Meta-analysis of number needed to treat for diagnosis of melanoma by clinical setting

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Objective: To provide a formal statistical comparison of the efficacy of melanoma detection among different clinical settings.

Methods: A systematic review and meta-analysis of all relevant observational studies on number needed to treat (NNT) in relation to melanoma was performed in MEDLINE. We performed a random-effects model meta-analysis and reported NNTs with 95% confidence intervals (CIs). The subgroup analysis was related to clinical setting.

Results: In all, 29 articles including a total of 398,549 biopsies/excisions were analyzed. The overall NNT was 9.71 (95% CI, 7.72-12.29): 22.62 (95% CI, 12.95-40.10) for primary care, 9.60 (95% CI, 6.97-13.41) for dermatology, and 5.85 (95% CI, 4.24-8.27) for pigmented lesion specialists.

Limitations: There is heterogeneity in data reporting and the possibility of missing studies. In addition, the incidence of melanoma varies among clinical settings, which could affect NNT calculations.

Conclusion: Pigmented lesion specialists have the lowest NNT, followed by dermatologists, suggesting that involving specialists in the diagnosis and treatment of pigmented skin lesions can likely improve patient outcomes. (J Am Acad Dermatol 2020;82:1158-65.)

Key words: dermatologic surgery; melanoma; melanoma in situ; number needed to excise; number needed to treat; oncology; pigmented lesions.

Melanoma is a devastating cancer with high morbidity and mortality. More than 178,560 melanomas were diagnosed in 2018 in the United States, and both the incidence and mortality have been steadily increasing for decades.[1] Importantly, this increase is not due to methods of detection or changes in clinical or histologic diagnosis.[2] Some studies have shown that the rise in incidence currently outpaces the rise in mortality,[3] leading to an increased number of patients at high risk and, therefore, future diagnoses. Although its incidence is increasing, melanoma remains relatively rare in the health care setting, making its quick and efficient diagnosis challenging.

An often-reported number for melanoma detection is the number needed to treat (NNT), or number needed to excise, which is the number of benign pigmented skin lesions excised compared to the number of confirmed melanomas. This metric varies widely depending on the clinical setting in which it is measured.[4] A quantitative understanding of our ability to diagnose melanoma is important for many

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reasons. First, unnecessary biopsies increase the false positive rate, leading to emotional and psychological stress on patients. Second, the real economic impact of these biopsies can be correctly evaluated only with an understanding of the NNT across clinical settings. This allows for an accurate analysis of the increased cost of specialty care versus the increased cost of a higher rate of negative biopsies. Third, this understanding will establish standards of care and allow various clinical settings to measure progress and set goals for improvement. Previously reported NNTs were analyzed solely based on practice setting or level of training.[4-8] Many factors influence a provider's decision to biopsy a suspicious lesion, including the patient's age, personal and family history, and site of the lesion. It is important to acknowledge that both patient anxiety and an individual physician's clinical experience influence the perceived need to biopsy.[9,10] Even physician compensation has been cited as a motivator.[11] The aim of this meta-analysis is to analyze all published data on NNTs across different clinical settings and to report the difference in melanoma detection efficacy among them. This will provide a systematic comparison of published reports on NNT for melanoma.

CAPSULE SUMMARY

- The number needed to treat for melanoma varies widely across clinical settings.
- Data from the present study highlight the fact that pigmented lesion specialists have the lowest number needed to treat for melanoma, followed by dermatologists. Understanding the variability in melanoma detection across clinical settings allows for better cost comparison.

METHODS

This study was approved by the Duke University institutional review board. This report was written in accordance to the Preferred Reporting Items for Systemic Reviews and Meta-Analyses (PRISMA) statement[12] whenever possible.

Search strategy and selection of relevant studies

All criteria for inclusion and exclusion of reports were determined before the literature search. To identify eligible studies, a comprehensive search strategy designed by a master of library and information science–trained librarian to identify all relevant studies of NNE or number needed to excise in relation to melanoma in the electronic database MEDLINE. English language articles were included from January 1995 through December 2016. Terms related to *melanoma*, *pigmented lesion*, *nevus/nevi*, *biopsy*, *number needed to treat*, and *number needed to excise* were searched with all available synonyms.

