Clinical Diagnosis of Skin Cancer

Enhancing Inspection and Early Recognition

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KEYWORDS

• Skin cancer • Melanoma • Screening • Detection • Diagnosis • ABCDE

KEY POINTS

- Early recognition and removal of melanoma and other skin cancers can help prevent significant morbidity and cancer-related deaths and is associated with increased survival.
- Numerous public health initiatives have been used to create awareness of the dangers of skin cancer and to help patients recognize suspicious lesions on themselves.
- Despite technological advancements, the cornerstone of diagnosis of skin cancer remains based on clinical recognition.

INTRODUCTION

Nonmelanoma (NMSC) and melanoma skin cancer are two of the most commonly diagnosed forms of human malignancy in the United States and worldwide.[1,2] NMSC is far more common but melanoma has a greater lethal potential. Cutaneous malignancy can cause significant morbidity and mortality and has an increased cost of therapy associated with advanced disease. Over the past century, the incidence of skin cancer has increased significantly. However, detection is happening earlier while prognosis is more favorable before disease becomes disfiguring or advanced. For all of these reasons, accurate and effective early clinical diagnosis of skin cancer continues to be paramount.

Over time, approaches for diagnosing NMSC have remained constant based on clinical inspection and patient history of any suspicious lesions that may be growing or changing. The diagnosis of melanoma has evolved significantly over the past century and now more melanomas are being detected at earlier stages. Clinical inspection and recognition of melanoma and NMSC continues to be the cornerstone of diagnosis and management for these cancers.

CONTENT

The clinical recognition of skin cancer has long been the foundation of identification and diagnosis of malignant skin lesions. Clinical diagnosis of NMSC has been unchanged over the past century. Typically, through patient history, lesions that are red, raised, topographically abnormal, growing, bleeding, crusting, or changing are identified and visually examined. Based on clinical expertise, a decision is made to biopsy and/or treat the suspicious lesions. New technologies now exist that are used in conjunction to increase the accuracy of clinical diagnosis

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(discussed elsewhere in this issue), but few have been widely adopted.

In contrast, diagnosis and treatment of melanoma has evolved significantly since this neoplasm was first recognized as a disease entity more than 200 years ago. The importance of early diagnosis of melanoma cannot be understated. Melanoma first grows horizontally within the epidermis (superficial or horizontal growth phase) and over time penetrates and grows vertically into the dermis (invasive or vertical growth phase).[3] Prognosis is directly proportional to the vertical depth of the neoplasm, so early detection has the potential to significantly limit disease burden and decrease cancer deaths. Most health care costs associated with melanoma occur with treatment of advanced disease demonstrating that there are also significant cost savings associated with earlier detection.[4]

Despite increasing incidence for all histologic subtypes and thicknesses of melanoma, the survival rates have steadily improved.[5] Overall 5-year survival rates for invasive melanoma increased from 82% to 93% from 1979 to 2008.[6] Earlier detection has generally led to a greater proportion of thinner depth lesions being removed, which typically are associated with improved outcomes. For thin lesions, treatment is usually surgical excision without the need for further work-up, which results in significant health care savings.

Although melanoma is now more frequently detected earlier, this has not always been the case. Before the 1980s, melanomas were often not diagnosed until gross clinical signs or metastatic disease was present and prognosis was generally poor. There were few advances that had occurred to improve patient awareness or clinician recognition because the clinical features of early melanoma were not well described. Diagnosis was typically made by inspection for gross clinical features including but not limited to extremely large size, bleeding, ulceration, and fungation. This led to a high disease burden and poor prognosis at the time of diagnosis.

The importance of early detection was first understood in the 1960s. Clark and colleagues[7] first correlated the level of histologic invasion, from the epidermis to the subcutaneous fat, with the likely progression and prognosis of disease. In 1970, Breslow[8] then demonstrated that prognosis was proportional to thickness, depth of invasion, and volume of the primary malignancy. He also noted that metastasis rarely occurred in lesions less than 0.76 mm in thickness. Since 1970 numerous studies have confirmed this concept that thinner lesions directly correlate with increased survival and better prognosis.[9] The goal of developing guidelines to detect melanoma earlier, when lesions were thinner and had a better prognosis, was therefore imperative to increase overall survival.

