Disclosure

World Congress of Melanoma, Brisbane, Oct 19, 2017

☐ I have no potential conflict of interest to report

☒ I have the following potential conflict(s) of interest to report

At the outset , I have to declare a conflict of interest: It is in my economic interest as a dermatopathologist that as many biopsies are taken as possible. In the following, I shall violate my own interests by suggesting just the opposite.

Detection of Melanoma –

The Earlier, the Better ?

W. Weyers
Center for Dermatopathology
Freiburg, Germany

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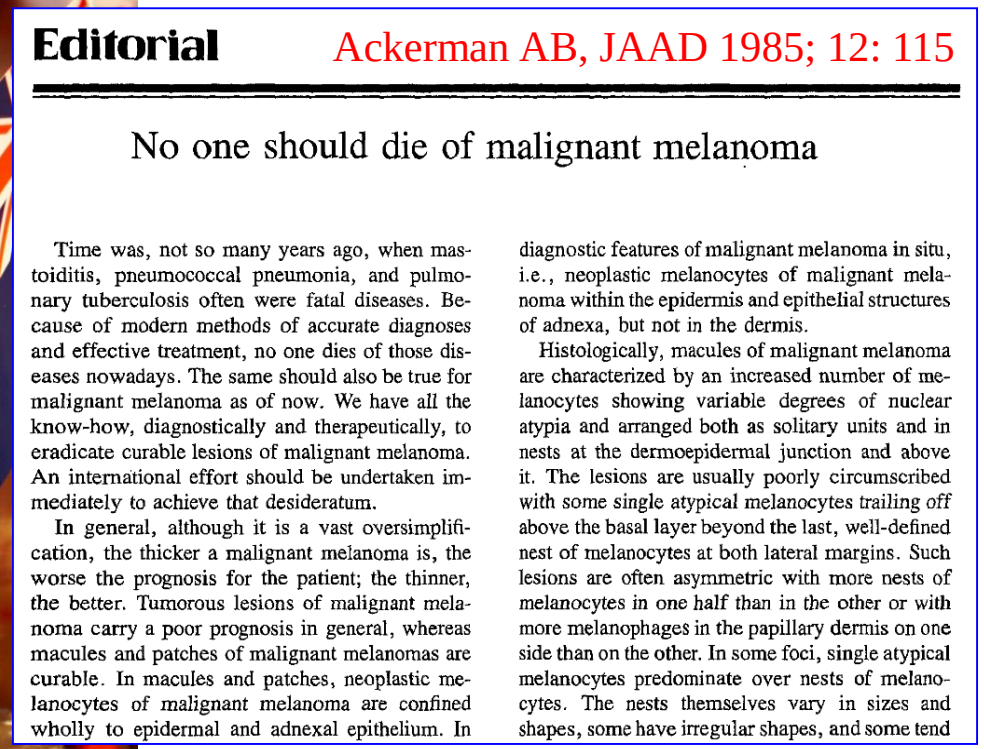

Editorial Ackerman AB, JAAD 1985; 12: 115

No one should die of malignant melanoma

Time was, not so many years ago, when mastoiditis, pneumococcal pneumonia, and pulmonary tuberculosis often were fatal diseases. Because of modern methods of accurate diagnoses and effective treatment, no one dies of those diseases nowadays. The same should also be true for malignant melanoma as of now. We have all the know-how, diagnostically and therapeutically, to eradicate curable lesions of malignant melanoma. An international effort should be undertaken immediately to achieve that desideratum.

In general, although it is a vast oversimplification, the thicker a malignant melanoma is, the worse the prognosis for the patient; the thinner, the better. Tumorous lesions of malignant melanoma carry a poor prognosis in general, whereas macules and patches of malignant melanomas are curable. In macules and patches, neoplastic melanocytes of malignant melanoma are confined wholly to epidermal and adnexal epithelium. In diagnostic features of malignant melanoma in situ, i.e., neoplastic melanocytes of malignant melanoma within the epidermis and epithelial structures of adnexa, but not in the dermis.

Histologically, macules of malignant melanoma are characterized by an increased number of melanocytes showing variable degrees of nuclear atypia and arranged both as solitary units and in nests at the dermoepidermal junction and above it. The lesions are usually poorly circumscribed with some single atypical melanocytes trailing off above the basal layer beyond the last, well-defined nest of melanocytes at both lateral margins. Such lesions are often asymmetric with more nests of melanocytes in one half than in the other or with more melanophages in the papillary dermis on one side than on the other. In some foci, single atypical melanocytes predominate over nests of melanocytes. The nests themselves vary in sizes and shapes, some have irregular shapes, and some tend

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Let me start with the famous quote by my close fatherly friend Bernard Ackerman: *“No one should die of malignant melanoma.”* That demand was made in 1985, at a time

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Time was, not so many years ago, when mastoiditis, pneumococcal pneumonia, and pulmonary tuberculosis often were fatal diseases. Because of modern methods of accurate diagnoses and effective treatment, no one dies of those diseases nowadays. The same should also be true for malignant melanoma as of now. We have all the know-how, diagnostically and therapeutically, to eradicate curable lesions of malignant melanoma. An international effort should be undertaken immediately to achieve that desideratum.

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when lesions such as this one were still very common: a rapidly growing nodule of melanoma on a flat lesion that had expanded slowly over many years. Formerly interpreted as a pre-existing nevus, it had become clear that the macular component of the lesion is part of the melanoma

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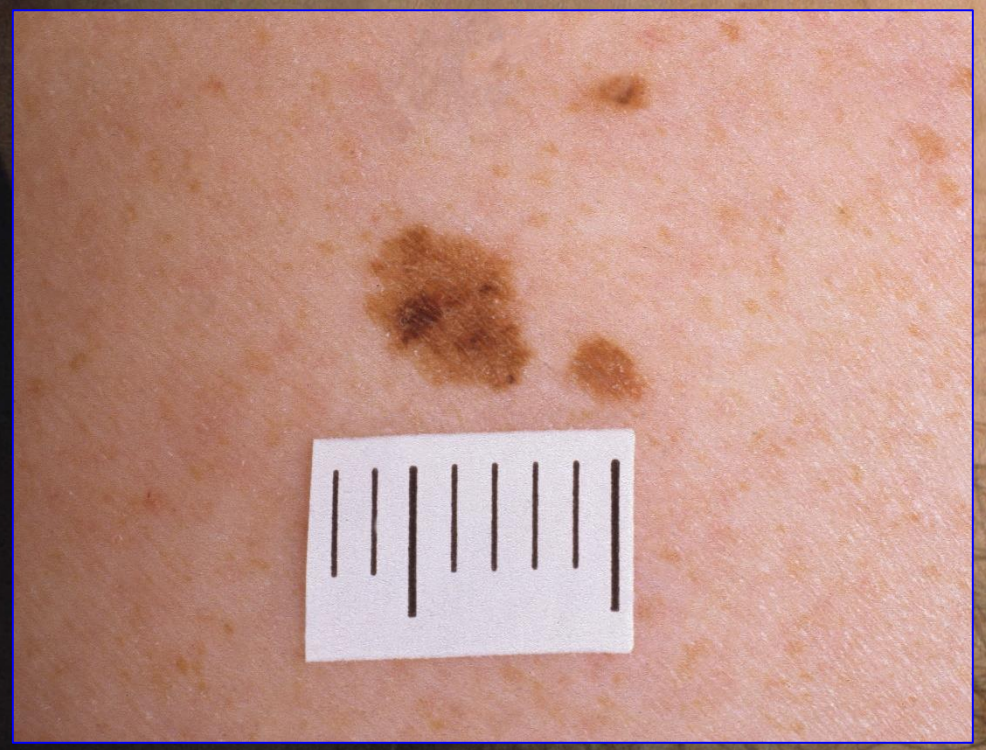
and can be distinguished reliably from nevi early-on in the vast majority of cases, both clinically



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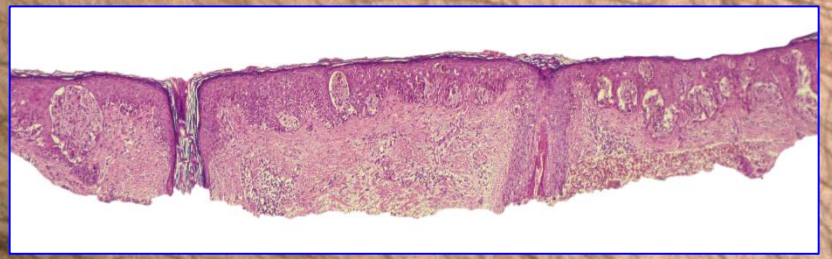
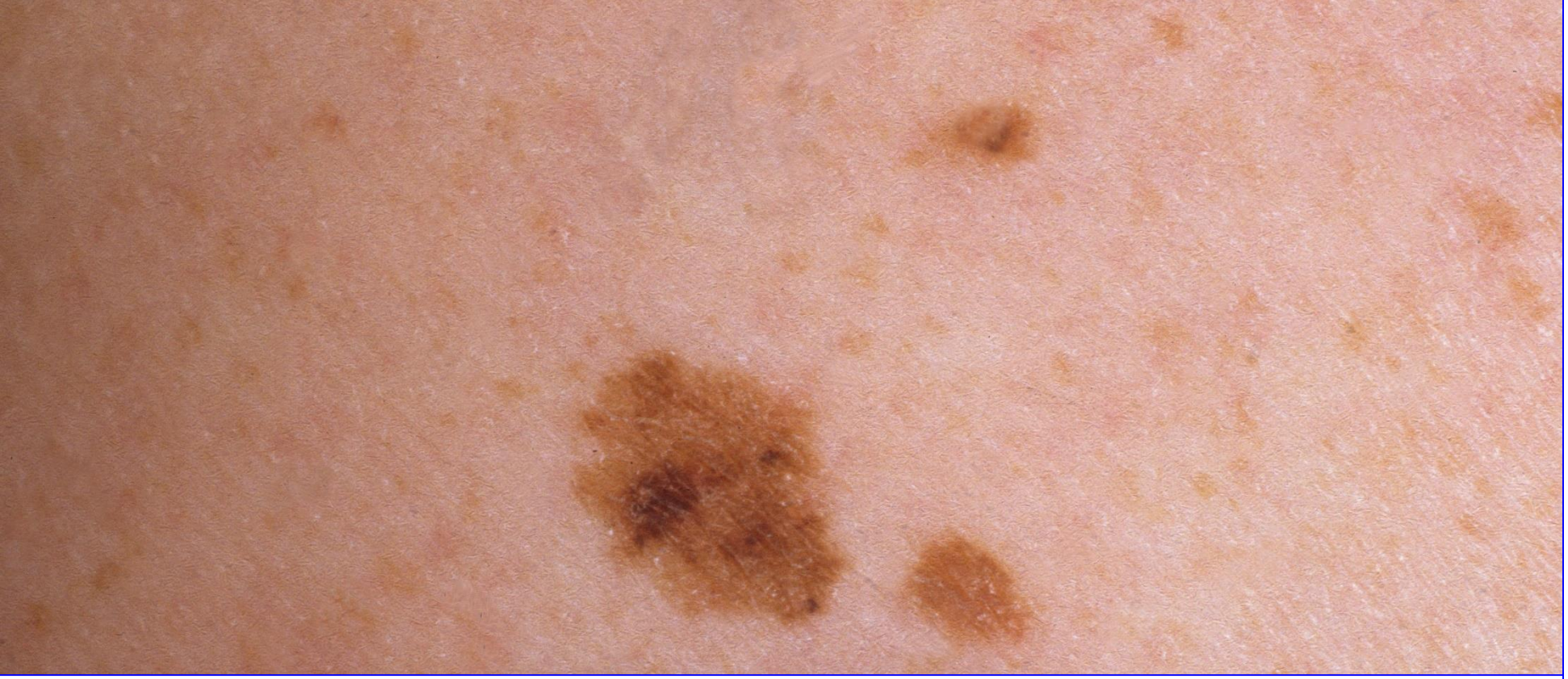
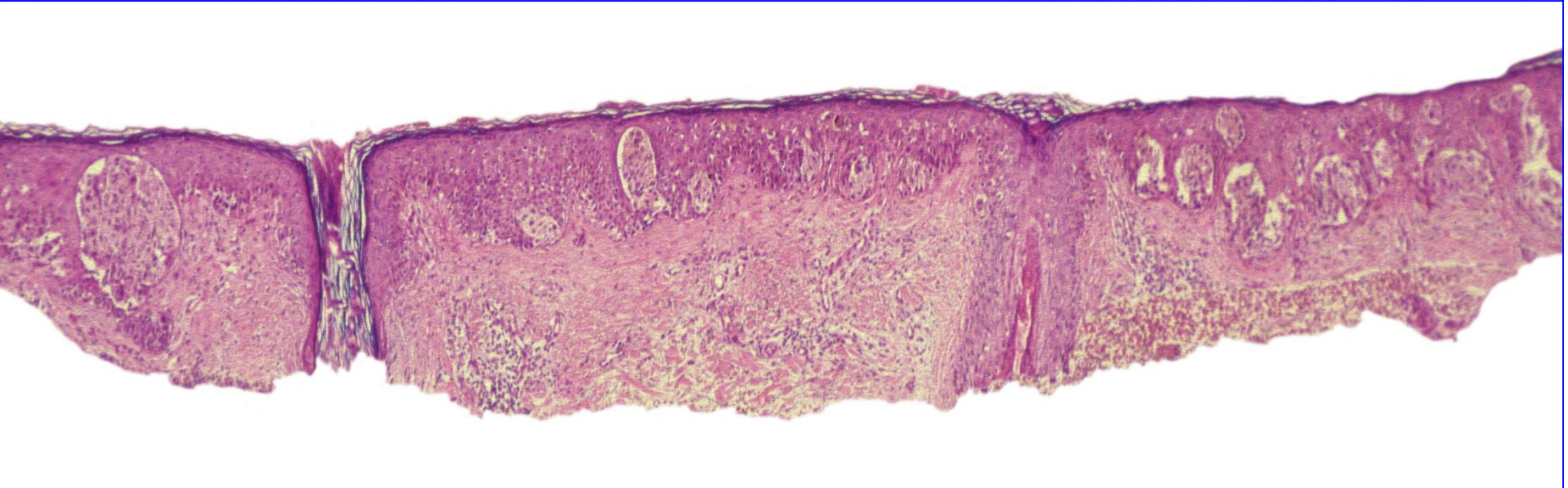


and histopathologically. Ackerman pointed out that most criteria for histopathologic diagnosis of melanoma pertain to changes in the epidermis so that diagnosis can be made at an in situ stage.





Because of easy recognition at an early stage and slow growth in the majority of cases, melanoma is an ideal candidate for cancer screening, and it is perplexing that the logic of cancer screening has been turned upside down by arguing that melanoma in situ is not a malignant disease because it cannot kill.