Our search yielded 790 articles, which were analyzed for inclusion. There were 5 articles not included in the initial search that were included in this analysis.[5,6,13-15] Titles and abstracts from the search results were assessed independently by 2 reviewers. Disagreements were resolved by 2 other reviewers. Subsequently, the full text and references of articles that met inclusion criteria were reviewed, and the data were extracted.[4-8,10,11,13-33] One study[34] found by our search included biopsies only from patients who were under longitudinal surveillance and at particularly high risk and was therefore excluded from statistical analysis.

Data extraction

Data from the selected studies were abstracted by using a standardized data extraction form. Several articles we evaluated published NNTs for different clinical settings over different periods of time and were therefore separated into different studies in our analysis.[4,13,23,27,33] General study characteristics (author, country of origin, type of study, clinic type, total number of biopsies, and total number of melanomas) were recorded. Each selected study was determined to include NNT data from primary care physicians only, combined data from primary care physicians and primary physicians with some dermatologic training, data from dermatologists only, combined data from dermatologists and dermatologists with some training in pigmented lesions, or data from pigmented lesion specialists only. Pigmented lesion specialists are dermatologists with a subspecialty in pigmented lesions. Whenever possible, the number of reported nevi without seborrheic keratosis (SK) was used for our NNT calculations. For some included studies, this necessitated subtracting the reported number of SKs from total biopsies. Other studies did not report specific numbers, and therefore included both nevi and SK in the NNT calculation.*

Statistical methods

The NNT with 95% confidence interval (CI) was calculated for all groups and according to specialty

*[5,6,8,10,11,13-16,19,21,22,24,27-30,32,33,35,36]

Abbreviations used:

CI: confidence interval
NNT: number needed to treat
REM: random-effects model
SK: seborrheic keratosis

(dermatologist, pigmented lesion specialist, and primary care). For each meta-analysis conducted, we first computed the overall log odds of melanoma diagnosis and its CIs given that the log odds are approximately normal for large samples. The log odds of melanoma are equal to $\log[p/(1-p)]$, with p representing the proportion of melanoma in biopsy. We then transformed the overall log odds estimate and 95% CI back to the original NNT units. By using this strategy, we calculated the overall NNT and the NNT according to specialty (dermatologist, pigmented lesion specialist, and primary care). Heterogeneity among studies was assessed using the Cochran Q and I^2 statistics. The studies were found not to share a common true effect; thus, for each meta-analysis, we used an inverse, variance-weighted, random-effects model (REM). Funnel plots were used to determine the likelihood of publication bias.[37] All analyses were performed with SAS, version 9.4 (SAS Institute Inc, Cary, NC).

RESULTS

A flowchart of search results is shown in Fig 1. After removal of duplicates, there were 795 papers to review; then, 748 were excluded based on the information in their title and abstract. Thus, 47 full-text original articles were evaluated. After reviewing these articles, we found that 29 studies fit our inclusion criteria and could be used in the meta-analysis. Table I summarizes data from all included studies.

Overall, data from 29 published reports, representing 36 individual studies and a total of 398,549 biopsies/excisions, were analyzed. NNT for melanoma in 36 individual studies grouped by specialty are plotted in Fig 2. The Q statistic for the log odds of all melanoma diagnoses was statistically significant (Q = 10,182.2; $P < .001$). The REM was then used to estimate the mean log odds with 95% CI and then transformed back to NNT, which was 9.71 (95% CI, 7.72-12.29; I^2 = 99.7%) (Fig 3). The funnel plot for this analysis showed a uniform distribution, indicating a low publication bias (Supplemental Fig 1; available via Mendeley at https://doi.org/10.17632/v47tpv9hrc.1)

Next, the NNT was calculated by specialty.

For 6 studies with NNT diagnosed by primary care physicians, the Q statistic was statistically significant (Q = 2557.3; $P < .001$). The overall NNT diagnosed by primary care physicians was estimated as 22.62 (95% CI, 12.95-40.10; I^2 = 99.8%; REM) (Fig 3). When 2 studies with the primary care/dermatologist designation were added, the combined NNT was 20.02 (95% CI, 13.07-30.99; I^2 = 99.8%; REM) (Supplemental Fig 2; available via Mendeley at https://doi.org/10.17632/v47tpv9hrc.1).

For dermatologists, 14 studies were included. The Q statistic for the log odds was again statistically significant (Q = 663.3; $P < .001$, and the overall NNT for dermatologists was estimated as 9.60 (95% CI, 6.97-13.41; I^2 = 98.0%; REM) (Fig 3).

