaging modalities to detect recurrences. Assumingly imaging in this meta-analysis is used as routine scan, but it is not explicitly defined. It showed ultrasound to be superior in detecting recurrence in the regional lymph nodes when compared to PET-CT, which in contrast was found to be the most effective modality to detect distant metastasis [36]. In our study, imaging performed on the basis of clinical suspicion proved more effective in detecting recurrences than routine imaging. Other studies have shown routine imaging methods to be inefficient to detect recurrences of melanoma and have not proven to prolong survival [37, 38].

The amount of follow-up visits and routine imaging performed in the Danish follow-up program is time-consuming for the patient and expensive in health care resources compared to the low number of recurrences detected. Furthermore, routine imaging has not shown to contribute to an increased life expectancy not even for patients with stage III melanomas [37], which is why scrutiny of the program's effectiveness is necessary. However, a Danish study from 2021 that included 161 patients concluded that routine PET/CT was effective and accurate when used for patients with high-risk melanoma. False-positive findings did, however, lead to a high number of extra tests including invasive procedures [39]. Routine PET/CT scans are highly effective in early detection of recurrence, but false-positives and limited gains in life expectancies may render the modality less efficient.



We found clinical examination by a physician to be the most effective modality to detect recurrent disease with a detection rate of nearly 40%. However, examination by a physician was not shown to be much more efficient than patient self-examination with a detection rate of 35%.

In most cases of imaging-detected recurrences, the scan was not performed as a routine scan but due to suspected recurrence. Based on this, it could be argued that examination performed by either a physician or the patient could be superior to routine imaging in detecting recurrences. Therefore, it should be considered whether imaging such as PET/CT and lymph node US should be reserved for cases with clinical suspicion in the intermediate-risk population.

Another clinical assessment tool worth considering for future use is confocal microscopy. It is a non-invasive high-resolution imaging tool that generates a horizontal view of the skin, where structures to the level of the upper dermis are projected to a screen at near-histological resolution [40]. Confocal microscopy has shown to be efficient in separating the benign lesions from the malignant when combined with clinical examination and dermoscopy [41]. In the future, it might improve diagnosis and assessment of larger lesions and assist in the evaluation of which areas are most suitable for biopsy as well as delineating margins prior to surgery. Whether confocal microscopy could play a role in detecting recurrence of melanoma in the skin is still to be sufficiently investigated, although it has shown promising results in studies with small study populations [42].

The sensitivity and specificity of confocal microscopy compared to SSE and regular clinical examination are still to be evaluated.

## Limitations

The inclusion rate of this study was 74%. The composition of the remaining 26% concerning disease stage is unknown and could potentially lead to selection bias.

Furthermore, the time frame and follow-up period are short. However, recurrences have shown to occur mainly within the first 2–3 years after diagnosis [28].

Another factor to consider when evaluating the finding of this study is that information on mitotic rate was not included. In 2019, it was not considered to influence stage and treatment and therefore, it was not noted in the patient medical journal. Mitotic rate is, together with Breslow thickness and ulceration, an important histopathologic factor and several other studies take this prognostic factor into account when evaluating prognosis [43, 44]. However, information about mitotic rate is not believed to change the data of recurrence detection or modality in this study.

## Conclusions

In conclusion, we found the risk of recurrence to be associated with disease stage. This was as expected and therefore, disease stage is considered to be a reasonable parameter to base the follow-up program for melanoma patients upon.

A high NNT for stage IB and IIA patients was observed during the first 2 years of follow-up. These patients constitute the majority of the cohort which is why the true benefit of the current follow-up program for these stages should be reconsidered. An increase in the interval between visits would reduce time and resource consumption significantly without compromising the safety for these two patient groups based on the results from our study.

Examination by a physician showed to be the most effective modality to detect recurrences followed by patient self-examination.

Imaging performed due to suspicion proved to be more efficient to detect recurrences than routine imaging. This finding could prompt further investigation to the matter, eventually leading to a reduction in the use of routine imaging in the low-risk stages, and replacing it with imaging due to suspicion.

**Author contribution** All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Julie Tastesen Johannessen, Tue Duy Nguyen, Sarah Holmboe, Mikkel Børsen Rindom, and Lars Bjørn Stolle. The first draft of the manuscript was written by Julie Tastesen Johannessen and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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## Declarations

**Ethical approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This study was approved by Region Midt (case no. 1–45-70–39-21) and the Board of Directors at Aarhus University Hospital, Denmark.

**Consent to participate** Informed consent was obtained from all individual participants included in the study.

**Conflict of interest** Julie Tastesen Johannessen, Tue Duy Nguyen, Sarah Holmboe, Mikkel Børsen Rindom, and Lars Bjørn Stolle declare no conflict of interest.

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