Perspectives in Pathology

Malignant Melanoma In Situ

WALLACE H. CLARK, JR, MD

Hum Pathol 1990; 21: 1197

Cancer is an entity because its development and evolution are comparable from one neoplastic system to the next, regardless of the inductive mechanism and differences in clinical and histologic appearance due to origin from different kinds of cells and tissues.[1-5] Cancer develops through a sequence of lesions; the lesions appearing seriatim are a manifestation of tumor progression.[6] One lesion which is a part of t... the... stri... epit... acte... sion... nor... having cells entirely above the dermal-epidermal basement membrane zone with some structural features of invasive melanomas, have been termed melanoma in situ. In this report, the histology possessing the following features is discussed as a possible candidate for designation as melanoma in situ. The individual cells are large and epithelioid, and have an abundance of finely divided pigments, giving the cytoplasm a tan, dusty appearance. The nuclei are large and hyperchromatic, and usually about 1.5 to 2 times the diameter of the surrounding keratinocytes. The

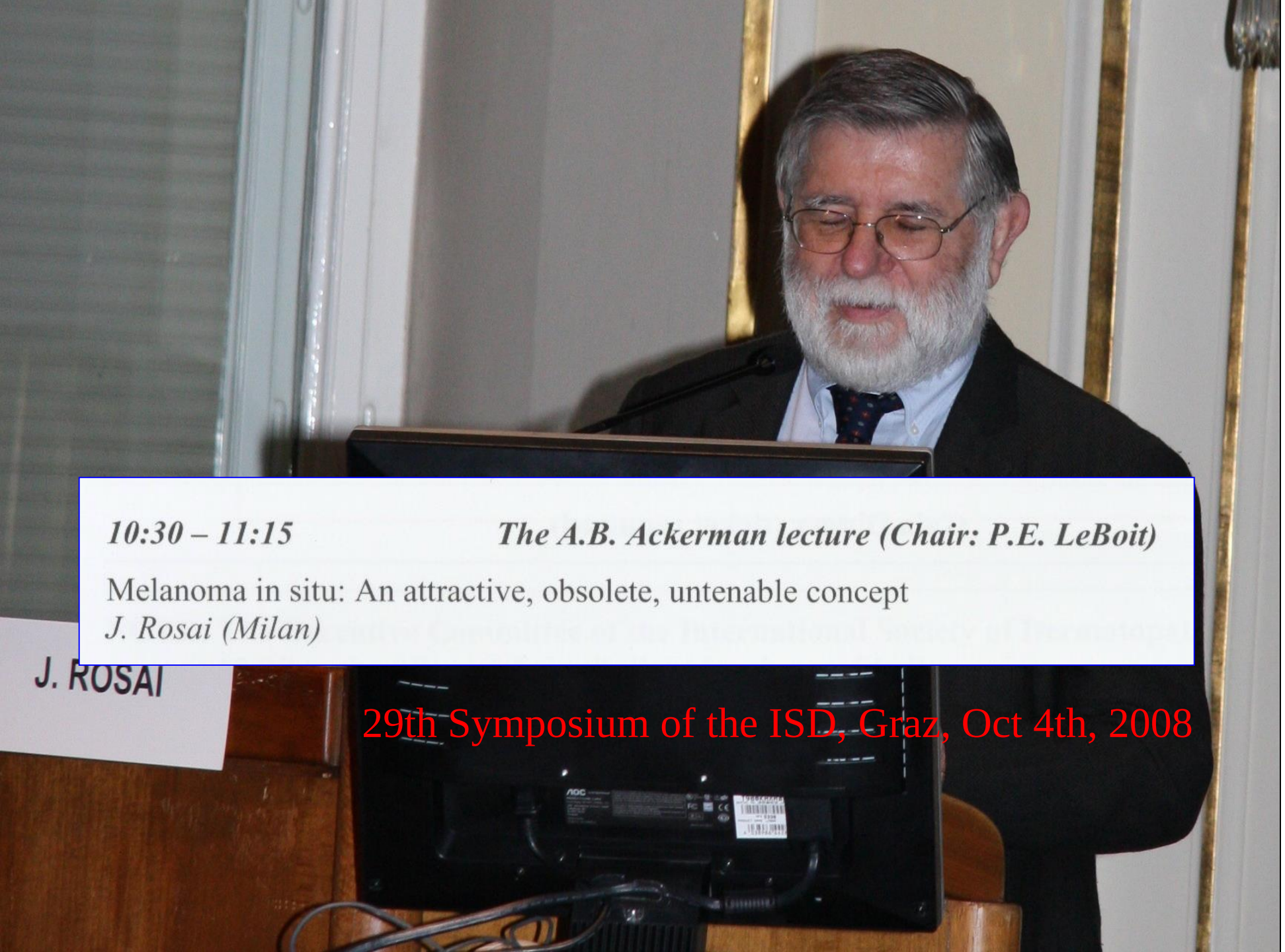
viated way of saying something that cannot be simply defined.[3] A definition may be derived from the structure and properties of a common primary lesion seen late in tumor progression. *Cancer is a population of abnormal cells showing temporally unrestricted growth preference (continually increasing numbers of cells in the population) over normal cells. Such abnormal cells invade surrounding tissues, traverse at least one basement membrane* ...ay ...hat ...s a ...de- ...re- ...nd manifest exogenous growth stimulus.

2. The parenchymal cells of a cancer have the ability to grow in the tissue compartment of origin and in the adjacent extracellular matrix (mesenchyme), requiring the traverse of a basement membrane zone.

3. The parenchymal cells of a cancer have a variable ability to grow in an extracellular matrix (mesenchyme) other than that of the original site. Growth in a distant mesenchyme requires the completion of the events of metastasis.

> The diagnosis of carcinoma in situ (melanoma in situ, malignancy in situ) is a contradiction in terms, the prototype of an oxymoron.

For example, Clark in 1990 spoke of melanoma in situ as *"a contradiction in terms, the prototype of an oxymoron,"*



10:30 – 11:15 ***The A.B. Ackerman lecture (Chair: P.E. LeBoit)***

Melanoma in situ: An attractive, obsolete, untenable concept
J. Rosai (Milan)

29th Symposium of the ISD, Graz, Oct 4th, 2008

and, more recently, Juan Rosai referred to it as an *"obsolete, untenable concept."* Those notions have been coupled

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Evaluation of Overdiagnosis of Breast Cancer in Screening with Mammography: Results of the Nijmegen Programme

PETRA H M PEETERS*, A L M VERBEEK*, H STRAATMAN*, R HOLLAND**, J H C L HENDRIKS†, M M

10:30 – 11:15 *The A.B. Ackerman lecture (Chair: P.E. LeBoit)*

Melanoma in situ: An attractive, obsolete, untenable concept
J. Rosai (Milan)

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After 12 years of screening for breast cancer in Nijmegen (1975–86), during which period six mammographic examination rounds were carried out, the extent of overdiagnosis was evaluated. Overdiagnosis is defined as a histologically established diagnosis of invasive or intraductal breast cancer that would never have developed into a clinically manifest tumour during the patient's normal life expectancy if no screening examination had been carried out. The whole 12-year period shows an excess of 11% of breast cancer cases in Nijmegen, compared with the neighbouring city of Arnhem, where no mass screening was performed. The incidence of breast cancers in Nijmegen in the period 1975–78 is higher, compared with the incidence rates in Arnhem; the rate ratio is 1.30. For the time-intervals 1979–82 and 1983–86 the rate ratios are 1.03 and 1.01 respectively with (0.89; 1.18) and (0.86; 1.16) as 95% confidence intervals. This leads to the conclusion that there is no evidence that screening programmes using modern mammography constitute a significant risk for overdiagnosis of breast cancers.

with a new definition of *"overdiagnosis"* advanced by epidemiologists in regard to breast cancer, namely, a *"histologically established diagnosis of invasive or intraductal breast cancer that would never have developed into a clinically manifest tumour during the patient's normal life expectancy if no screening examination had been carried out."*

But how should anybody know in advance whether or not a histopathologically established malignant neoplasm would develop into a clinically manifest tumour? And what if the patient exceeds his or her *"normal life expectancy"*?

Skin biopsy rates and incidence of melanoma: population based ecological study

H Gilbert Welch, Steven Woloshin, Lisa M Schwartz

BMJ 2005; 331: 481

Abstract

Objectives To describe changes in skin biopsy rates and to determine their relation with changes in the incidence of melanoma.
Design Population based ecological study.
Setting Nine geographical areas of the United States.
Participants Participants of the Surveillance Epidemiology and End Results (SEER) programme aged 65 and older.
Main outcome measures For the period 1986 to 2001, annual skin biopsy rates for each surveillance area from Medicare claims and incidence rates for melanoma for the same population.
Results Between 1986 and 2001 the average biopsy rate across the nine participating areas increased 2.5-fold among people aged 65 and older (2847 to 7222 per 100 000 population). Over the same period the average incidence of melanoma increased 2.4-fold (45 to 108 per 100 000 population). Assuming that the occurrence of true disease was constant, the extra number of melanoma cases that were diagnosed after carrying out 1000 additional biopsies was 12.6 (95% confidence interval 11.2 to 14.0). After controlling for a potential increase in the true occurrence of disease, 1000 additional biopsies were still associated with 6.9 (3.1 to 10.8) extra melanoma cases diagnosed. Stage specific analyses suggested that 1000 biopsies were associated with 4.4 (2.1 to 6.8) extra cases of in situ melanoma diagnosed and 2.3 (0.0 to 4.6) extra cases of local melanoma, but not with the incidence of advanced melanoma. Mortality from melanoma changed little during the period.
Conclusion The incidence of melanoma is associated with biopsy rates. That the extra cases diagnosed were confined to early stage cancer while mortality remained stable suggests overdiagnosis—the increased incidence being largely the result of increased diagnostic scrutiny and not an increase in the incidence of disease.

disease.[1 3 7] Finally, whenever physicians look more closely for melanoma, they find more cases.[7-10]

Population based data have not been reported on skin biopsies, the critical end point of surveillance. We examined data from Medicare, a nationwide health insurance for older Americans, to determine whether changes in the biopsy rate relate to the incidence of melanoma.

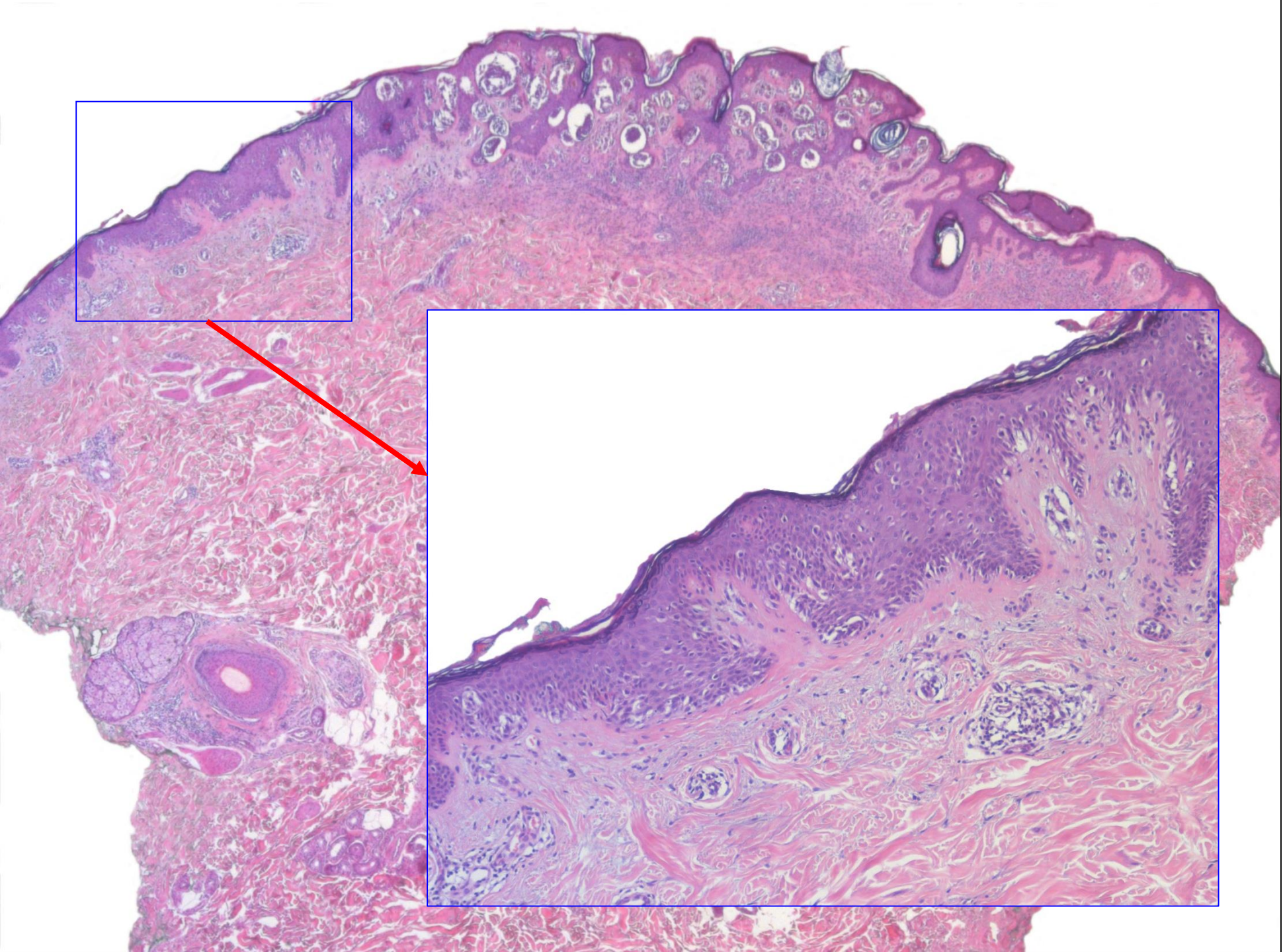
Methods

We used Medicare claims to obtain annual population based rates of skin biopsy for patients aged 65 and older in each of the nine geographical areas included in the US National Cancer Institute's Surveillance Epidemiology and End Results (SEER) programme from 1986 to 2001. We calculated the biopsy rates for each of 14 years (claims were unavailable for 1991 and 1992). To obtain the annual incidence of melanoma for the same population, we used the programme's statistical software (SEER*Stat, version 5.3.0).[11] We obtained stage specific incidence rates using the surveillance programme's four histological disease stages (in situ, local, regional, and distant) and summed them to produce an incidence rate for all stages combined. Using SEER*Stat's incidence based mortality method we also calculated melanoma incidence and disease specific mortality for all nine geographical areas combined.