For the 12 studies with pigmented lesion specialists, the Q statistic was statistically significant (Q = 461.1; $P < .001$), and NNT by specialists was calculated to be 5.85 (95% CI, 4.24-8.27; I^2 = 97.6%; REM) (Fig 3). When 2 additional studies with the dermatologist/specialist designation were added, the combined NNT was 6.23 (95% CI, 4.72-8.36; I^2 = 97.6%; REM) (Supplemental Fig 3; available via Mendeley at https://doi.org/10.17632/v47tpv9hrc.1).

A general linear mixed model was created to compare NNT between 2 types of physicians (dermatologists vs primary care physicians, dermatologists vs pigmented lesion specialists, primary care physicians vs pigmented lesion specialists). The NNT of the primary care physicians was found to be 2.52 times greater than that of the dermatologists (95% CI, 1.31-4.85, P = .008). The NNT for the dermatologists was 1.77 times greater than that for the pigmented lesion specialists (95% CI, 1.01-3.09, P = .045), and the NNT for the primary care physicians was 4.50 times greater than that for the pigmented lesion specialists (95% CI, 2.43-8.34, $P < .001$).

DISCUSSION

Understanding how the level of training and practice setting of physicians treating melanoma affect the ability to accurately diagnose and treat melanoma is essential. To our knowledge, this study is the first to compile all current information on NNT across various practice settings and perform a systematic statistical comparison.

We showed that pigmented lesion specialists have the lowest NNT, followed by dermatologists. Although many factors are at play, more specialized training and experience likely provide them with better intuition as to which lesions to biopsy. Additionally, the frequency of high-risk patients encountered by specialists is likely variable. Another important consideration is the role of referrals. Paine et al found that the more suspicious a general practitioner is of malignancy, the more likely

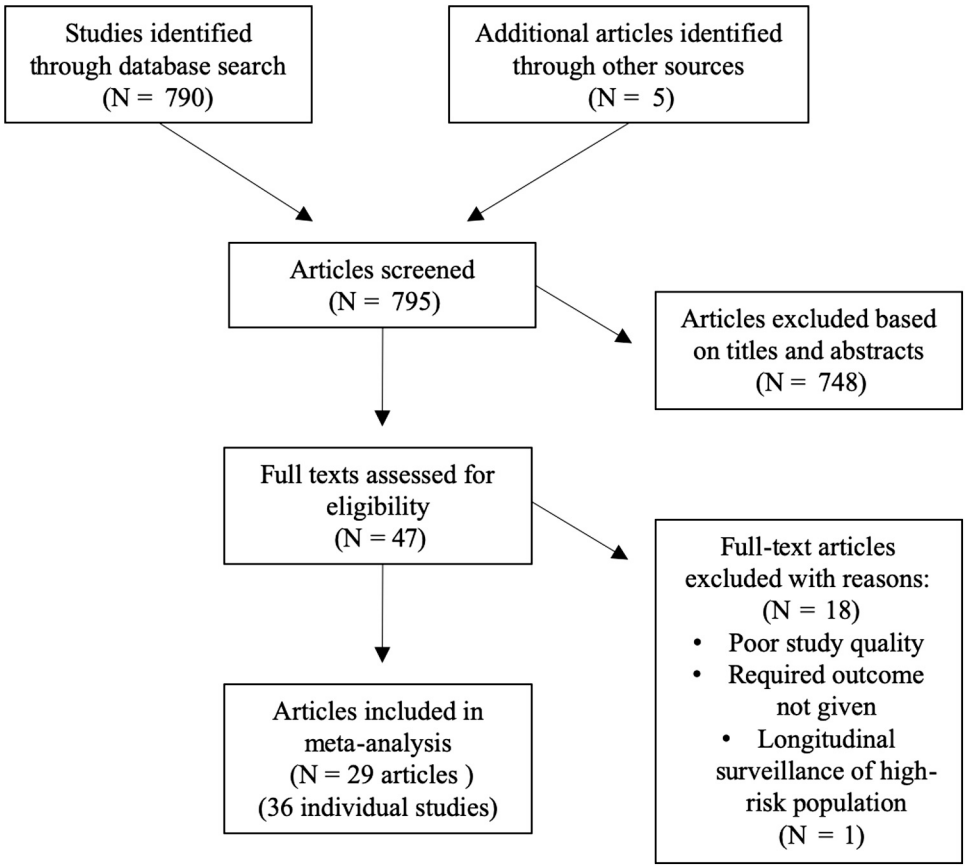

Fig 1. Flow chart of search and study selection process.

he/she is to refer the patient to see a specialist.[38] This could decrease the NNT for specialists but also increase the NNT for primary care providers, who see a much lower frequency of melanomas in their practice.[27] Because there is no published study that examined the potential effects of referral bias on NNT calculations across clinical settings, a prospective study is likely needed in the future to further evaluate this.