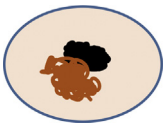
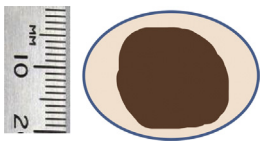
Before the 1980s, the clinical characteristics of early melanoma were not well described. Detecting melanoma was typically a learned entity based on many years of clinical experience. There was a critical need to educate less-experienced dermatologists, other physicians, and the general public on features of early melanoma to improve disease outcomes. In 1985, dermatologists at New York University devised the ABCD (*A*symmetry, *B*order irregularity, *C*olor variegation, *D*iameter >6 mm) acronym to help aid in the clinical diagnosis of early melanoma.[10] This study demonstrated that these parameters were some of the most commonly encountered clinical features seen in early melanomas and served as a guideline for atypical features that should be potentially concerning in pigmented skin lesion (PSL)s.

The ABCDs were intended to help describe and differentiate early, thin melanomas that might be confused with benign PSLs. Its straightforward nature allowed it to be used by clinicians and laypeople to identify potentially suspicious lesions before gross symptoms occurred. Ulcerated and elevated features were excluded because they were suggestive of more advanced disease. In 2004, a fifth parameter was added to the mnemonic, E (*E*volving), making it the ABCDE criteria (**Table 1**).[11] The addition of E improved the ability to recognize melanoma earlier because it includes lesions that are changing size, shape, or color and does not preclude lesions less than 6 mm.

Because of the diverse nature of early melanoma, one or more of the ABCDEs may be lacking, especially in early disease. Diameter has been the most controversial parameter, because as early diagnosis has improved, many melanomas less than 6 mm wide are now being identified. However, recent studies have reconfirmed that diameter remains a useful differentiating parameter.[12]

The ABCDE criteria have been verified in multiple studies that have demonstrated their sensitivity, specificity, and diagnostic accuracy.[13–16] The sensitivity and specificity of these parameters when used individually ranges from 57% to 90% and 59% to 90%, respectively.[17] Determining quantitative ABCDs through the use of computer image analysis has reinforced these findings.[18] Sensitivity and specificity both increase when criteria are used in conjunction with one another. Additionally, studies have demonstrated high interrater reliability and objectivity in assessing these clinical features, enhancing their utility as a screening measure.[19]

Table 1
ABCDE tools for detection of early melanoma

	Description	Illustration
Asymmetry	Lesions cannot easily be divided in half so that one half looks like the other.	
Border irregularity	Borders are typically not well defined and are irregularly shaped.	
Color variegation	One or more colors or variations in color. Colors frequently include black, brown, and tan. Less frequently red, white, or blue may be present.	
Diameter	Most early melanomas are >6 mm (approximately the size of a pencil eraser).	
Evolving	Lesions that are changing in size, shape, color, topography, sensation, consistency or to the surrounding skin.	

With the advent of the ABCDEs the level of diagnosis of melanoma improved for dermatologists and nondermatologists.[20] The ABCDE parameters are well known and frequently used by groups including the American Academy of Dermatology and the American Cancer Society. Like any tool, the ABCDEs have strengths and limitations (ie, may not be as effective in recognizing early nodular melanoma), but for now they remain a valuable component of the early detection campaign against melanoma.[21]

In addition to the ABCDEs, other clinical diagnostic paradigms have been developed to enhance the early recognition and diagnosis of melanoma. The revised Glasgow seven-point checklist includes three major criteria (change in size/new lesion, change in shape, change in color) and four minor criteria (diameter >7 mm, inflammation, crusting or bleeding, and sensory changes) (**Table 2**).[22] The presence of any of the major criteria is an indication for a referral and the additional presence of any minor criteria reinforces the need for referral. One study evaluating the

Table 2
Revised Glasgow 7-point checklist

Major Features[a]	Minor Features[b]
Change in lesion size	Inflammation
Irregular pigmentation	Itch or altered sensation
Irregular border	Larger than other lesions (diameter >7 mm)
	Oozing/crusting of lesion

[a] Presence of any of the major features is an indication for a referral.
[b] Additional presence of any minor features reaffirms the need for referral.

sensitivity and specificity of the Glasgow checklist found a sensitivity of 100% and a specificity of 37% for 165 evaluated lesions.[23] Other studies of only melanomas have demonstrated higher specificity.[24] The Glasgow checklist has been less widely adopted than the ABCDEs, likely because of its greater complexity with similar efficacy in identifying concerning PSLs.