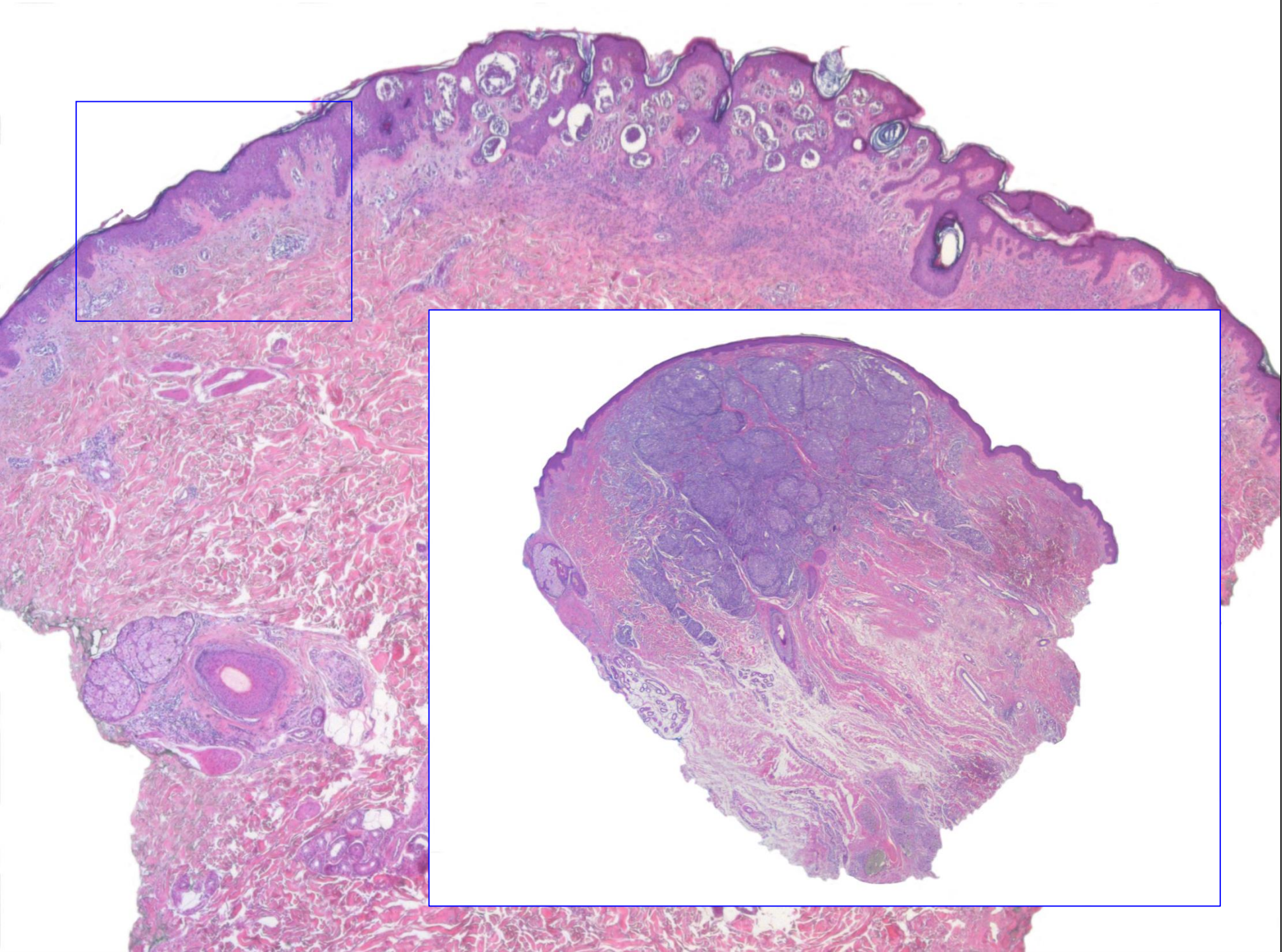
Analysis

We used multiple linear regression to explore the relation between biopsy rate (independent variable) and melanoma rate (dependent variable). The unit of analysis was the surveillance programme's area in an individual year (nine areas, 14 years, 126 observations). To control for regional differences that may affect incidence (for example, latitude, racial composition, practice style) we included an indicator variable for area in all analyses. Our baseline analysis predicts the effect of 1000 additional biopsies on the number of melanoma diagnoses. The implicit

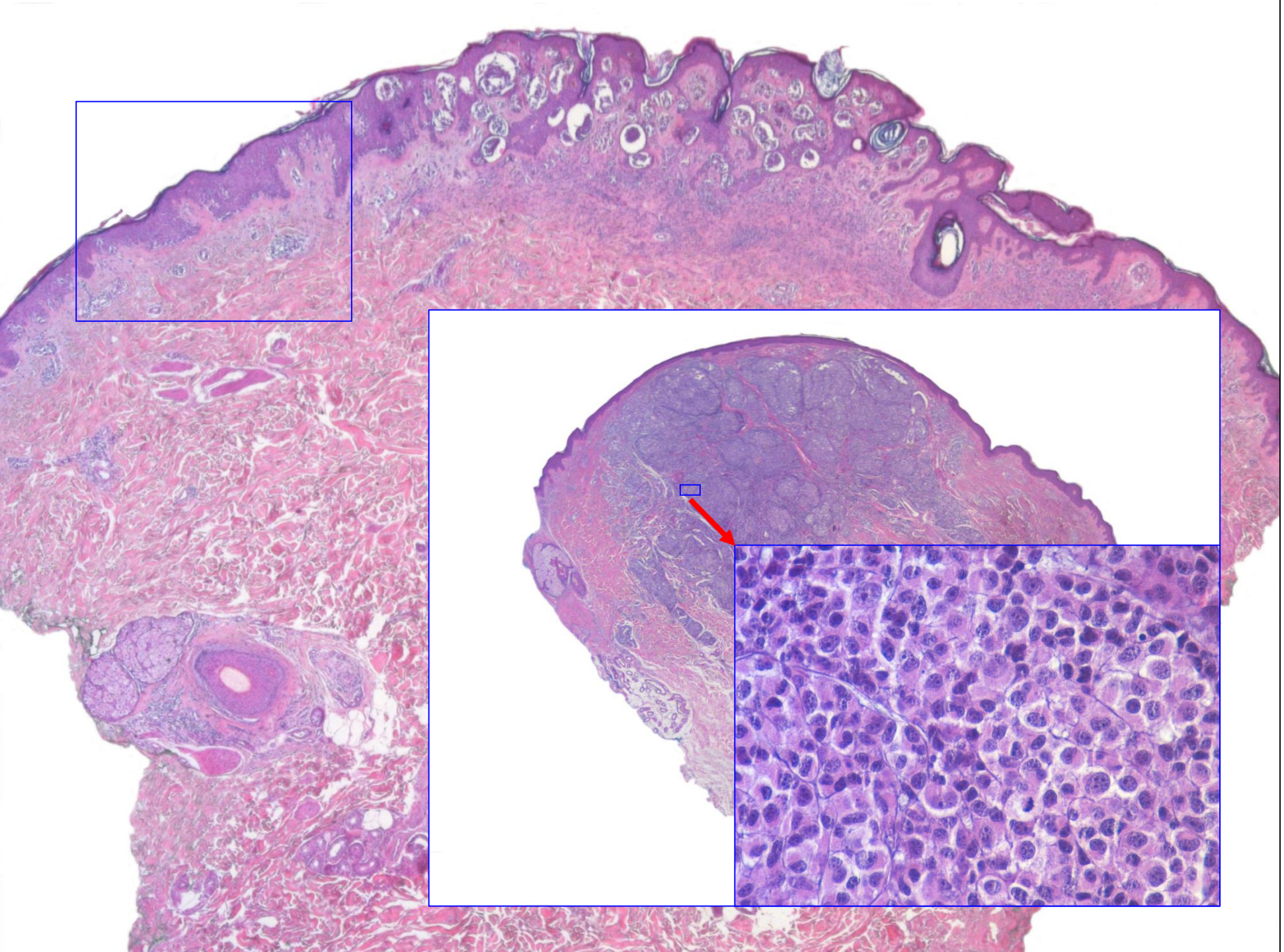
That definition is clearly untenable but, nonetheless, it has become accepted worldwide and has been been applied to all types of malignant neoplasms, including melanoma. In 2005, Welch found a strong correlation between skin biopsy rates and the incidence of melanoma, noted that *"the extra cases diagnosed were confined to early stage cancer,"* and attributed that phenomenon to overdiagnosis.
This conclusion was based on statistics.



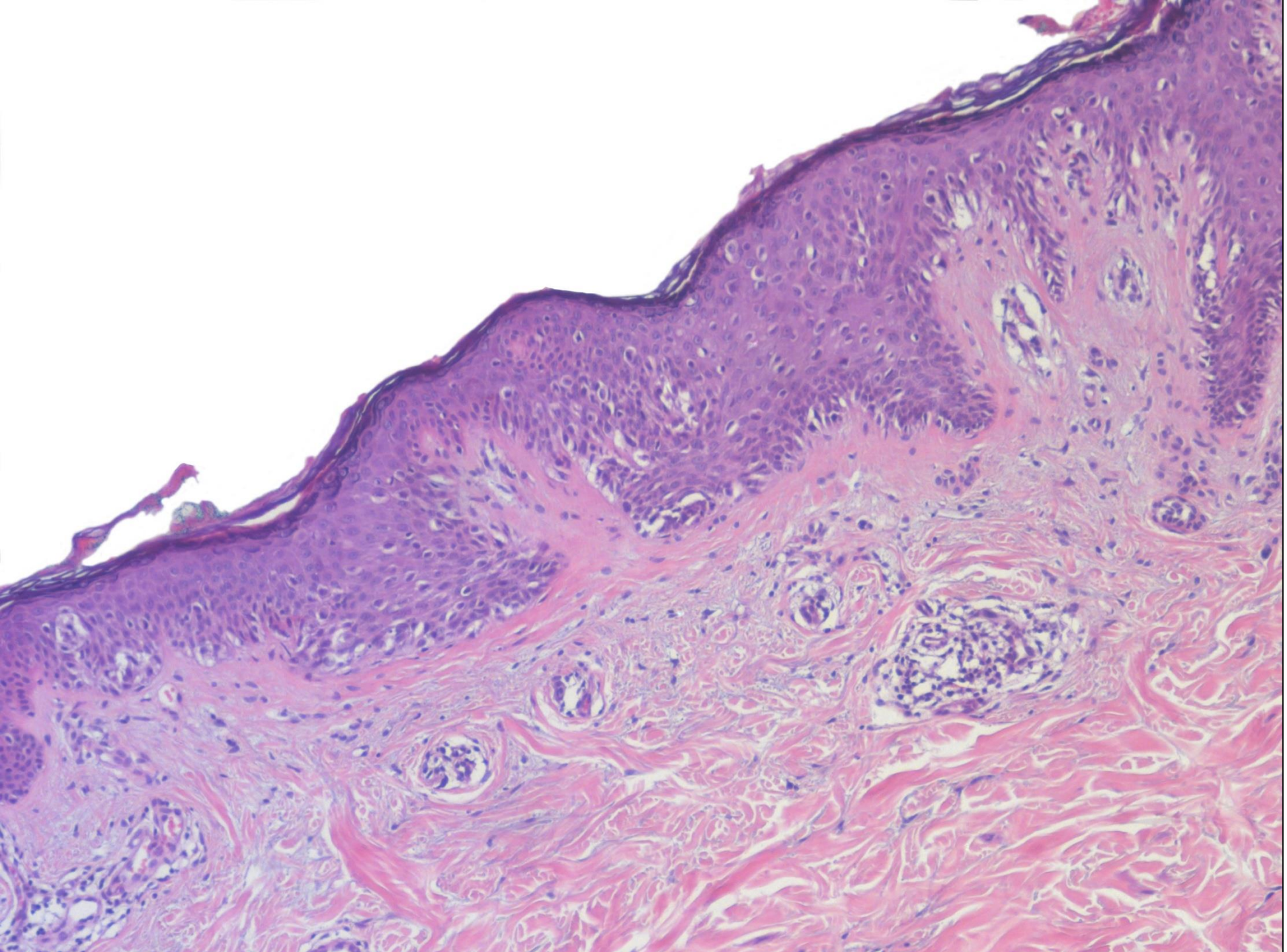
Here we have a practical example: a melanoma in situ at the edge of a congenital nevus. In the terminology of epidemiologists, the melanoma in situ is *“early stage cancer”* or *“inconsequential cancer,”* and it has even been suggested to avoid the label of cancer for such lesions because it represents “overdiagnosis.” This may be the case, but only if the lesion is excised completely. Unfortunately, this melanoma in situ was present in only one of several sections, all the others showing the nevus exclusively, and the relevant section was overlooked.



Two years later, the diagnosis of melanoma was no “overdiagnosis” any more



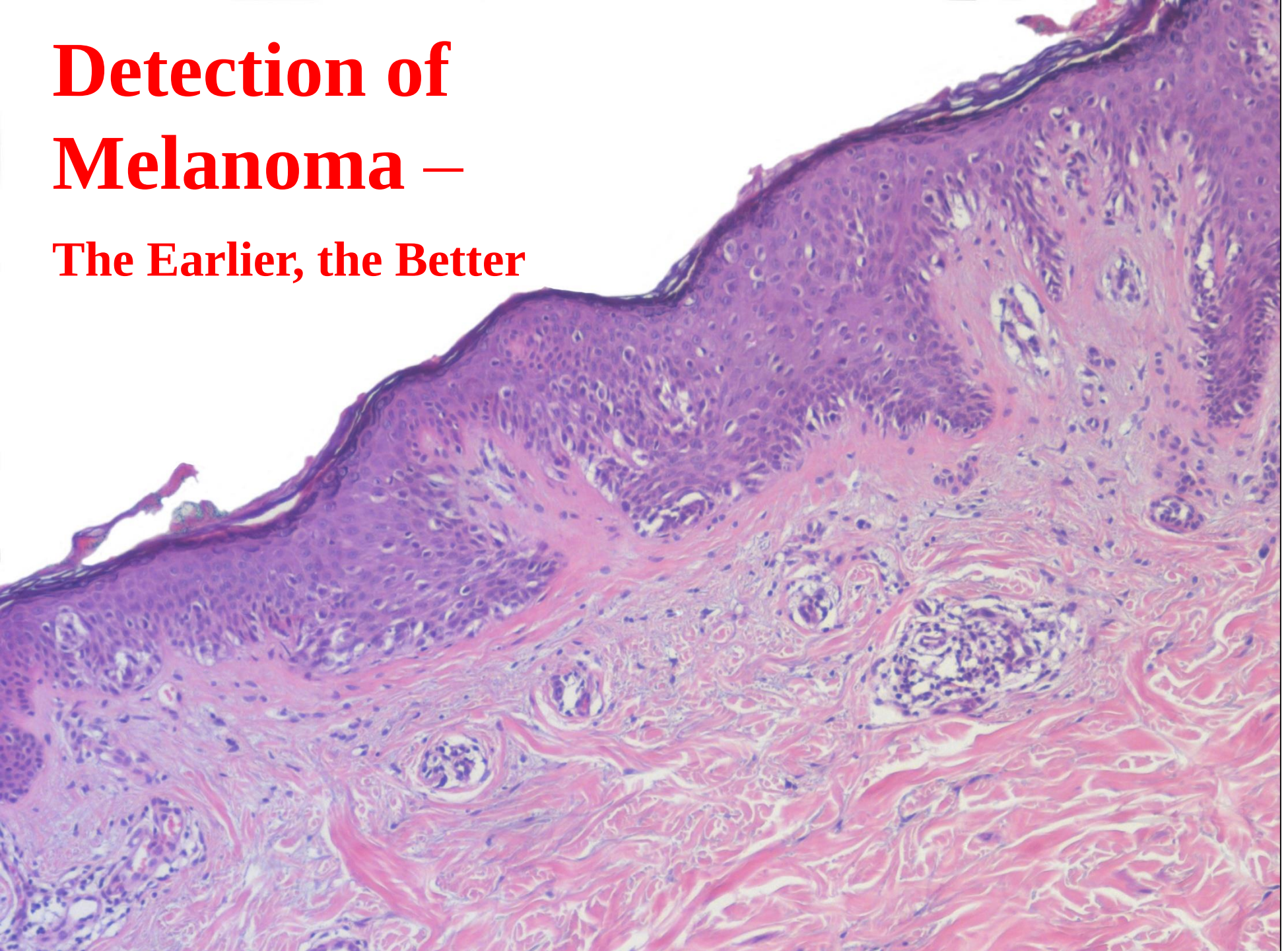
because the lesion was no longer “inconsequential.” This example illustrates the purpose of cancer screening, namely, to prevent “inconsequential” cancer from becoming consequential. The diagnosis of melanoma should have been made



at the in-situ stage, and it could have been made at that stage because criteria for melanoma were fulfilled: predominance of single melanocytes, poorly confined nests, melanocytes in all reaches of the epidermis. Here it is really true:

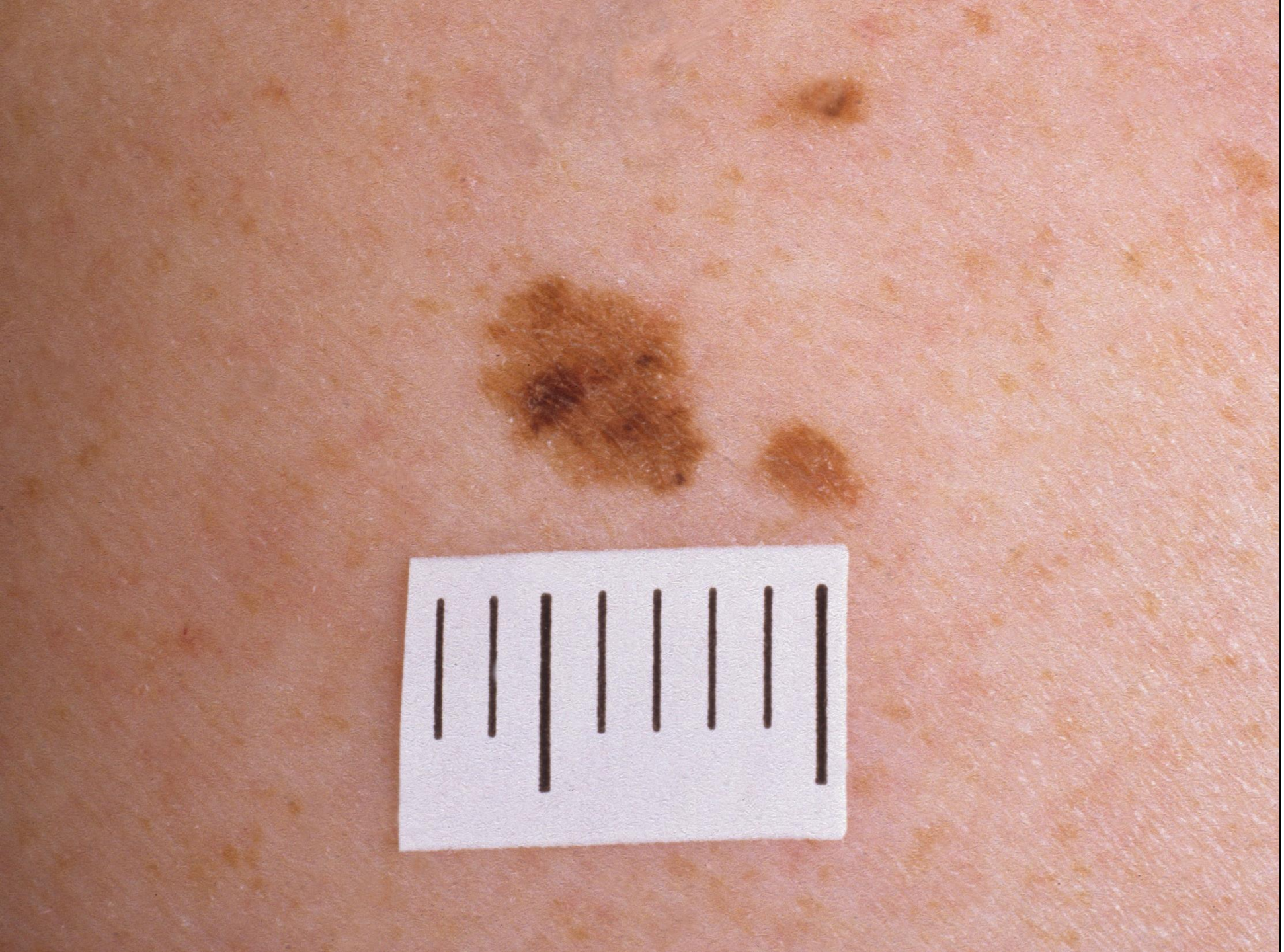
Detection of Melanoma –

The Earlier, the Better

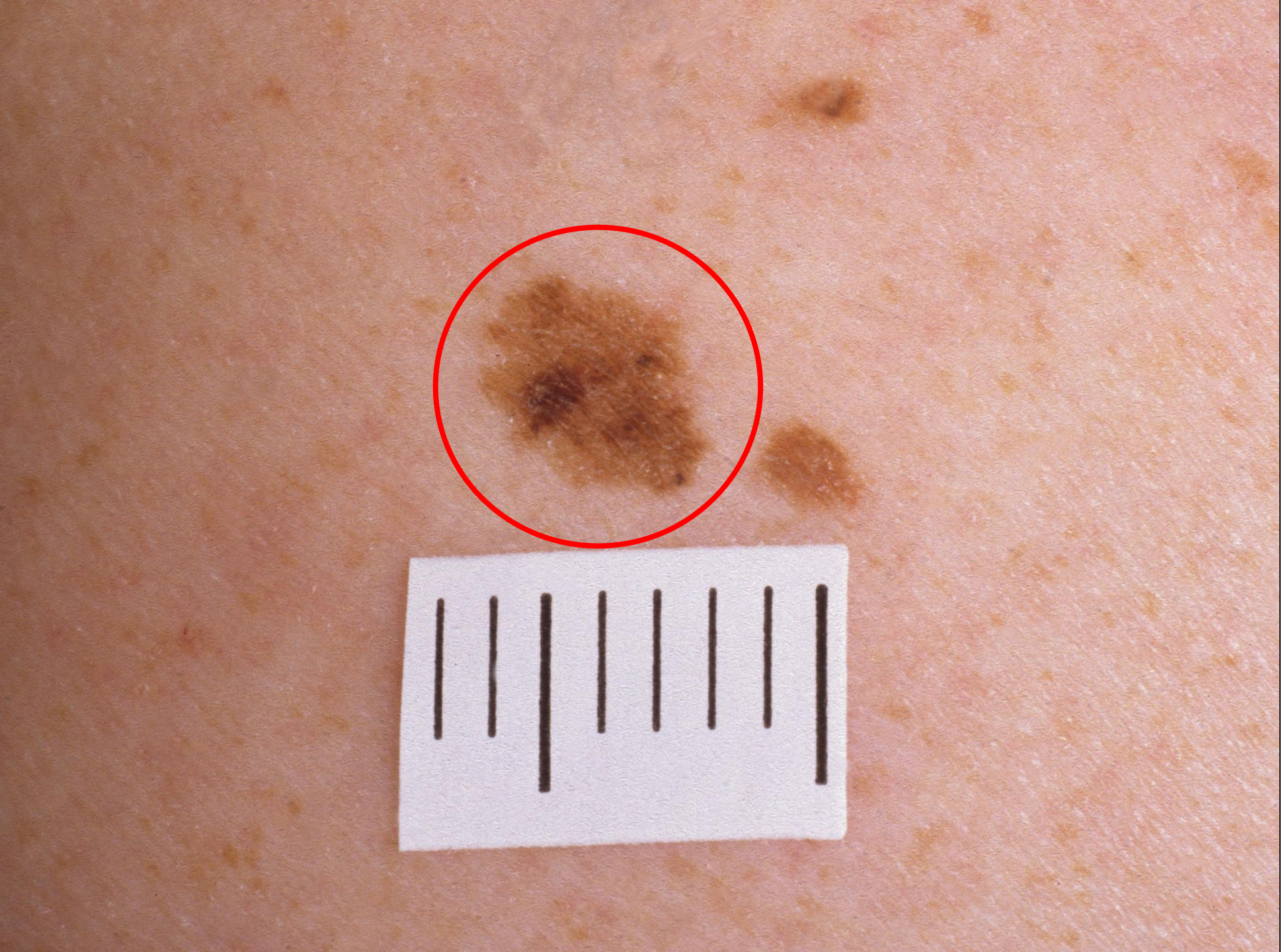


"Detection of melanoma – the earlier, the better."

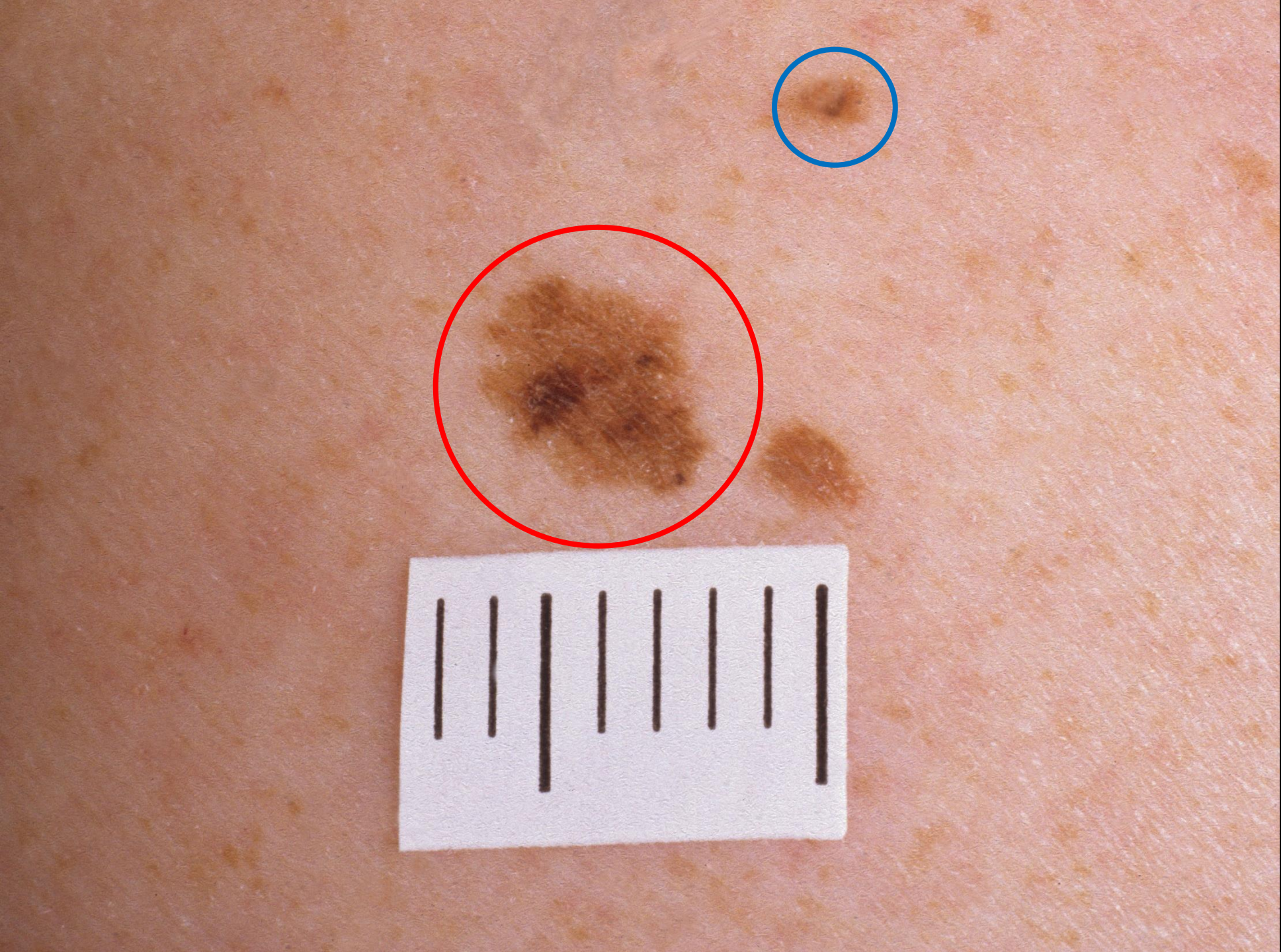
However, it is true only if the melanoma can be recognized.



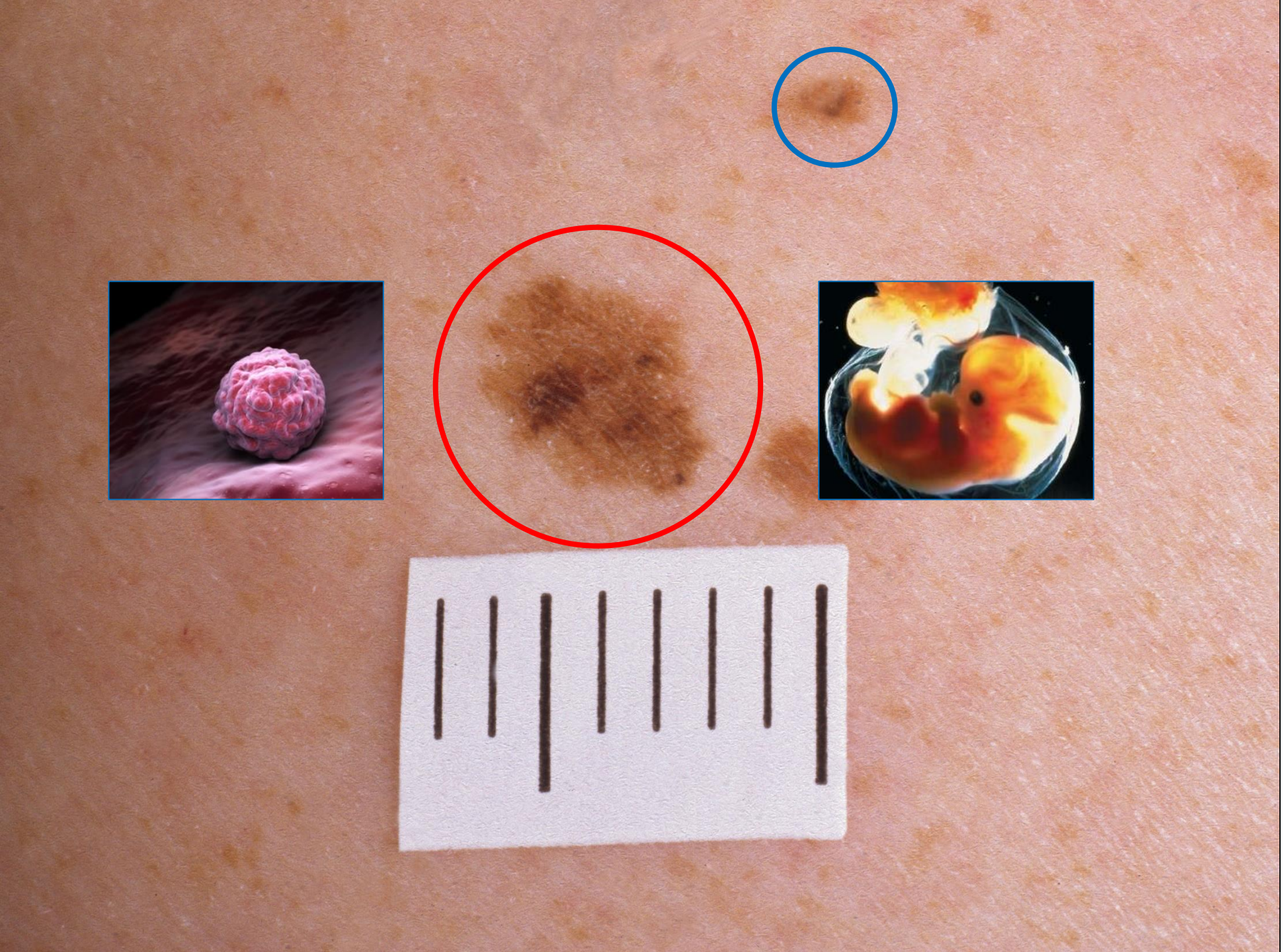
In general, detection is possible at an in-situ stage, but the earlier one wants to interfere, the more difficult detection becomes.