Although we did not compare physicians and advanced practice providers, existing studies show a similar relationship between level of training and NNT. Nault et al[15] found a significantly higher NNT for advanced practice providers, primarily nurse practitioners, compared with physicians. Anderson et al[39] also found a significantly higher NNT for physician assistants compared with physicians (39.4 vs 25.4). They did note that physician assistants were less likely to see patients with significant risk factors such as a personal history of melanoma.

The use of dermoscopy in the detection of melanoma has been shown to directly affect the NNT. Kittler et al[40] found that diagnostic accuracy with the use of dermoscopy was significantly higher. However, this difference was observed only with its use by specialists, and its use by untrained or less experienced physicians showed no improvement versus clinical inspection alone. Lorentzen et al[41] compared the use of dermoscopy between experts and nonexperts in the detection of melanoma and found a sensitivity of 0.83 and 0.69, respectively (P = .04). Its use in the expert group doubled the positive likelihood ratios. Because positive predictive value directly correlates with prevalence, this may account for some of the variation seen between specialty clinics and nonexpert settings. Binder et al[42] found that nonexpert use of dermoscopy led to a decrease in sensitivity. Others have shown that the use of dermoscopy, although not significantly improving melanoma detection, does lead to a decrease in the number of lesions biopsied.[43,44] Unfortunately, the limitations of this meta-analysis did not allow for us to directly compare NNT with or without dermoscopy due to unavailability of data or inconsistencies in reporting. Further studies are indicated to more formally analyze how its use affects the NNT in different clinical settings.

There appear to be geographic differences that may contribute to NNT, even within consistent practice settings. Comparing a few examples of numbers reported from dermatologists, for example, Green et al[5] calculated an NNT of 26 in Miami,

Table I. Summary of selected studies (n = 36)[3-8,10,113]

