MELANOMA CARE OPTIONS™

JUNE 2007

DERMATOLOGY EDITION

Main Contributing Authors

Sancy Leachman, MD, PhD, Editor

Ashfaq A. Marghoob, MD, FAAD,
Clinical Author
Barriers to Care Author

Vernon K. Sondak, MD, Author

Co-authors/Reviewers

Jane L. Messina, MD
Co-author, High-Risk Localized Melanoma

Susan M. Swetter, MD
Steering Committee Editor, Working Group Leader

Issue 1: Identifying and Profiling Melanoma Patients

Editor's Note . . .

This issue of *Melanoma Care Options* addresses the challenges associated with identifying and profiling melanoma patients. The cases described involve the controversial topics of early melanoma detection using mole mapping and dermoscopy, genetic testing, markers of high-risk thin melanoma, and management of pediatric melanoma. The cases focus on diagnostic challenges, risk assessment as related to additional therapy and follow-up, and our evolving understanding of the basic biology of melanoma. Self-assessment questions are incorporated into each of the 4 cases so that you can choose your management strategy before reading the available data in support of a specific decision point. The opinions herein are those of the respective authors and are likely to evolve as new research findings emerge and the collective clinical experience expands.

In addition, we are excited to introduce customized content that relates to the barriers to care that you face as a practitioner managing melanoma day-to-day.

As faculty editor of *Melanoma Care Options*, I would like to thank you for taking the time to read this first issue in a series of 3 newsletters. I look forward to your input and welcome your thoughts regarding the management of the cases described in this publication.

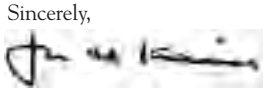
Sincerely,

SANCY LEACHMAN, MD, PHD

A note from the Chairmen/Steering Committee Editor

Welcome to the first issue of the 2007 Melanoma Care Options publication series from the Melanoma Care Coalition, which was formed in 2004 to foster an interdisciplinary approach to melanoma care. We are pleased to announce that the Melanoma Care Coalition recently won the 2007 Alliance for Continuing Medical Education's Award for Outstanding CME Collaboration for its innovative programming. In response to your requests and to the emerging focus of continuing education on systems barriers affecting provision of optimal patient care, we have incorporated specific material beyond the previous clinical content in these issues. Therefore, alongside the clinical content, you will find articles addressing barriers to care that affect melanoma management in the fields of dermatology, medical oncology, and surgical oncology. In addition, stepping outside of our previous disease-state approach from last year, we have dealt with the clinical content from the perspective of clinical steps in melanoma management, regardless of disease stage. This, the first of a series of 3 publications, addresses the identification and profiling of patients with melanoma; the second focuses on evaluating therapeutic options; and the third concerns pulling this information together in the management of melanoma in special circumstances. We hope that you find this new approach invigorating and thought provoking. As always, we welcome your thoughts on the series and encourage you to participate in other Melanoma Care Coalition programs—see www.melanomacare.org for other Melanoma Care Coalition offerings. Thank you for participating in this interdisciplinary dialogue, which promises to improve our ability to care for patients.

Sincerely,



JOHN M. KIRKWOOD, MD

MERRICK I. ROSS, MD, FACS

Co-Chairs, Melanoma Care Coalition Steering Committee

SUSAN M. SWETTER, MD
Steering Committee
Editor/Working Group Leader

Continuing Medical Education Information

Instructions for participation:
- Read the case presentations and comments in the newsletter
- Complete the posttest questions and evaluation form at the end of the newsletter, and fax or mail them to our office

To receive a maximum of 1.5 *AMA PRA Category 1 Credits*™ for this activity:
- Within 4 weeks of successful completion, you may access your credit transcript at http://ccehs.upmc.edu/
- 70% of your posttest answers must be correct for you to receive a certificate of credit

To receive up to 1.5 CNE credits for this activity:
- Within 4 weeks of successful completion, a certificate will be mailed to the address provided
- 70% of your posttest answers must be correct for you to receive a certificate of credit

Target Audience

This activity is directed toward dermatologists, dermatologic surgeons, surgical and medical oncologists, general surgeons, oncology nurses, primary care physicians, and other healthcare professionals who treat or screen for melanoma.