This lesion is an in-situ melanoma,



but how about this one that looks remarkably similar? One cannot be sure because it is simply too small; if it is another melanoma, it did not have enough time to develop features that make it recognizable.



just as one cannot recognize a human being at an early stage of embryogenesis. And if one tries to interfere at that stage, overdiagnoses are inevitable, not those fulfilling the definition of epidemiologists, but true overdiagnoses, i.e., melanocytic nevi misinterpreted as melanoma.

Clinical dermatology • **Original article**

CED
Clinical and Experimental Dermatology

The number of benign moles excised for each malignant melanoma: the number needed to treat

S. Sidhu, O. Bodger, N. Williams* and D. L. Robertst

*The Welsh Institute of Dermatology, University Hospital of Wales, Cardiff, UK; School of Medicine, Swansea University, UK; and Departments of *Histopathology and †Dermatology, Singleton Hospital, Swansea, UK*

doi:10.1111/j.1365-2230.2011.04148.x

Summary

Background. The ratio … elanoma (MM) diagnosed, i.e. the numb… l indicator of diagnostic accuracy and … nd may have personal implications for …

Aim. To assess the NNT … g a population of 600 000, and to comp… ries.

Methods. This was a ret… ns excised over a 5-year period (2005–20… s: benign naevi (BN), dysplastic naevi … calculated as (BN + DN + MM)/MM.

Results. In total, 4691 … was 6.3, with a range of 4.9–11.3 for e… ean NNT was 7.6 for female and 4.8 for … BN (n = 3534; 75%) than with DN (n = … representation was similar in the DN and MM groups, but had a disproportionately female bias in the

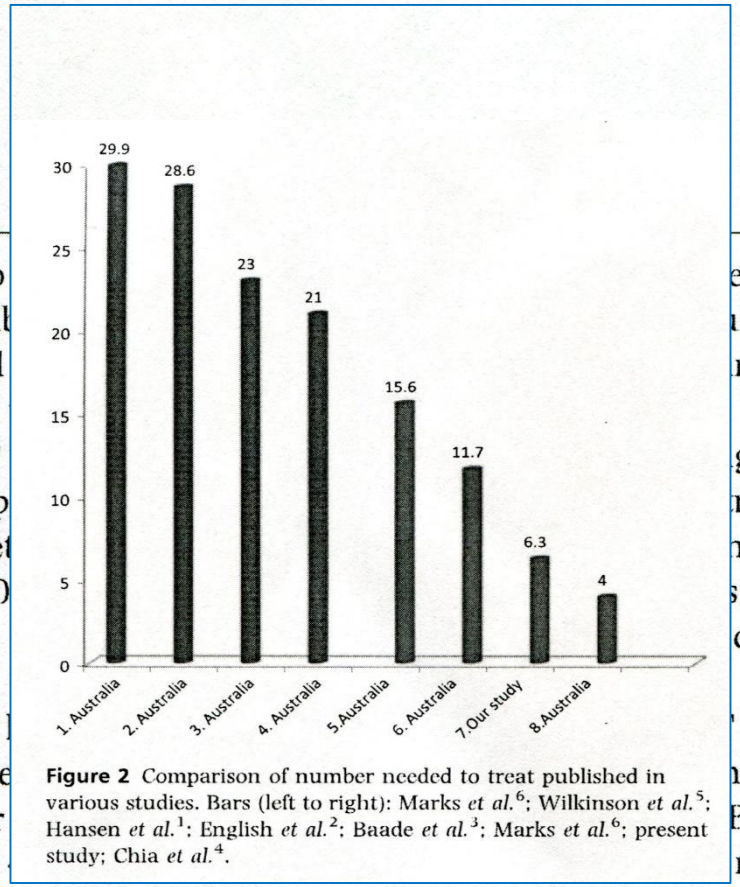


Figure 2 Comparison of number needed to treat published in various studies. Bars (left to right): Marks *et al.*[6]; Wilkinson *et al.*[5]; Hansen *et al.*[1]; English *et al.*[2]; Baade *et al.*[3]; Marks *et al.*[6]; present study; Chia *et al.*[4].

One problem is clinical overdiagnosis. The ratio of benign moles excised for each melanoma, also known as the *"number needed to treat,"* varies considerably between different studies. I recently looked at our own figures, i.e., the ratio between nevi and melanomas at a laboratory of dermatopathology in Germany where regular skin cancer screening has been implemented nine years ago,

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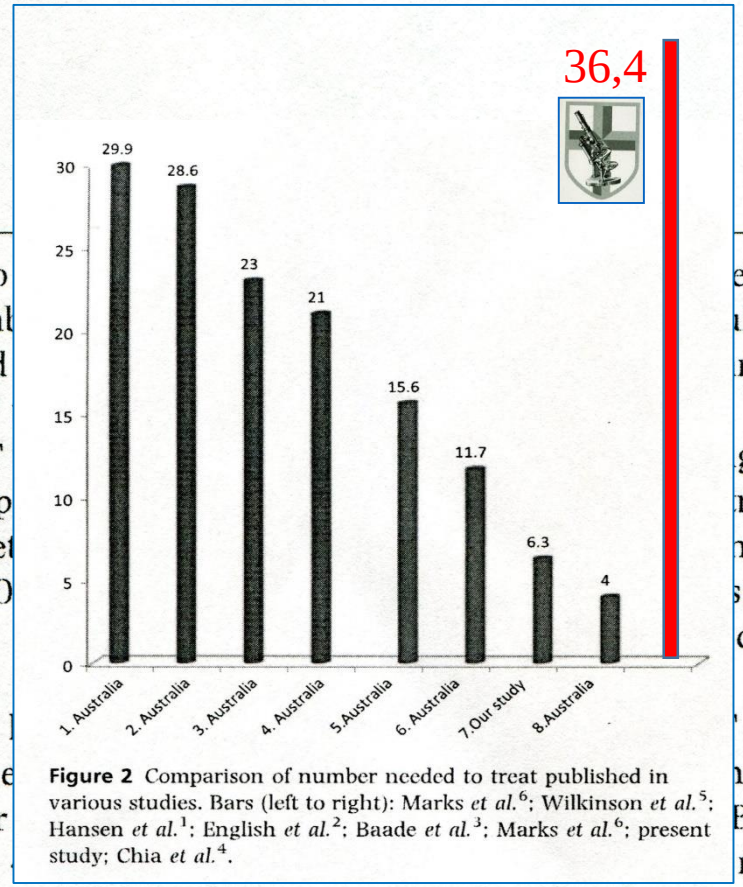

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and our numbers were far higher. Most of the nevi submitted to our lab were very small,

too small to exhibit criteria for clinical diagnosis of melanoma such as an irregular border or irregular distribution of pigment. In the absence of such criteria, the vast majority of pigmented lesions are going to be melanocytic nevi, rather than melanomas,

Addressing overdiagnosis and overtreatment in cancer: a prescription for change

Lancet Oncol 2014; 15: e234

Laura J Esserman, Ian M Thompson, Brian Reid, Peter Nelson, David F Ransohoff, H Gilbert Welch, Shelley Hwang, Donald A Berry, Kenneth W Kinzler, William C Black, Mina Bissell, Howard Parnes, Sudhir Srivastava

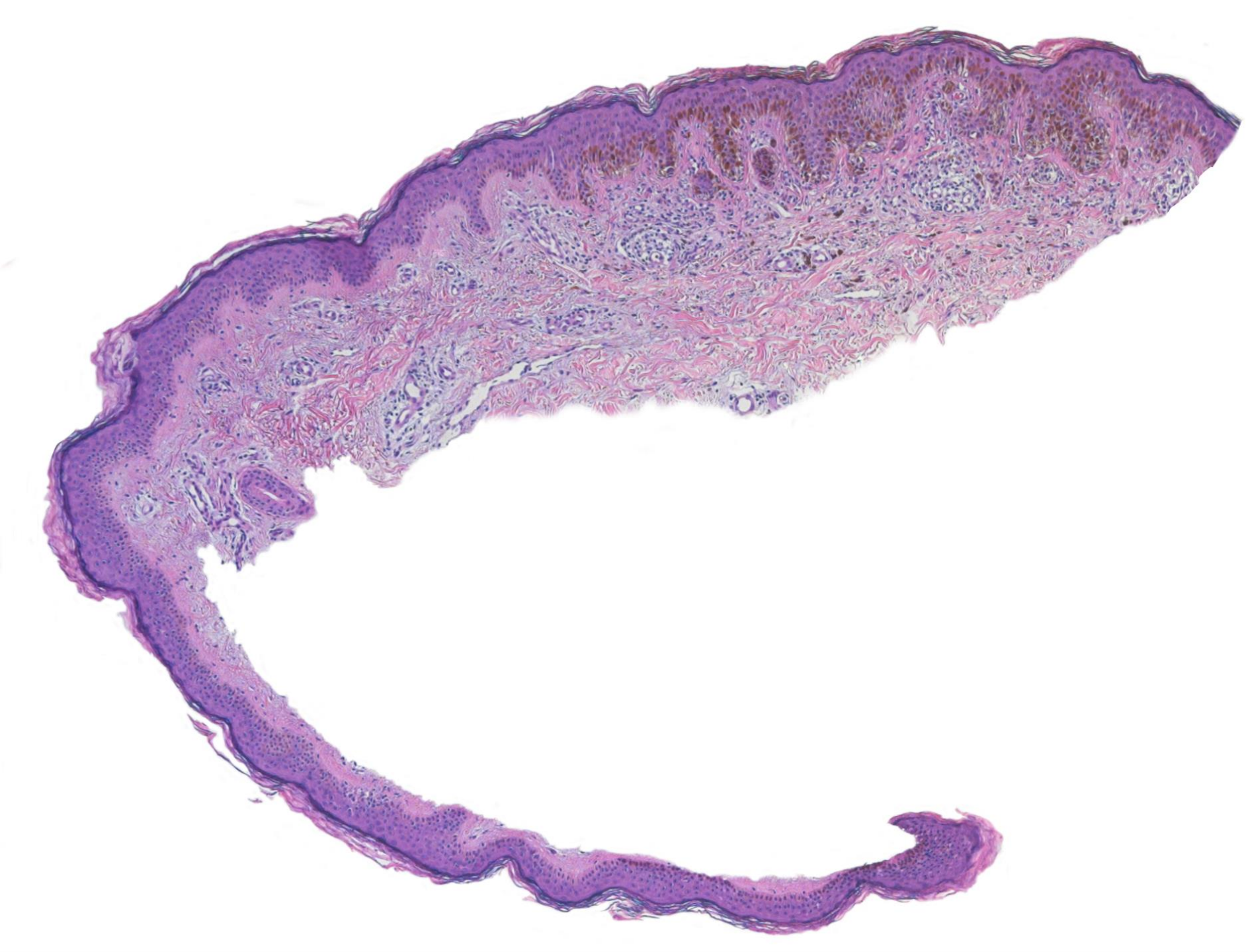
A vast range of disorders—from indolent to fast-growing lesions—are labelled as cancer. Therefore, we believe that several changes should be made to the approach to cancer screening and care, such as use of new terminology for indolent and precancerous disorders. We propose the term indolent lesion of epithelial origin, or IDLE, for those lesions (currently labelled as cancers) and their precursors that are unlikely to cause harm if they are left untreated. Furthermore, precursors of cancer or high-risk disorders should not have the term cancer in them. The rationale for this change in approach is that indolent lesions with low malignant potential are common, and screening brings indolent lesions and their precursors to clinical attention, which leads to overdiagnosis and, if unrecognised, possible overtreatment. To minimise that potential, new strategies should be adopted to better define and manage IDLEs. Screening guidelines should be revised to lower the chance of detection of minimal-risk IDLEs and inconsequential cancers with the same energy traditionally used to increase the sensitivity of screening tests. Changing the terminology for some of the lesions currently referred to as cancer will allow physicians to shift medicolegal notions and perceived risk to reflect the evolving understanding of biology, be more judicious about when a biopsy should be done, and organise studies and registries that offer observation or less invasive approaches for indolent disease. Emphasis on avoidance of harm while assuring benefit will improve screening and treatment of patients and will be equally effective in the prevention of death from cancer.

Biopsy samples are taken from hundreds of thousands of benign lesions … In addition to needless morbidity, these interventions cost billions of dollars.

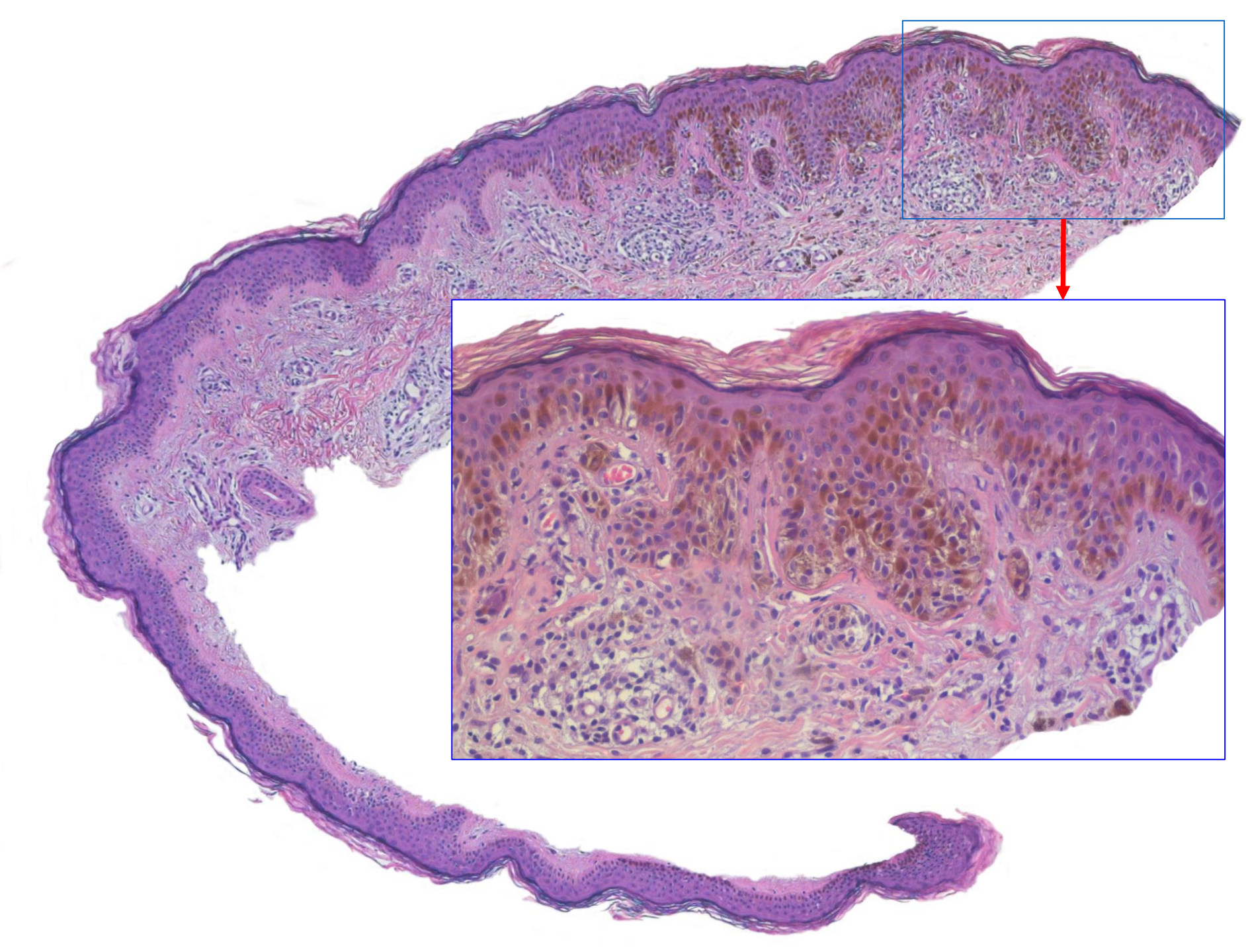
and epidemiologists are right to deplore that *"biopsy samples are taken from hundreds of thousands of benign lesions … In addition to needless morbidity, these interventions cost billions of dollars."*

The problem of trying to detect melanomas at the earliest possible stage, however, is not only overdiagnosis clinical, but also histopathological.