Study	Year	Specialty	NMR	NNT	Melanoma, n (%)	Total Biopsy/ Excision, N	Melanoma in situ, %	Lesions used to calculate
Ahnlide et al[16]	2014	D	5.54	6.81	252 (15)	1717	49.6	Nevi, SK
Argenziano et al[17]	2008	S	3.42	4.42	12 (23)	54	50	Nevi
Argenziano et al (study 1)[4]	2012	P	28.49	29.49	7263 (3)	214,122	36.8	Nevi
Argenziano et al (study 2)[4]	2012	S	7.69	8.69	9910 (12)	86,093	14.1	Nevi
Baade et al[14]	2008	P	10.82	19.59	152 (5)	2977	36.2	Nevi, SK
Bauer et al[18]	2005	S	15.50	16.50	2 (6)	33	100	Nevi
Carli et al[19]	2003	S	5.56	6.75	16 (15)	108	25	Nevi, SK
Carli et al[20]	2004	S	8.51	9.57	319 (10)	3053	46.4	Nevi
Carli et al[10]	2004	S	4.00	5.33	15 (19)	80	NR	Nevi, SK
Chia et al[21]	2008	D	NR	3.52	195 (28)	686	NR	Pigmented lesions
English et al[22]	2003	P	18.96	29.03	295 (3)	8563	39	Nevi, SK
English et al[11]	2004	P	19.53	29.37	160 (3)	4699	38.8	Nevi, SK
Esdaile et al (study 1)[23]	2014	D	2.46	3.46	188 (29)	650	23.9	Nevi
Esdaile et al (study 2)[23]	2014	S	1.74	2.74	266 (36)	730	37.2	Nevi
Green et al[5]	2004	D	26.14	26.14	156 (4)	4078	NR	Nevi, SK
Haenssle et al[24]	2006	D	12.02	12.02	53 (8)	637	52.8	Melanocytic
Hansen et al[6]	2009	P	22.25	30.49	348 (3)	10,612	38.5	Nevi, SK
Kittler et al[26]	2006	DS	4.48	5.48	91 (18)	499	58.2	Nevi
Kittler et al[25]	2000	S	8.38	9.38	8 (11)	75	62.5	Nevi
Marks et al (study 1)[27]	1997	PD	10.77	15.64	707 (6)	11,055	33.8	Nevi, SK
Marks et al (study 2)[27]	1997	PD	7.97	12.53	1099 (8)	13,766	41.1	Nevi, SK
Menzies et al[28]	2001	S	7.14	8.57	7 (12)	60	71.4	Nevi, SK
Nault et al[15]	2015	D	NR	21.39	23 (5)	492	NR	Pigmented lesions
Rolfe et al[29]	2012	D	6.18	11.47	55(9)	631	56.0	Nevi, SK
Rosendahl et al[30]	2012	P	NR	9.25	2367 (11)	21,900	NR	Pigmented lesions
Sidhu et al[31]	2012	D	5.25	6.25	750 (16)	4691	NR	Nevi
Soares et al[7]	2009	D	9.20	10.51	147 (10)	1545	49.7	Nevi
Soltani-Arabshani et al[32]	2015	DS	10.82	14.56	165 (7)	2402	46.7	Nevi, SK
Terushkin et al (study 1)[13]	2010	D	12.17	13.92	12 (7)	167	NR	Nevi, SK
Terushkin et al (study 2)[13]	2010	D	12.55	14.09	11 (7)	155	NR	Nevi, SK
Terushkin et al (study 3)[13]	2010	S	2.54	3.77	13 (27)	49	NR	Nevi, SK
Terushkin et al (study 4)[13]	2010	S	5.83	7.67	6 (13)	46	NR	Nevi, SK
Tromme et al (study 1)[33]	2012	D	8.86	9.86	93 (10)	917	20.4	Nevi
Tromme et al (study 2)[33]	2012	D	7.11	8.11	74 (12)	600	36.5	Nevi
Tromme et al (study 3)[33]	2012	S	2.09	3.09	64 (32)	198	37.5	Nevi
Wilson et al[8]	2012	D	7.67	14.64	28 (7)	410	NR	Nevi, SK

D, Dermatologist; *DS*, dermatologist with specialized training; *NMR*, nevi-melanoma ratio; *NNT*, number needed to treat; *NR*, not reported; *P*, primary care physician; *PD*, primary care physician with dermatologic training; *S*, specialist; *SK*, seborrheic keratosis.

compared with 15 for Wilson et al[8] in North Carolina, 9 for Soares[7] et al in Arizona, 13 for Marks et al[27] in Australia, and approximately 3 for Esdaile et al[23] in the United Kingdom. We included 14 studies reporting data from dermatologists only and found an NNT of 9.6. However, these 14 studies ranged from an NNT of 3.5 to 26.1. Although geographic differences play a role, we found that analyzing all published data by clinical setting, irrespective of geography, gives the best estimation of NNT. More studies from consistent regions are needed to formally analyze geographic variations.

Because our meta-analysis covers cases that range over more than 20 years, it is quite possible that the NNT was not stable throughout that period. A multicenter survey of more than 300,000 cases found that between 1998 and 2007, there was an improvement in NNT for skin cancer specialists but not for nonspecialists.[4] Conversely, Wang et al[45] showed that between 2000 and 2015, there was an increase in per capita skin biopsies in the Medicaid population without a corresponding increase in excision rates, suggesting an increase in NNT over time.