The "ugly duckling" sign is another commonly used clinical diagnostic tool to recognize lesions suspicious for melanoma. This is based on the assumption that patients with many nevi tend to have normal nevi that resemble one another morphologically[25] or signature nevi.[26] This concept implies that a PSL that looks morphologically different from the signature nevi of a patient should be considered suspicious, even if it does not fulfill the ABCDE or seven-point criteria. Although the predictive value of the ugly duckling sign has not been systematically evaluated, it has been shown to be sensitive for dermatologists and nondermatologists.[27]

Routine self-skin examination (SSE) is another tool that reinforces the educational experience that patients have beyond their physician-driven total body skin examination. Monthly SSE can alert patients to any new or changing lesions, which can be brought to the attention of their dermatologist for further evaluation to enhance early recognition (**Figs. 1–3**). SSE may be associated with a reduced risk of melanoma-associated mortality.[10,28] Although the efficacy of SSE is still debated, it is a free, noninvasive, and nondangerous method that allows the patient to serve as a partner for their early detection efforts.

Other less commonly known diagnostic parameters for clinically identifying melanoma exist. The CUBED (*C*olored lesions different from skin color, *U*ncertain diagnosis, *B*leeding lesions, *E*nlarging lesions despite therapy, *D*elay in healing beyond

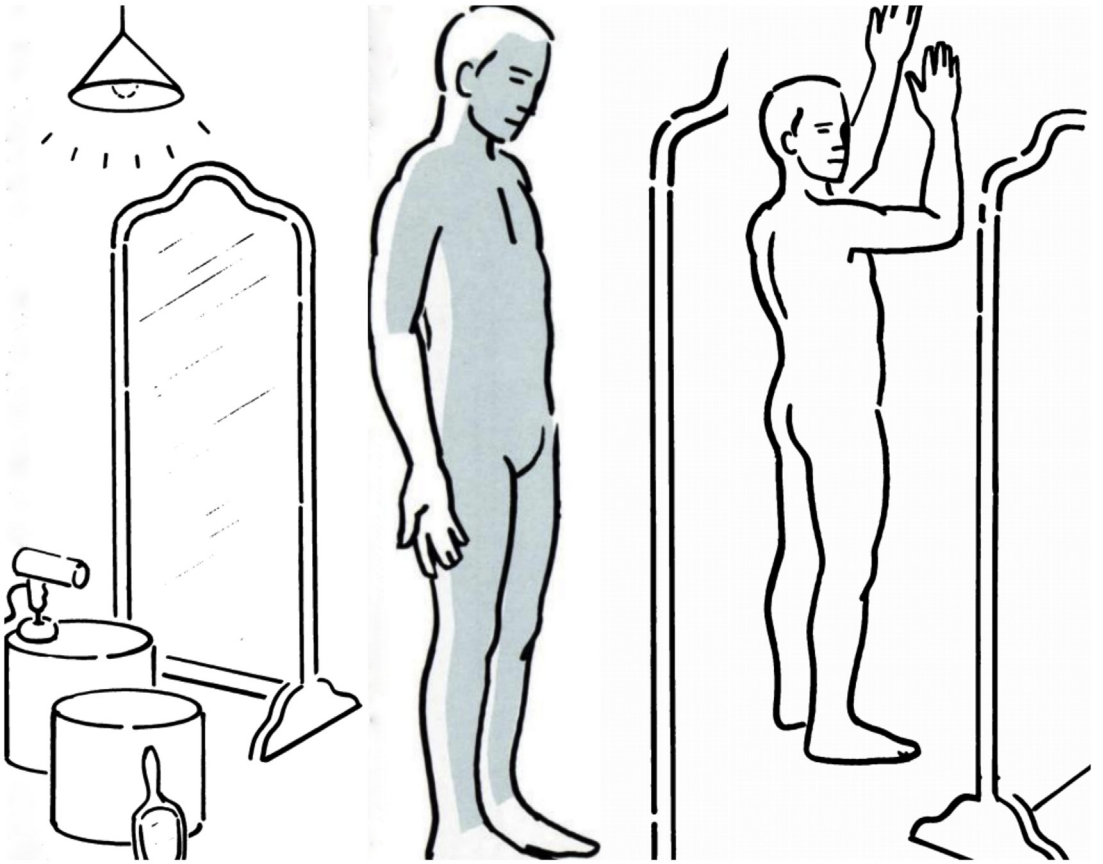


Fig. 1. Self-examination equipment includes a full-length mirror, a handheld mirror, a blow dryer, and two stools in a well-lit room. The front of the body should be inspected in a full-length mirror. Then the sides should be examined by turning to one side and raising your arms with the palms. (*From* Friedman RJ, Rigel DS, Kopf AW. Early detection of malignant melanoma: the role of physician examination and self-examination of the skin. CA Cancer J Clin 1985;35:146–9; with permission.)