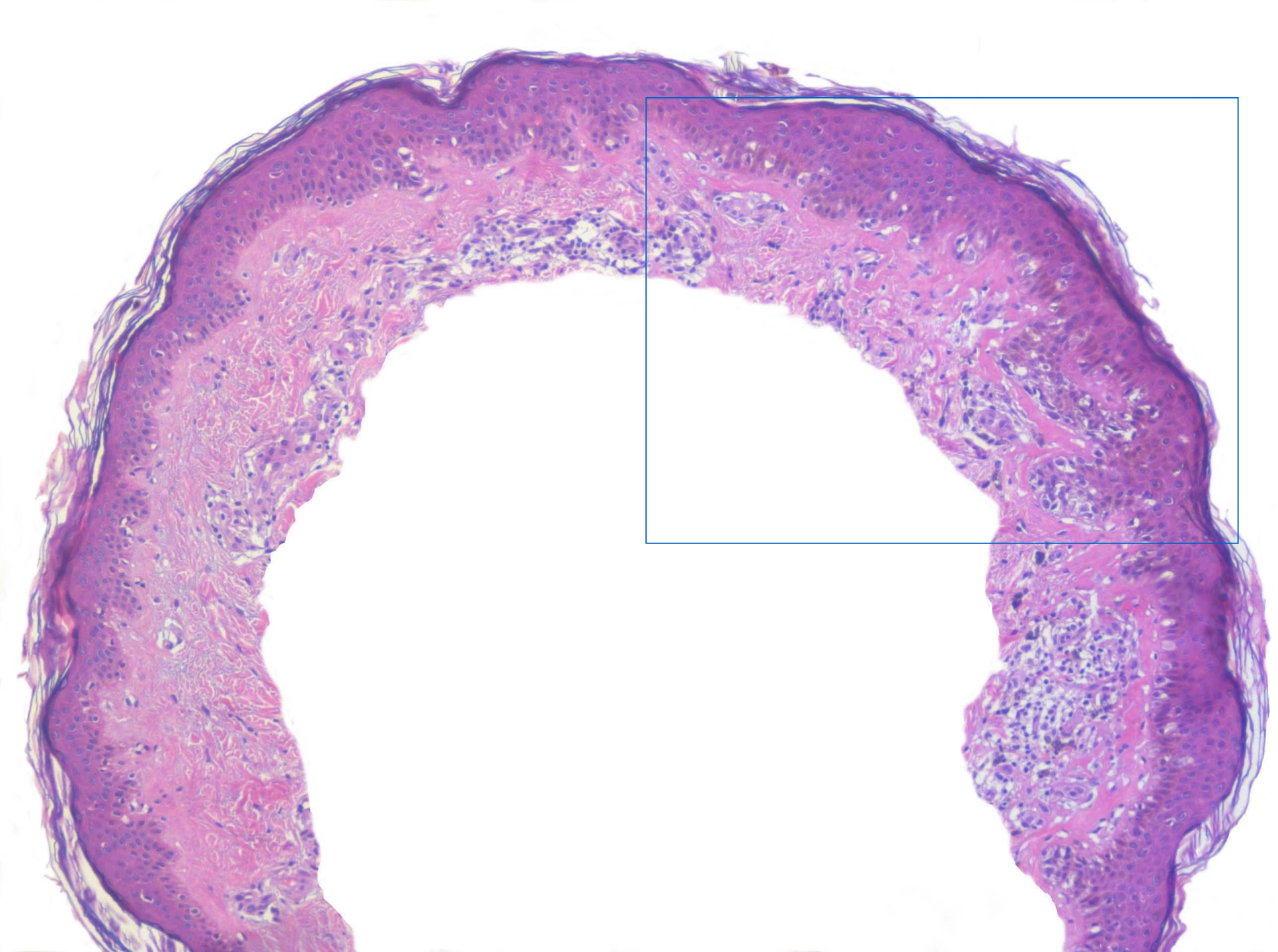
Of course, histopathologic diagnosis is usually possible at an earlier stage, but in principle, histopathologists are confronted with the same dilemma as clinicians:



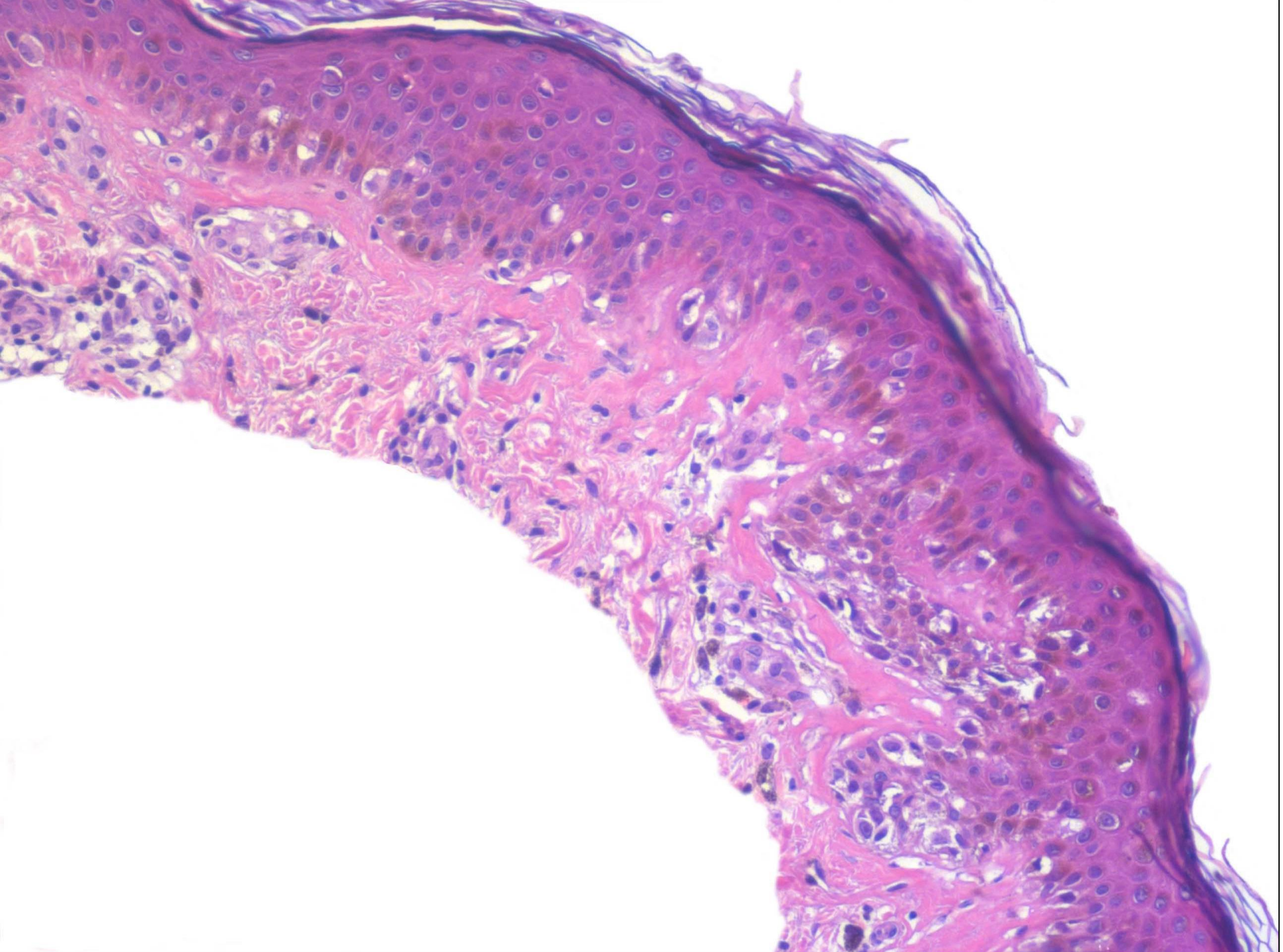
if an incipient melanoma is not given the time for characteristics to develop that are crucial for diagnosis, the latter remains equivocal. For example, a few cells in the dermis may be extremely helpful for distinction between nevus and melanoma.



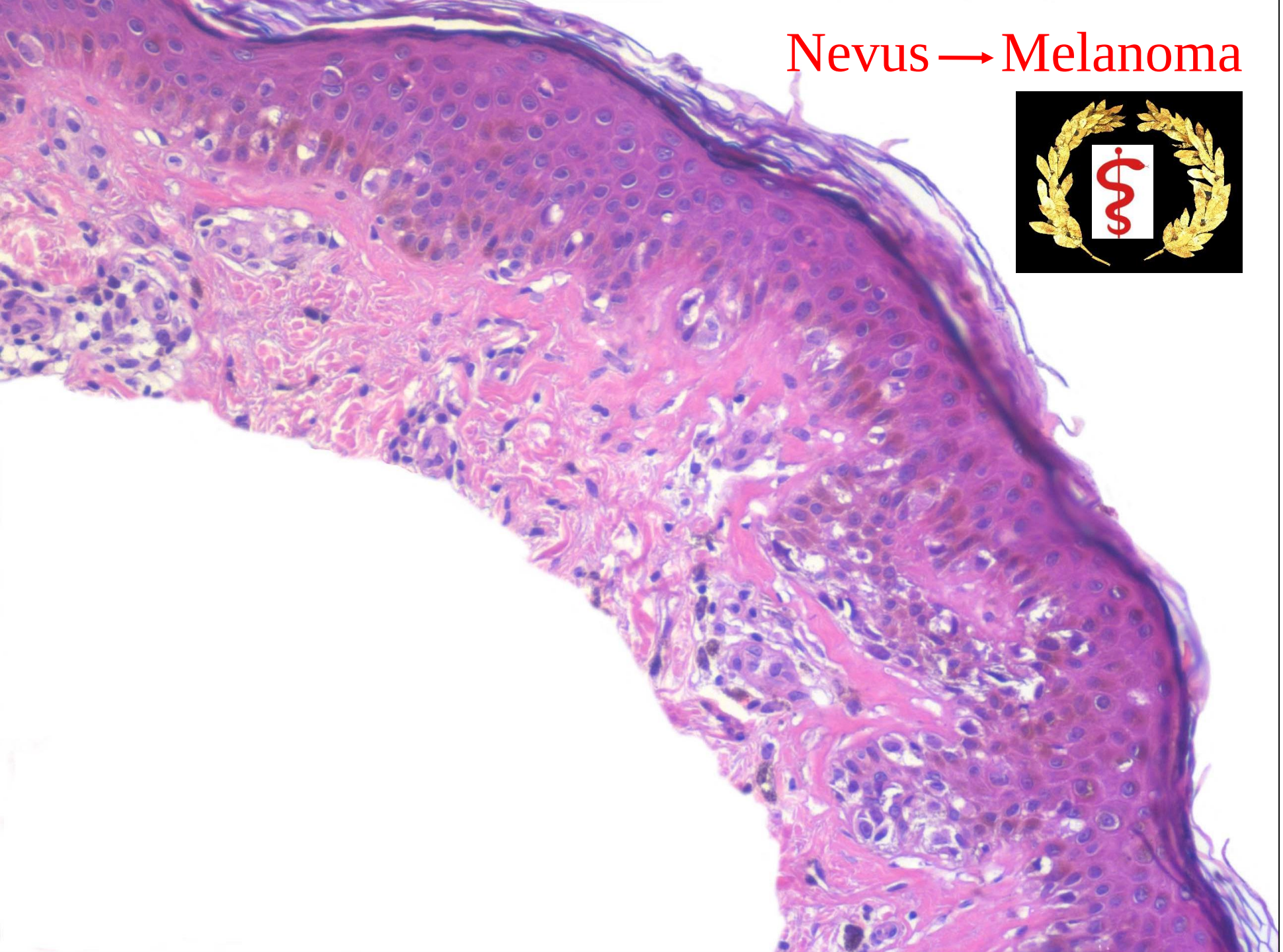
Were it not for those nests in the dermis, one might be tempted to invoke the diagnosis of melanoma in situ in this lesion because of some melanocytes above the junction.



Another example removed at an earlier stage. There is no dermal component. Single melanocytes predominate over nests because there are no discrete nests – they were not given the time to form –,



and there are some melanocytes above the junction. This is probably a nevus, but a melanoma in situ cannot be excluded, and because nobody wants to overlook a melanoma, overdiagnoses are common. Because what happens in the event of error?



Nevus → Melanoma

If a benign lesion is classified as malignant, one gets a medical laurel wreath because patients believe they have been saved;

Nevus → Melanoma

Melanoma → Nevus

if a malignant lesion is classified as benign, it may recur and one may be taken to court. This is a strong incentive to err on the malignant side.

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Journal of
Cutaneous Pathology

Perspectives in Dermatopathology

The melanoma 'epidemic', a dermatopathologist's perspective

Over the past several decades, the rise in melanoma incidence has been termed "epidemic." However, detailed analysis of mortality data suggests that the true incidence of melanoma has not increased dramatically. Dermatopathologists, who hold a key position in the diagnosis of melanoma, should have unique insight into this quandary. Factors contributing to the apparent melanoma epidemic likely include intense screening, sampling of earlier lesions, medical-legal pressures, imperfect diagnostic methodology, and lack of a usable gold standard. Consequences of the apparent melanoma epidemic are also explored herein.

Keywords: melanoma, epidemic, pathology, dysplastic nevus

Glusac EJ. The melanoma 'epidemic', a dermatopathologist's perspective.
J Cutan Pathol 2011; 38: 264–267. © 2011 John Wiley & Sons A/S.

Earl J. Glusac

Department of Pathology and Dermatology,
Yale University School of Medicine,
New Haven, CT, USA

Prof. Earl J. Glusac, MD,
Department of Pathology and Dermatology,
Yale University School of Medicine,
New Haven, CT, USA
Tel: +1 203 785 4094
Fax: +1 203 785 6869
e-mail: earl.glusac@yale.edu

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The so-called "melanoma epidemic" is probably caused, in part,

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I believe that the overdiagnosis of melanoma is arguably the most difficult problem that we face in dermatopathology today.