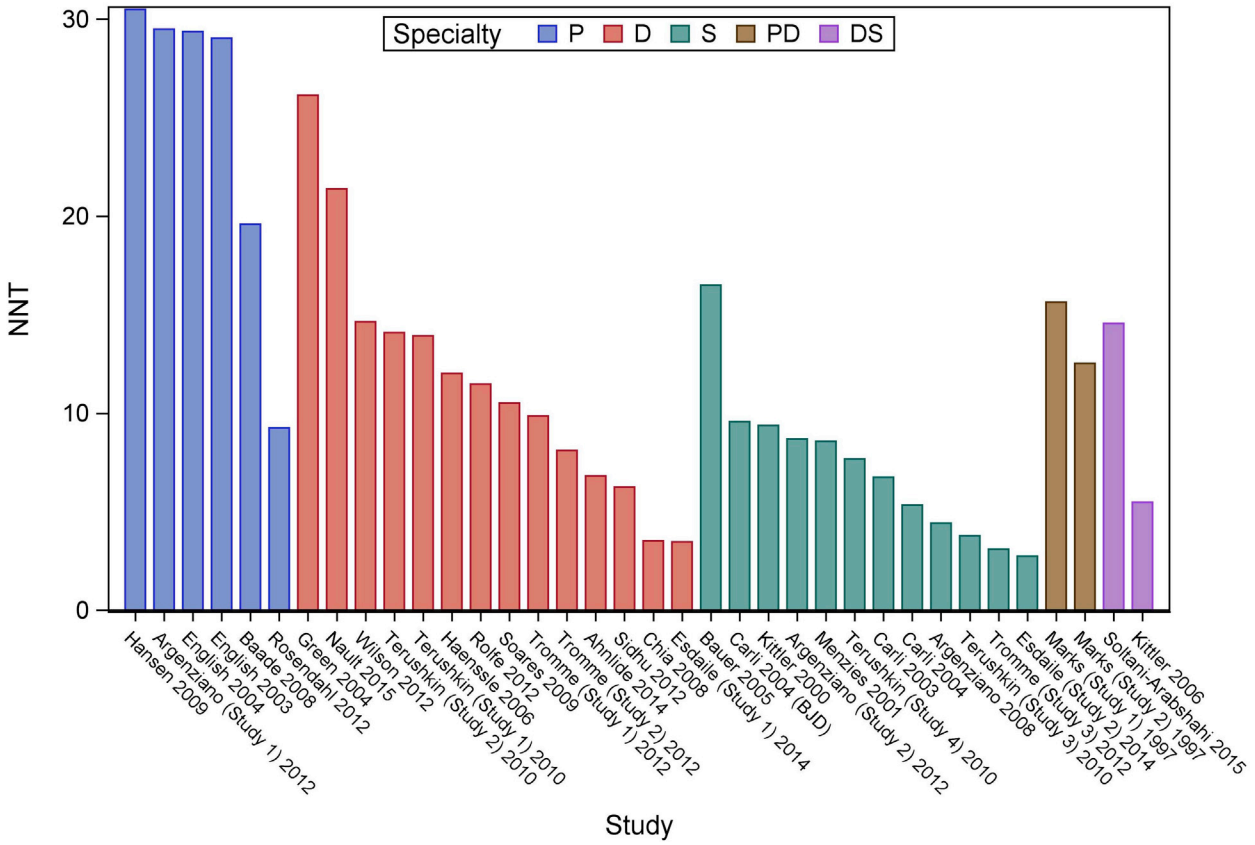

Fig 2. Bar graph of the number needed to treat (NNT) for melanoma in 29 published articles (36 individual studies). The dashed line represents the overall NNT for all studies evaluated. *D*, Dermatologist; *DS*, dermatologist with some specialized training in pigmented lesions; *P*, primary care physicians; *PD*, primary care physician with dermatologic training; *S*, specialists.

The current meta-analysis has limitations. First, there was the inconsistency in data reports, resulting in imperfect and potentially incomplete comparisons across studies. For example, many studies included SKs or pigmented basal cell carcinomas in their number of biopsies and NNT calculations. It was not possible to mitigate these inconsistencies when specific numbers of SK were not reported. Second, we pooled data from different studies despite high heterogeneity. Additionally, the definition of *pigmented lesion specialist* varied geographically, creating difficulties in classifying data in the right category. Finally, it is unclear how referral bias would affect the calculation of NNTs across clinical settings, and it is likely that baseline patient characteristic differences at primary care clinics versus pigmented lesion specialty clinics could skew the calculations of NNTs. Criteria for referral to a pigmented lesion specialty clinic may include patients with a high number of nevi, personal history of previous melanoma, or family history of melanoma. However, there are data to support the notion that patients at higher risk are more likely to receive their initial care from a primary care physician and have their melanomas detected during a routine skin check.[46]

The treatment of melanoma and other skin cancer is associated with significant cost to patients and health care systems.[14] As the disease stage progresses, the cost of treatment increases rapidly. One study estimated the 5-year cost of treating malignant melanoma in situ at $4,648.48 compared with $159,808.17 for stage IV melanoma.[47] Another study found that the cost savings from early diagnosis of a single melanoma justifies 170 biopsies of benign lesions.[48] However, in an Australian open-access skin cancer clinic staffed by family practitioners providing consultations solely for diagnosing and treating skin cancers and suspicious skin lesions, the NNT for melanoma was calculated to be as high as 287.[49] This suggests that there is great variation in the NNT between different practitioner groups, and cost effectiveness must be properly studied and considered. With the large economic burden of health care, particularly in the United States, we must improve the efficacy of melanoma detection.