Statement of Need

The prognosis of melanoma worsens significantly with increasing disease stage. The melanoma community has supported extensive melanoma screening efforts, with the goal of early detection to improve outcomes. Once patients are identified, another essential step is appropriate staging and risk assessment, which helps drive therapeutic and follow-up strategies. This publication focuses on methods to identify patients with melanoma as well as methodology to profile these identified patients so that appropriate management and follow-up strategies can be employed.

Learning Objectives:

After completing this activity, the participants will be better able to:
- List the benefits of mole mapping and dermoscopy in the early recognition of melanoma
- Describe the role of genetic testing in melanoma
- Compare and contrast pathologic markers of high-risk cutaneous melanoma
- Describe the differential diagnosis of pediatric melanoma

Accreditation and Credit Designation

The University of Pittsburgh School of Medicine is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians. The University of Pittsburgh School of Medicine designates this educational activity for a maximum of 1.5 *AMA PRA Category 1 Credits*™. Each physician should claim only those credits commensurate with the extent of his or her participation in the activity.

1.5 contact hours of Continuing Nursing Education will be granted by the University of Pittsburgh School of Nursing. The University of Pittsburgh School of Nursing is an approved provider of continuing nursing education the Pennsylvania State Nurses Association (PSNA), an accredited approver by the American Nurses Credentialing Center's Commission on Accreditation.

We gratefully acknowledge an educational grant from Schering-Plough Corporation in support of this activity.

Contributing Authors and Disclosures

Sancy Leachman, MD, PhD
Assistant Professor
Huntsman Cancer Institute and the Department of Dermatology
University of Utah Health Sciences Center
Salt Lake City, Utah
Speaker's Bureau: Myriad Genetic Laboratories

Ashfaq A. Marghoob, MD, FAAD
Associate Professor of Dermatology
Memorial Sloan-Kettering Cancer Center
Hauppauge, New York
No financial relationships to disclose

Vernon K. Sondak, MD
Chief
Division of Cutaneous Oncology
H. Lee Moffitt Cancer Center
Professor, Departments of Interdisciplinary Oncology and Surgery
University of South Florida College of Medicine
Tampa, Florida
Speakers' Bureaus: Schering Oncology Biotech, Pfizer Inc

Douglas S. Reintgen, MD
Director
Lakeland Regional Cancer Center
Lakeland, Florida
Speaker's Bureau: Schering Oncology

Thomas E. Olencki, DO
Clinical Professor
Division of Hematology/Oncology
James Cancer Hospital and Solove Research Institute
Ohio State University
Columbus, Ohio
Speaker's Bureau: Schering-Plough Corporation

Michael Bihari, MD
Freelance Medical Writer
Falmouth, Massachusetts
No financial relationships to disclose

Jane L. Messina, MD
Associate Professor
USF College of Medicine
Department of Pathology & Medicine
Co-Director, Dermatology Laboratory
Director, Pathology Residency Training Program
Tampa Florida
No financial relationships to disclose

Date of Original Release: June 10, 2007
Expiration Date: June 10, 2008
Date of last review: June 10, 2007

Steering Committee

Publisher
PharmAdura, LLC
523 Route 303
Orangeburg, NY 10962
publisher@pharmadura.com

Managing Editor
Joseph Burns
No financial relationships to disclose.

Art Director
Laurie Lohne, Creative MediaWorks

Scientific Directors
Lisa A. Faltyn, PhD
No financial relationships to disclose.
Tracey Mahoney, PhD
No financial relationships to disclose.

This newsletter is published by PharmAdura, LLC, Orangeburg, New York.

Melanoma Care Coalition Faculty

Bruce J. Averbook, MD
Associate Professor of Surgery
Metro Health Medical Center
Case Western Reserve University
Cleveland, Ohio
Speakers' Bureau: Schering Oncology Biotech

Matthew T. Ballo, MD
Associate Professor of Radiation Oncology
University of Texas M.D. Anderson Cancer Center
Houston, Texas
No financial relationships to disclose

Ernest C. Borden, MD
Director
Center for Cancer Drug Discovery & Development
Cleveland Clinic Cancer Center and Lerner Research Institute
The Cleveland Clinic Foundation
Cleveland, Ohio
Consultant: Cleveland Biolabs; Speakers' Bureaus: Novartis Pharmaceuticals Corporation, Pfizer Inc