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Fax: +1 203 785 6869
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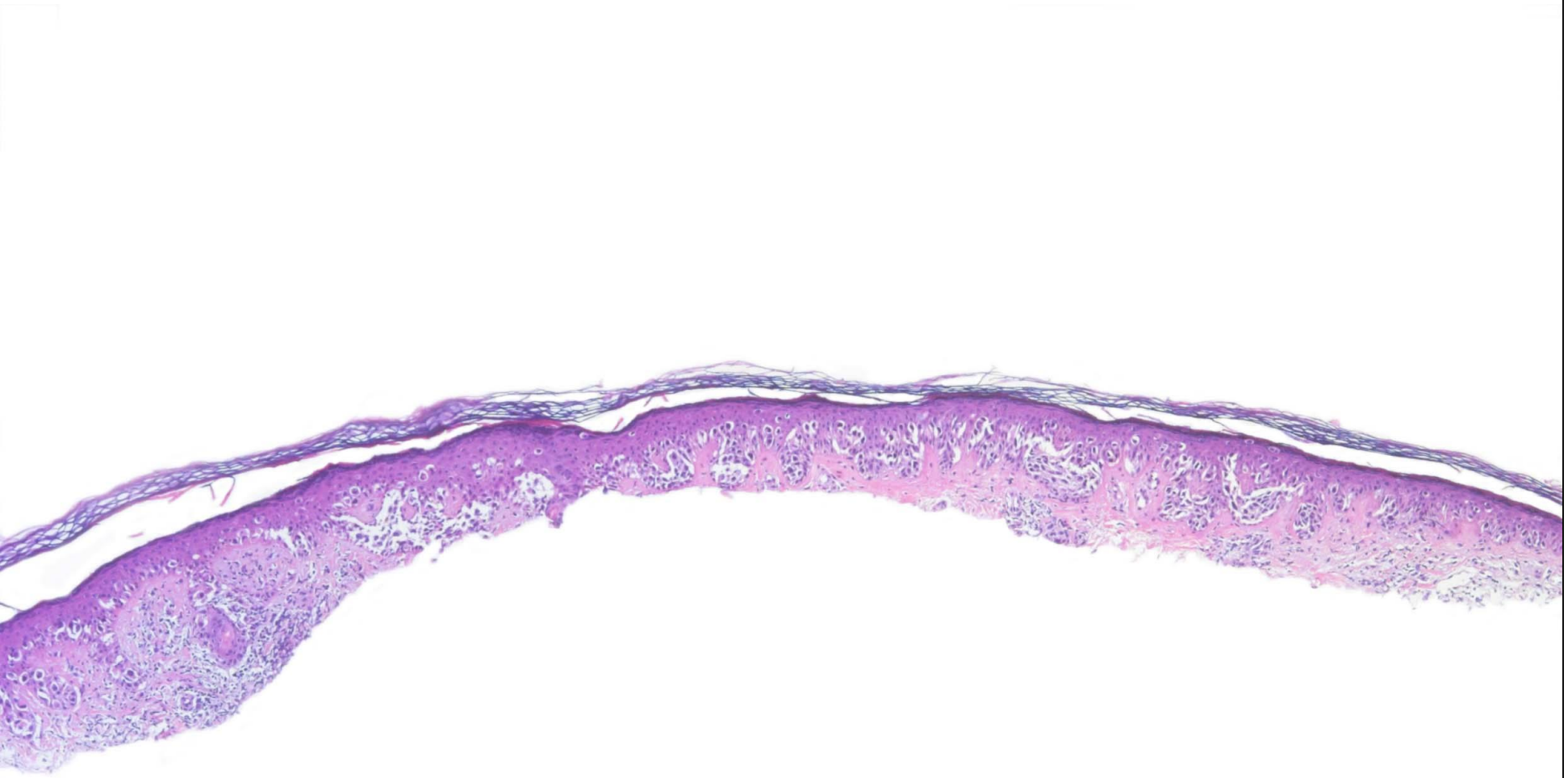
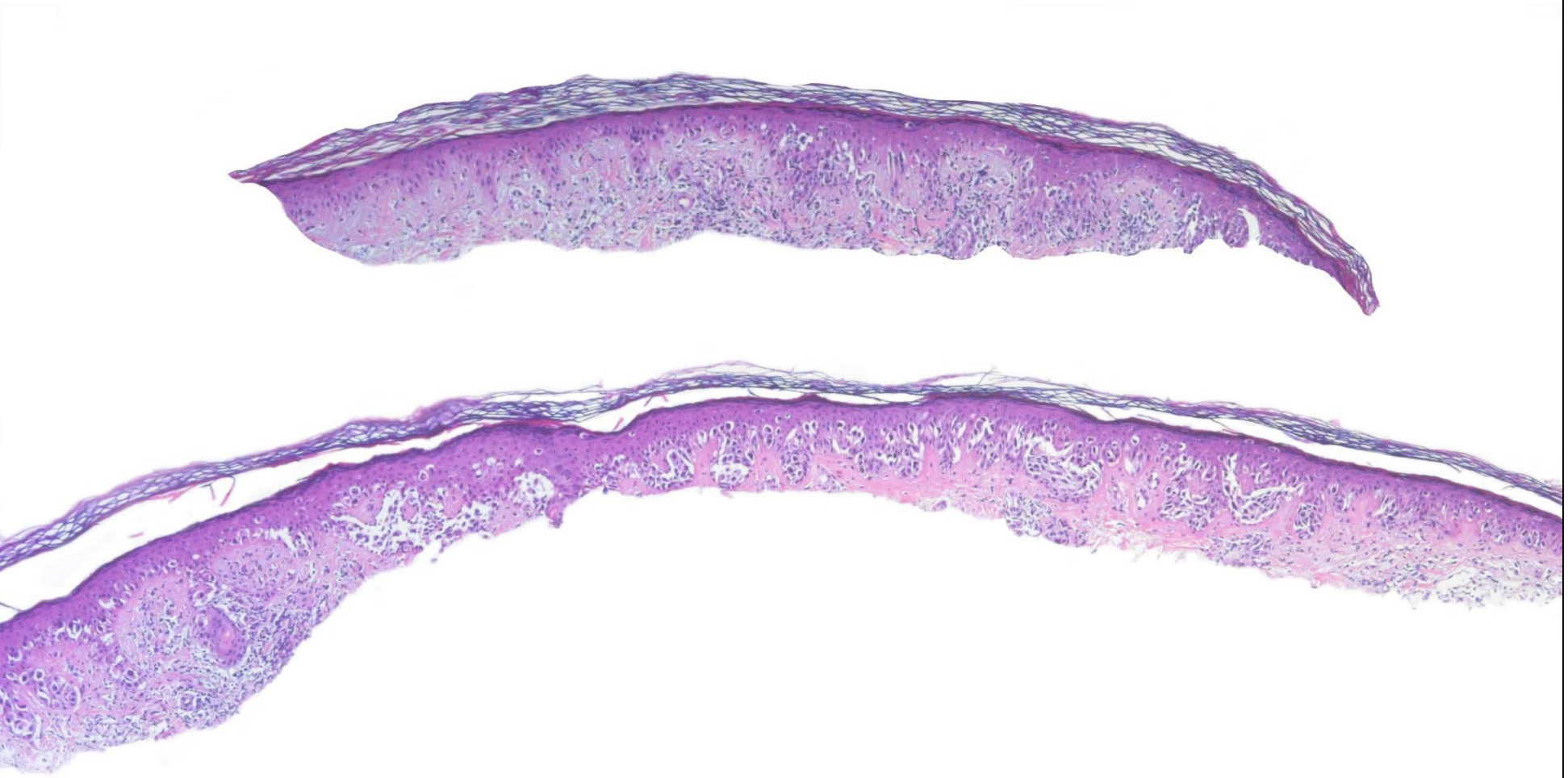
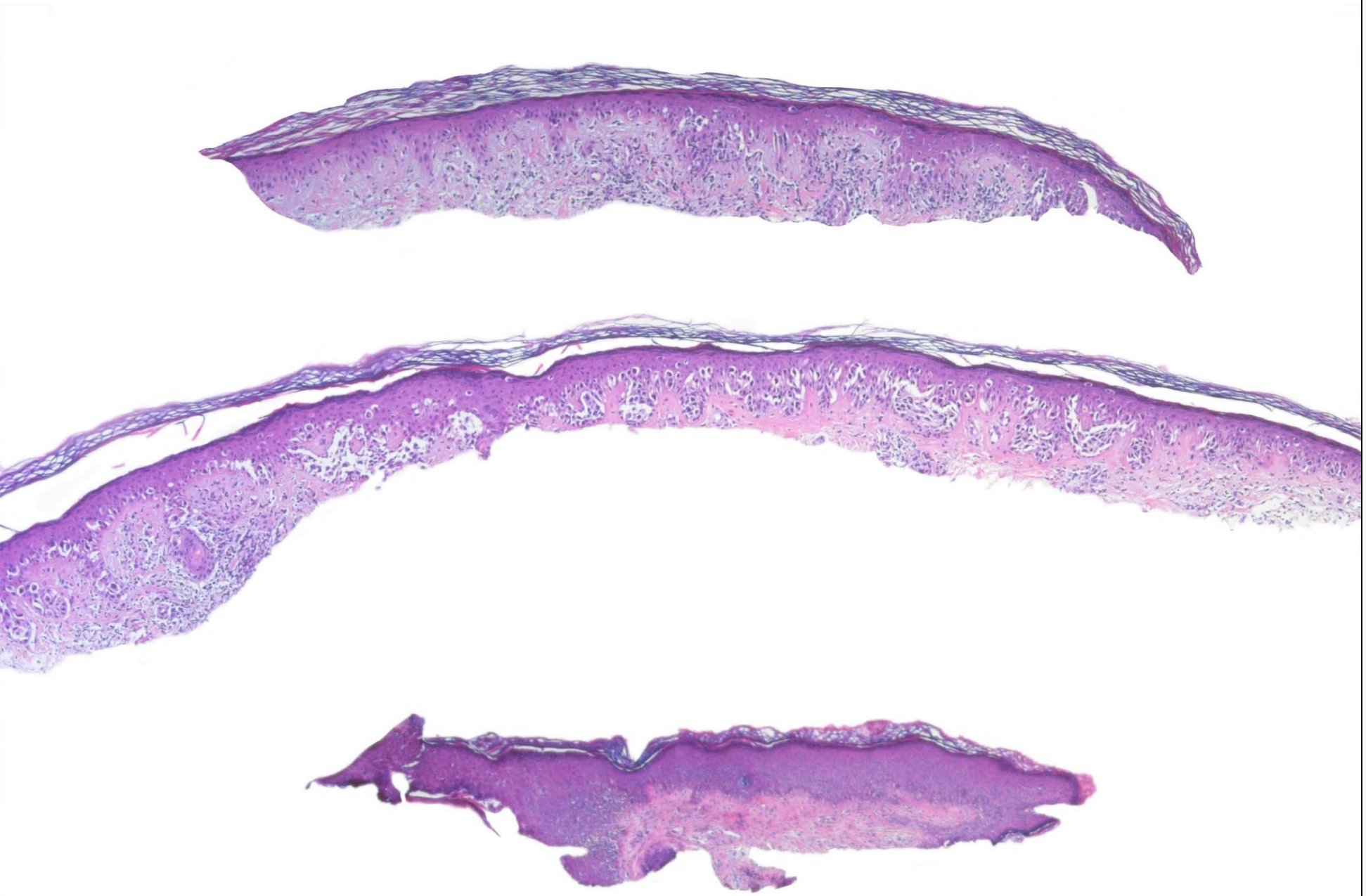
by *"overdiagnosis of melanoma"* which has been referred to as *"arguably the most difficult problem that we face in dermatopathology today."*



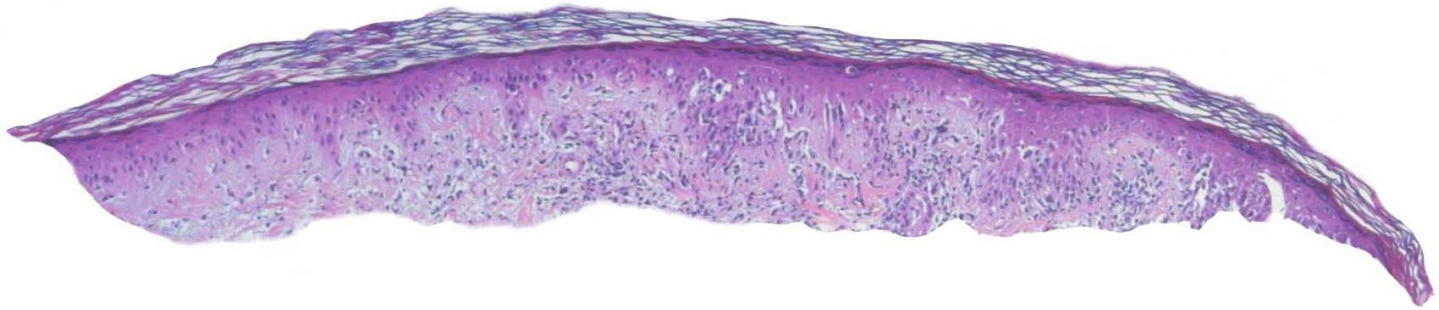
That problem is aggravated by poor biopsy technique. Incomplete biopsies are becoming increasingly common, and they impede interpretation of findings tremendously. The flippancy with which biopsies are being performed is enhanced by a low degree of clinical suspicion. It is my experience that, the smaller the lesion is,

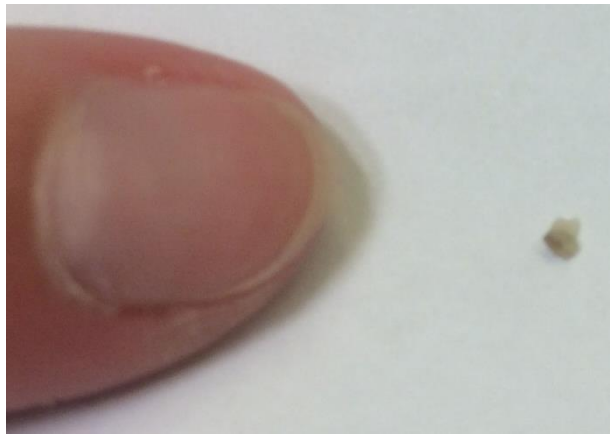


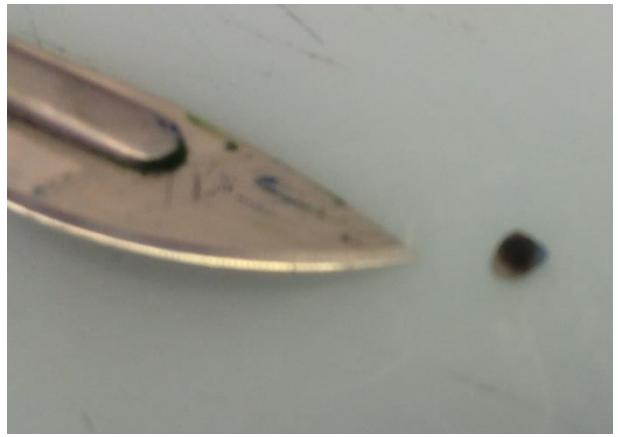
the more inadequate is the biopsy specimen, the consequence being that a definite diagnosis of melanoma is substituted by vague suspicion,

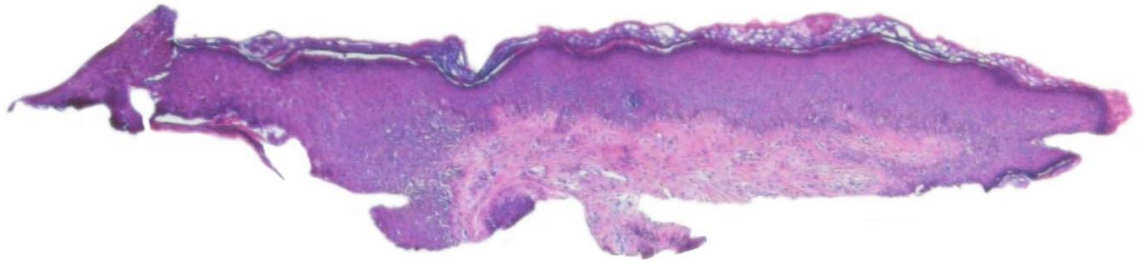


until a histopathologic diagnosis can no longer be made.