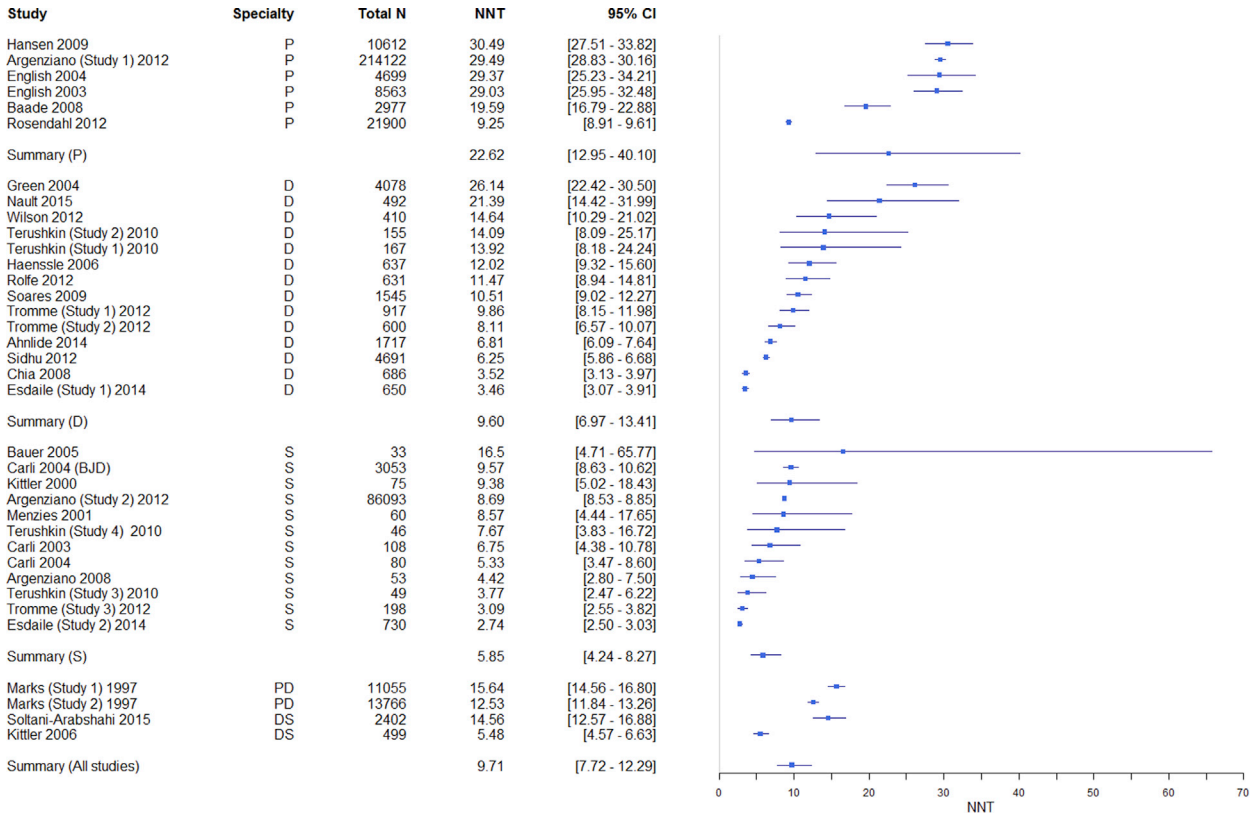

Fig 3. Forest plot of NNT for melanoma in 29 published articles (36 individual studies). *D*, Dermatologists; *P*, primary care physicians; *S*, specialists; *DS*, dermatologist with some specialized training in pigmented lesions; *PD*, primary care physician with dermatologic training; *NNT*, number needed to treat.

In conclusion, in this meta-analysis, we found that pigmented lesion specialists have the lowest NNT, followed by dermatologists, suggesting that involving specialists and/or dermatologists in the care of patients with many nevi or at high risk of melanoma can likely lead to improved clinical outcome.

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