Tania Bridgeman, RN, PhD
Director of Clinical Path Development
University of California, Irvine Medical School
Orange, California
No financial relationships to disclose

Clara Curiel-Lewandrowski, MD*
Assistant Professor of Dermatology
University of Arizona
Tucson, Arizona
No financial relationships to disclose

David E. Elder, MB, ChB, FRCPA*
Professor of Pathology & Laboratory Medicine
Hospital of the University of Pennsylvania
Philadelphia, Pennsylvania
Grant Research Support: NIH/NCI, EU Framework

Marc S. Ernstoff, MD
Professor of Medicine
Dartmouth-Hitchcock Medical Center
Lebanon, New Hampshire
Grants/Research Support: National Institutes of Health, Bristol-Myers Squibb, Berlex Laboratories, Chiron Inc, Schering-Plough Corporation, Pfizer Inc; Consultant: Chiron Inc; Speakers' Bureaus: Berlex Laboratories, Chiron Inc, Schering-Plough Corporation, Pfizer Inc

Lawrence E. Flaherty, MD
Professor of Medicine and Oncology
Karmanos Cancer Institute
Wayne State University
Detroit, Michigan
Grants/Research Support: Schering-Plough Corporation, Chiron Therapeutics, Celgene, Bayer; Consultant: Bayer; Speaker's Bureau: Schering-Plough Corporation, Glaxo Smith Kline

James S. Goydos, MD, FACS
Associate Professor of Surgical Oncology
Robert Wood Johnson Medical School
Cancer Institute of New Jersey
New Brunswick, New Jersey
Speaker's Bureau: Schering-Plough Corporation

James M. Grichnik, MD, PhD*
Associate Professor
Duke University Medical Center
Durham, North Carolina
Founder and Major Shareholder: DigitalDerm, Inc; Consultant/Grants: Electro-Optical Systems Inc.

Caron M. Grin, MD
Clinical Professor of Dermatology
University of Connecticut Health Center
Farmington, Connecticut
Speaker's Bureau: Schering-Plough Corporation

James G. Jakowatz, MD
Director
Melanoma Center
Associate Professor of Surgery
University of California, Irvine Medical Center
Orange, California
No financial relationships to disclose

Mohammed Kashani-Sabet, MD
Associate Professor of Dermatology
Director, Melanoma Center
UCSF Cancer Center
University of California San Francisco School of Medicine
San Francisco, California
Consultant: Schering-Plough; Speaker's Bureau: Schering-Plough Corporation

Douglas Kondziolka, MD, MSc, FRCSC, FACS
Vice-Chairman of Neurological Surgery
Professor of Radiation Oncology
University of Pittsburgh
Pittsburgh, Pennsylvania
Consultant: Elekta Instruments

David H. Lawson, MD
Professor of Hematology/Oncology
Winship Cancer Institute
Atlanta, Georgia
Grants/Research Support, Consultant, and Speakers' Bureaus: Chiron Therapeutics, Schering-Plough Corporation, Berlex Laboratories

Sancy Leachman, MD, PhD*
Associate Professor
Huntsman Cancer Institute
Department of Dermatology at the University of Utah Health Sciences Center
Salt Lake City, Utah
Speaker's Bureau: Myriad Genetic Labortories

Patricia K. Long, MSN, FNP*
Physician Extender/Nurse Practitioner
University of North Carolina
Chapel Hill, North Carolina
No financial relationships to disclose

Ashfaq A. Marghoob, MD, FAAD*
Associate Clinical Member
Clinical Director, Skin Care Center
Memorial Sloan-Kettering Cancer Center
Hauppauge, New York
No financial relationships to disclose

R. Dirk Noyes, MD, FACS
Co-Director
Surgical Oncology
Multidisciplinary Melanoma Clinic
University of Utah
Huntsman Cancer Institute
Salt Lake City, Utah
Speaker's Bureau: Schering-Plough Corporation

Steven J. O'Day, MD
Chief of Research
Director of Melanoma Program
The Angeles Clinic and Research Institute
Los Angeles, California
Grants/Research Support: Berlex Laboratories, Chiron Therapeutics, Novartis, Schering-Plough Consultant: Synta Pharmaceuticals