Those small lesions are probably nevi, but one simply cannot be sure, and a re-excision usually does not clarify the situation because most re-excision specimens contain either no or only small remnants of the lesion that defy interpretation.

Predictive value of biopsy specimens suspicious for melanoma: Support for 6-mm criterion in the ABCD rule

Razieh Soltani-Arabshahi, MD,[a] Carol Sweeney, PhD,[b,c] Benjamin Jones, BSc,[d] Scott R. Florell, MD,[a] Nan Hu, PhD,[b,e] and Douglas Grossman, MD, PhD[a,e]
Salt Lake City, Utah

Objective: Clinical detection of melanoma can be challenging. The number of biopsy specimens performed to diagnose 1 melanoma is a measure of efficiency of skin cancer detection, but few data are available to describe this measure from US health care. We studied the diagnosis of melanoma among biopsy specimens of clinically concerning pigmented lesions at an academic dermatology department.

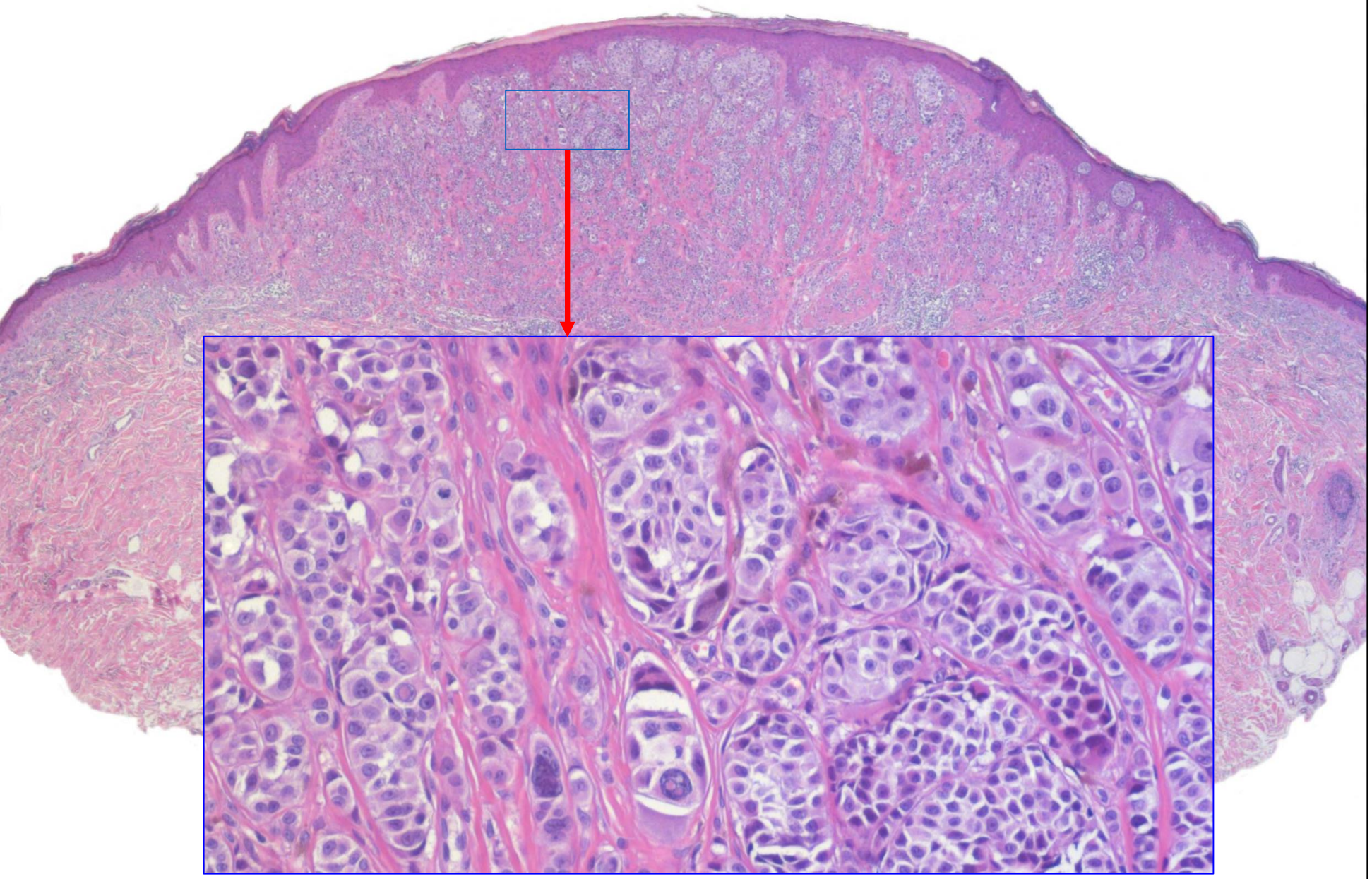
Methods: We searched for all biopsy specimens that were performed because of clinical suspicion of melanoma in 2013. Characteristics of the patient, lesion, and clinician performing the biopsy, and the final pathology diagnosis were recorded.

Results: A total of 2643 biopsy specimens from 2213 patients submitted by 43 providers were included. Melanoma was diagnosed in 165 cases (positive predictive value 6.4%, 95% confidence interval 5.5%-7.4%). Older age ($P < .001$), male gender ($P = .045$), and nontrunk location ($P < .001$) were predictors of higher probability of melanoma detection. Lesions larger than 6 mm in size had higher positive predictive value 11.5% (8.8%-14.1%) than smaller lesions 2.6% (1.6%-3.6%).

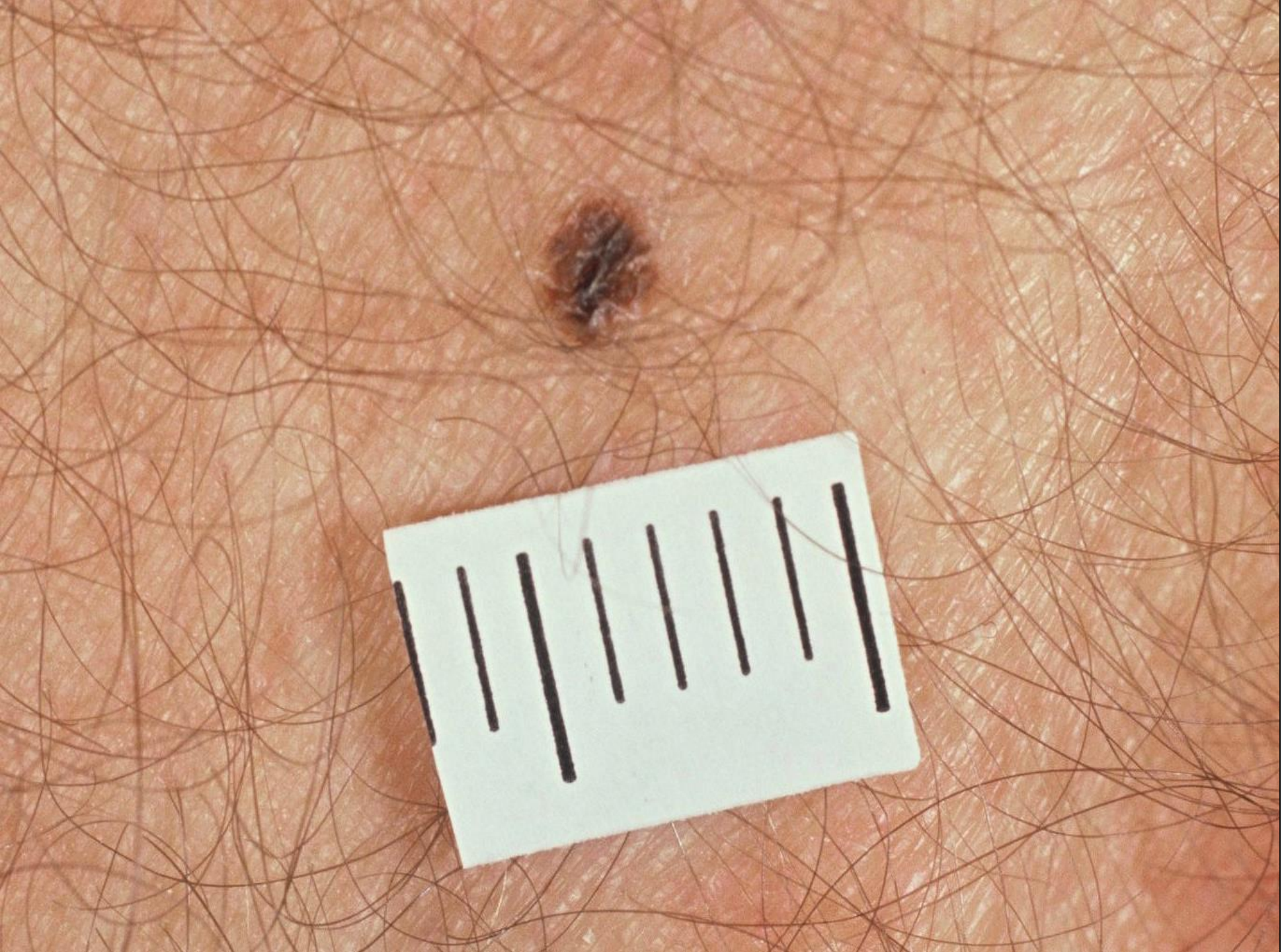
Limitations: Factors influencing the decision to biopsy a lesion may be difficult to evaluate retrospectively.

Conclusion: At an academic medical center, 16 clinically concerning lesions were biopsied to diagnose 1 melanoma. Biopsy specimens of clinically concerning pigmented lesions larger than 6 mm on older men had the highest yield. (J Am Acad Dermatol 2015;72:412-8.)

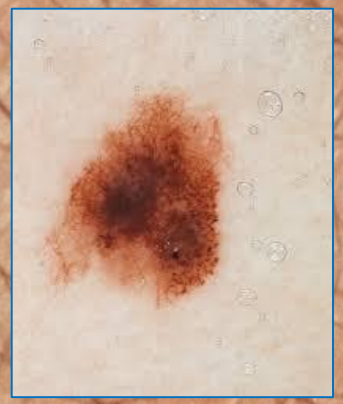
Because *"clinical detection of melanoma can be challenging,"* it has been suggested recently to postpone biopsies until lesions measure 6 mm in size. Such lesions have a *"higher positive predictive value,"* clinical – and I may add: histopathologic – assessment is more reliable, and the vast majority of lesions are still thin and curable by simple excision.

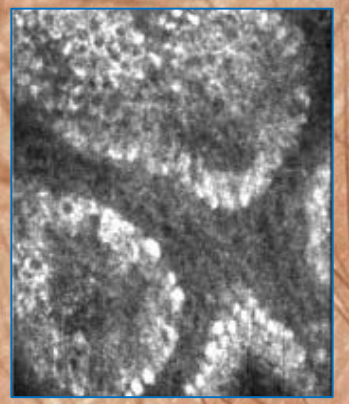


Of course, there are exceptions, namely, melanomas of small diameter that acquire considerable depth early-on, but those lesions are usually not spotted by cancer screening anyhow because they tend to be domed and scarcely pigmented.

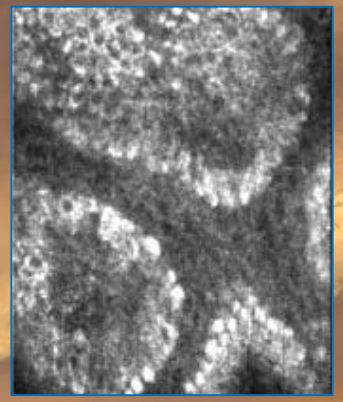


Most melanomas grow slowly and need not be biopsied until they have unfolded their true nature.

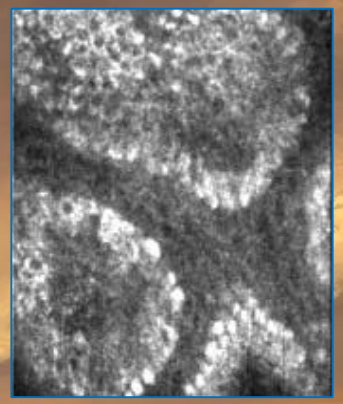


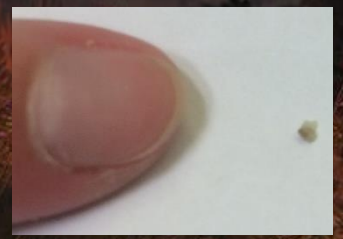


I acknowledge that clinical diagnosis can be accelerated by techniques such as dermatoscopy and confocal microscopy. Obviously, if clear-cut criteria for malignancy are detectable in smaller lesions, the latter should be excised. However, the reliability of adjunctive techniques is also hampered by an early stage of development, and those techniques are either not generally available or not generally applied with sufficient expertise. The wide spectrum of diagnostic avenues demonstrated at this meeting

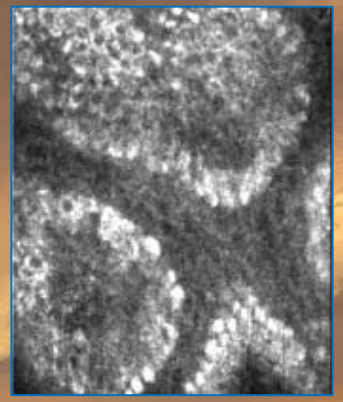


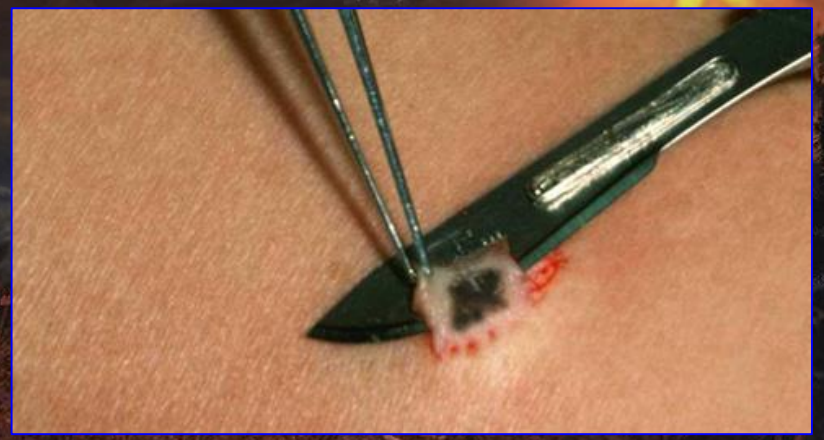
reminds of an ivory tower; the reality of current practice is probably reflected better





by some of the pictures just shown. For the time being,





I believe that, in general, patients would be served by a shift in management to later, fewer, but better biopsies.