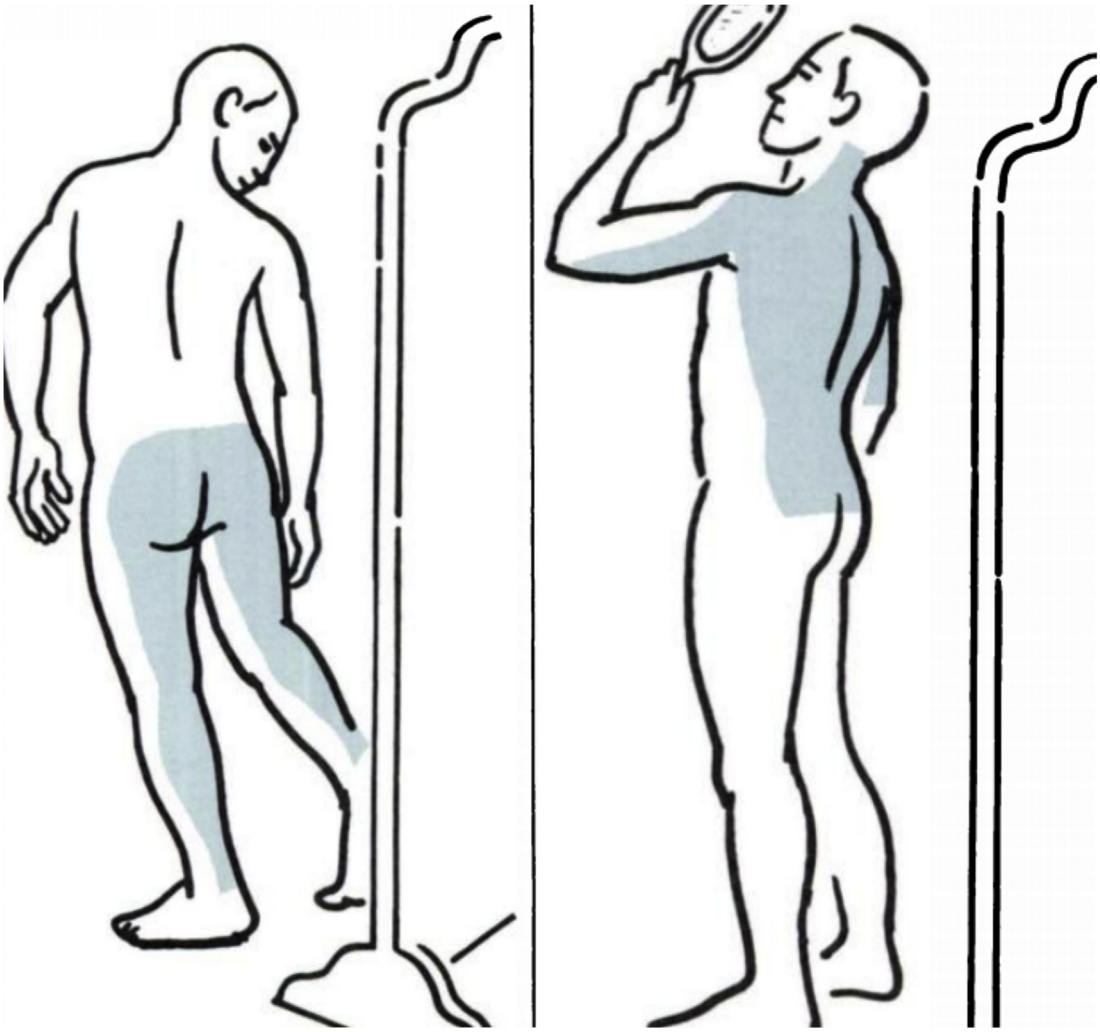


Fig. 2. The back of your legs and buttocks should be examined in a full-length mirror. The handheld mirror is used with your back facing the full-length mirror to examine the back of the neck, back, and scalp. (*From* Friedman RJ, Rigel DS, Kopf AW. Early detection of malignant melanoma: the role of physician examination and self-examination of the skin. CA Cancer J Clin 1985;35:146–9; with permission.)