Thomas E. Olencki, DO
Clinical Professor
Division of Hematology/Oncology
James Cancer Hospital and Solove Research Institute
Ohio State University
Columbus, Ohio
Speakers' Bureaus: Schering-Plough Corporation

David W. Ollila, MD
Associate Professor of Surgery
Director, Multidisciplinary Melanoma Program
University of North Carolina School of Medicine
Chapel Hill, North Carolina
No financial relationships to disclose

Victor G. Prieto, MD, PhD
Professor of Pathology
University of Texas M.D. Anderson Cancer Center
Houston, Texas
No financial relationships to disclose

Douglas S. Reintgen, MD
Director
Lakeland Regional Cancer Center
Lakeland, Florida
Speaker's Bureau: Schering Oncology

Krista M. Rubin, MS, RN, FNP-C
Nurse Practitioner
Center for Melanoma
Massachusetts General Hospital
Division of Hematology/Oncology
Boston, Massachusetts
Speaker's Bureau: Schering-Plough Corporation

Wolfram Samlowski, MD
Professor
Department of Oncology
Huntsman Cancer Institute
University of Utah
Salt Lake City, Utah
Grants/Research Support: Pfizer Inc; Speakers' Bureaus: Pfizer Inc, Bayer, AOI, Sci Med; Stockholder: Amgen Phizer, Chiron, Glaxo Smith Kline

Vernon K. Sondak, MD*
Chief
Division of Cutaneous Oncology
H. Lee Moffitt Cancer Center
Professor
Departments of Interdisciplinary Oncology and Surgery
University of South Florida College of Medicine
Tampa, Florida
Speakers' Bureaus: Schering Oncology Biotech, Pfizer Inc

Kenneth K. Tanabe, MD
Chief
Division of Surgical Oncology
Massachusetts General Hospital
Associate Professor of Surgery
Harvard Medical School
Boston, Massachusetts
Speaker's Bureau: Schering-Plough Corporation

Alan Valentine, MD
Associate Professor of Medicine
University of Texas M.D. Anderson Cancer Center
Houston, Texas
No financial relationships to disclose

Robert W. Weber, MD
Associate Director
Northern California Melanoma Center
St Francis Memorial Hospital
San Francisco, California
No financial relationships to disclose

Richard L. White, Jr, MD, FACS
Clinical Associate Professor
Department of Surgery
Carolinas Medical Center
Blumenthal Cancer Center
Charlotte, North Carolina
Speakers' Bureaus: Schering Oncology, Chiron Therapeutics

*Indicates Melanoma Care Coalition faculty members who contributed to the generation of content for this newsletter.

Barriers-to-Care for Patients with Melanoma: Medicolegal Aspects of Early Detection

By Ashfaq A. Marghoob, MD, FAAD, and Michael Bihari, MD

A number of studies have analyzed and documented malpractice claims related to a misdiagnosis of melanoma and show that an incorrect diagnosis of melanoma often leads to a malpractice lawsuit.

According to Troxel, the misdiagnosis of melanoma is a major cause of malpractice claims involving pathologists and dermatologists.[1] Troxel analyzed surgical and cytology malpractice claims and reported that 13% of the claims involved the misdiagnosis of melanoma and that 70% of these claims were for a false-negative diagnosis. Troxel also found that the single most common reason for filing a malpractice suit against a pathologist was a false-negative diagnosis of melanoma.[2]

Does Time to Diagnosis Make a Difference?

Weinstock, noting the steady improvement in melanoma survival, attributes this improvement to increased awareness of melanoma and the excision of primary lesions at an early stage.[3] Weinstock states that, "The central irony of melanoma is that most ultimately fatal lesions were visible on the surface of the skin at a curable phase in their evolution."

Several recent studies have investigated prolonged wait times for an appointment with a dermatologist and found that there was no correlation between melanoma thickness at the time of diagnosis and the time from either the first recognition of changes or from the first physician examination to diagnosis.[4,5]

According to Ashfaq A. Marghoob, MD, a dermatologist at Memorial Sloan-Kettering Cancer Center in New York, and a well known expert in melanoma, "There is no evidence to suggest that the lack of access to a timely diagnosis of melanoma is a major factor in subsequent malpractice lawsuits. The issue is more related to misdiagnosis of the condition by the clinician."