2 months) criteria were developed to help diagnose melanoma of the foot and nail. If any two of the characteristics are present, it is an indication for referral for evaluation of the suspicious lesion.[29] In addition, many authors have attempted to modify the ABCDEs with the addition of other characteristics in hopes of increasing diagnostic accuracy, but none of these iterations have been proven to be superior or widely adopted.[21]

These systematic approaches for the evaluation of PSLs have helped dermatologists and lay people improve their ability to clinically recognize early melanoma. Although none of the previously mentioned methods are perfect, they provide simple guidelines that are used by dermatologists, general practitioners, and lay people to recognize warning signs of early melanoma.

Because of its diverse nature, clinical recognition of melanoma is challenging even for experienced dermatologists. To make the clinical diagnosis of melanoma, one must have a high index of suspicion. A thorough knowledge of clinical features of melanoma, characteristics of different variants of melanoma, and the clinical features of other PSLs that need to be differentiated from melanoma is imperative. Additionally, knowledge of factors associated with increased risk of developing melanoma including family or personal history of melanoma, presence of many nevi, sunburn history, and fair skin types must also be taken into account.

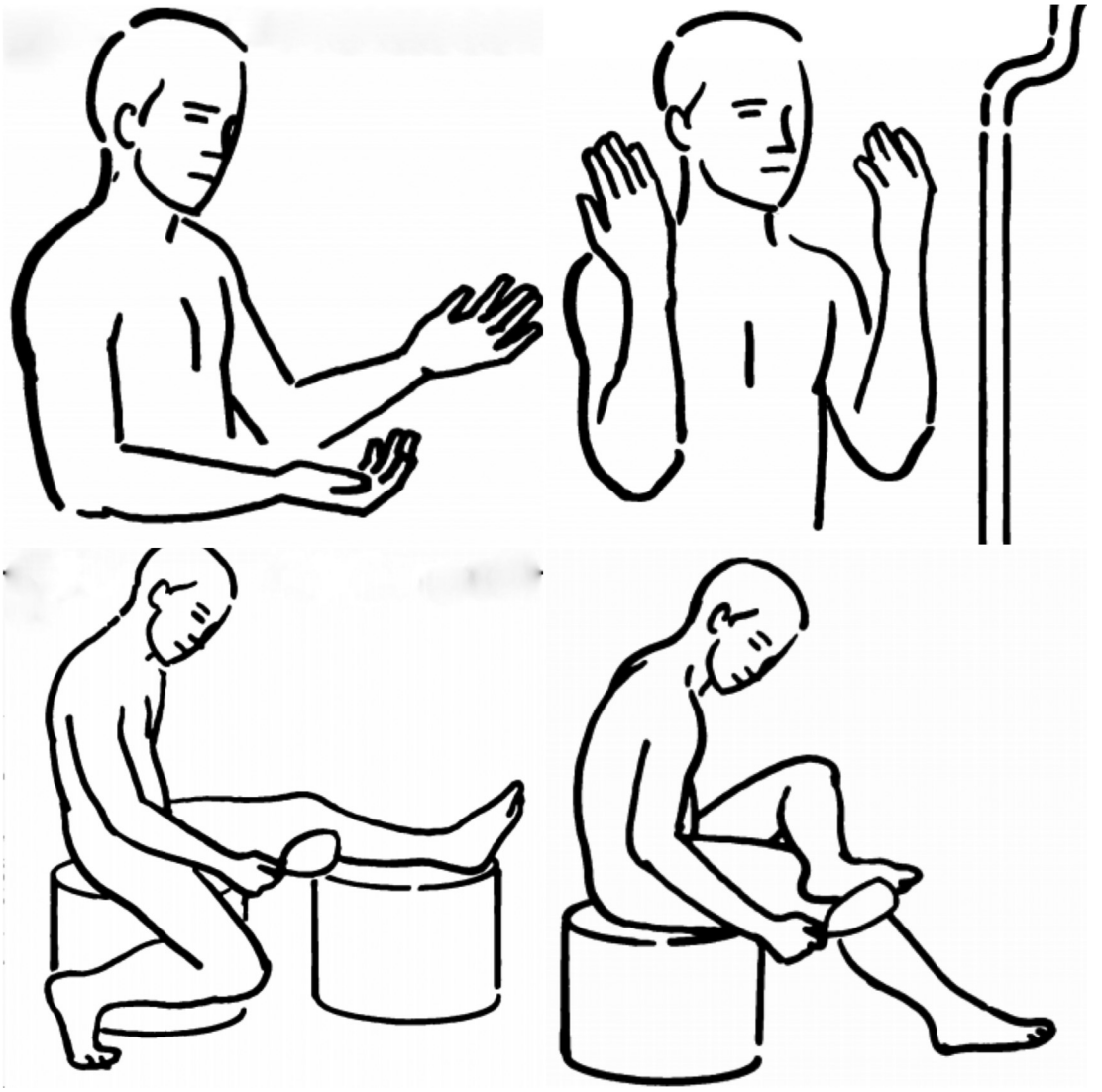


Fig. 3. The hands and arms should be inspected carefully visually and using a full-length mirror. Legs and soles should be examined one leg at a time using a handheld mirror to visualize the entire surface area. (*From* Friedman RJ, Rigel DS, Kopf AW. Early detection of malignant melanoma: the role of physician examination and self-examination of the skin. CA Cancer J Clin 1985;35:146–9; with permission.)

The actual sensitivity for diagnosis of early melanoma in the clinical setting is difficult to assess. The biopsy ratio (the proportion of melanoma to total number of biopsied PSLs) is not a useful parameter because, in the case of a potentially lethal malignancy, erring on the side of overbiopsying carries less risk than underbiopsying leading to missed cancer. The best way to assess accuracy is through reader studies where dermatologists are given images of biopsy-confirmed lesions and asked to provide a presumptive diagnosis. Several reader studies have shown sensitivities between 71% and 82% for dermatologists at identifying early melanoma based on their decision to biopsy depending on appearance alone.[30,31] Greater sensitivities are achieved in clinical practice in specialized pigmented lesion centers.[32]

New technologies have been developed that can help further improve the accuracy of skin cancer beyond clinical inspection alone. These include whole-body photography, dermoscopy, reflectance confocal microscopy, optical coherence tomography, multispectral imaging and analysis, and smartphone-based applications (all discussed elsewhere in this issue). Despite these advances in technology, it continues to take a

trained dermatologist and a good set of eyes to help identify which lesions are suspicious and should be screened to use these technologies most efficiently.[33]

Other public health measures are now being used to promote earlier clinical detection of NMSC and melanoma. Patient education initiatives with descriptions of concerning lesions and instructions for home SSEs can help improve patients' ability to detect suspicious lesions. Annual physician-driven total body skin examinations can help to recognize and remove suspicious lesions. More frequent physician examinations are useful in high-risk patients who have personal history of skin malignancy, family history of melanoma, history of high number of nevi, or personal or family history of dysplastic nevi. Mass skin screening programs have also been undertaken by the American Academy of Dermatology and various other volunteer groups to enhance secondary prevention and to provide a teachable moment to educate patients on skin cancer.

SUMMARY

Despite the many technological advancements occurring in skin cancer diagnosis, visual evaluation continues to be paramount in this process. The clinical evaluation of melanoma has been significantly refined over the past 30 years. Although guidelines have helped clinicians become more familiar with the features of melanoma, it still takes a high index of suspicion and thorough knowledge of the patient's history to most efficiently diagnose skin cancer.

Neville Davis[34] once said "unlike other cancers, which are generally hidden from view, malignant melanoma writes its message in the skin with its own ink and it is there for all of us to see. Some see, but do not comprehend." The same holds true for NMSC. Even though cutaneous malignancy is in plain sight, many people cannot readily recognize it. Over the past half century, clinical diagnosis of melanoma and survival rates of skin cancers have improved steadily as a function of patient education and public health initiatives. Although clinical examination will continue to be augmented by new technologies that allow physicians to better "comprehend" what they are seeing, technology will never be able to supersede an experienced clinician with a good set of eyes to choose the proper lesions to screen.

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