(continued on page 21)

Barriers-to-Care for Patients with Melanoma: Lack of Effective Websites, Advocacy Groups

By Douglas S. Reintgen, MD, Ashfaq A. Marghoob, MD, FAAD, Thomas E. Olencki, DO, and Michael Bihari, MD

A number of healthcare providers and consumers are concerned about a perceived lack of credible information on the Internet about melanoma and that melanoma-related advocacy groups are too splintered to have a significant effect.

Internet Health Seeking Behavior Increases

According to recent research from the Pew Internet & American Life Project, more Americans are online and relying on the Internet for important health information for themselves and others.[1] Pew researchers noted that the Internet plays a major role for e-caregivers (those caregivers who seek Web-based information), 58% of whom say that the most important source of information they use is something they have found online. In contrast, only 38% of e-caregivers said that offline health information was their most important source.

A study from the National Cancer Institute's Cancer Information Service examined the relationship of patient behavior and self-efficacy with use of the Internet.[2] The study shows that patients newly diagnosed with cancer view the Internet as an important tool for obtaining information and for boosting their confidence to make informed decisions.

Looking at online behavior related to cancer information, data from the 2003 Health Information National Trends Survey documented that the most frequently searched topic among cancer information seekers was site-specific information,

(continued on page 22)

INTRODUCTION

Although the nation's leading cancer organizations have touted the stabilizing incidence rates of cancer in the United States, the occurrence of melanoma continues to rise.[1] In 2007, an estimated 60,000 new cases of invasive and 48,000 cases of in situ melanoma will be diagnosed.[2] In the United States, melanoma of the skin is the sixth most common type of new cancer cases in both men and women, representing 4% of all new cancer diagnoses in each gender.[2]

For most patients, diagnosis of melanoma in early stages translates into good survival. The long-term survival rate for patients with uncomplicated thin melanoma (<1 mm) is greater than 90%, while the rate for lesions thicker than 1 mm is from 50% to 90%. In contrast, only about 20% to 60% of patients with nodal involvement and less than 10% with distant metastatic disease will survive 5 years.[3] Fortunately, most patients are now diagnosed with localized melanoma. Indeed, 65% of invasive cutaneous melanomas reported in the National Cancer Institute's Surveillance, Epidemiology, and End Results cancer registry were thin melanomas (ie, less than 1 mm in thickness).[4,5] Yet, with nearly 1 in 5 patients presenting with regional lymph node or distant metastatic disease, further improvement needs to be made in our ability to identify patients with an early stage melanoma.[2] Moreover, patients with thin melanoma can die from the disease—and although the survival rates are generally good, thin melanomas make a relatively high contribution to overall melanoma mortality because of the sheer number of lesions encountered at this stage. For example, Gimotty and colleagues found that 15% of melanoma deaths result from metastases of thin lesions.[5] Yet only a relatively small percentage of these thin lesions can be considered high risk and warranting of aggressive therapeutic approaches. Therefore, investigators have focused on identifying the characteristics of thin melanomas at high risk of metastasis.

This publication addresses key issues in identifying and profiling patients with melanoma. The cases address methods of screening patients to better detect early disease; how to assess risk based on the genetic profile in patients with melanoma and/or their family members; how to determine the risks and management strategies for patients with thin melanomas; and how to identify and manage pediatric melanoma, which is relatively rare but of great concern. Through the use of these profiling and identification techniques, melanoma may be diagnosed earlier when the prognosis is much more favorable.

CASE 1 RECOGNITION OF EARLY MELANOMA: THE ROLE OF MOLE MAPPING AND DERMOSCOPY

By Ashfaq A. Marghoob, MD, FAAD
Case Contributions From: James M. Grichnik, MD, PhD and Patricia K. Long, MSN, FNP

CASE PRESENTATION

A 36-year-old white man presents with numerous moles (Figure 1). While he is not worried about any particular mole, he is concerned because he has so many nevi in addition to a family history of melanoma. In the past, he has had moles removed and reports that they were all dysplastic.

A total-body skin examination reveals the presence of numerous clinically atypical nevi. Although numerous and worrisome, none of the nevi are thought to be melanoma by clinical or dermoscopic examination.

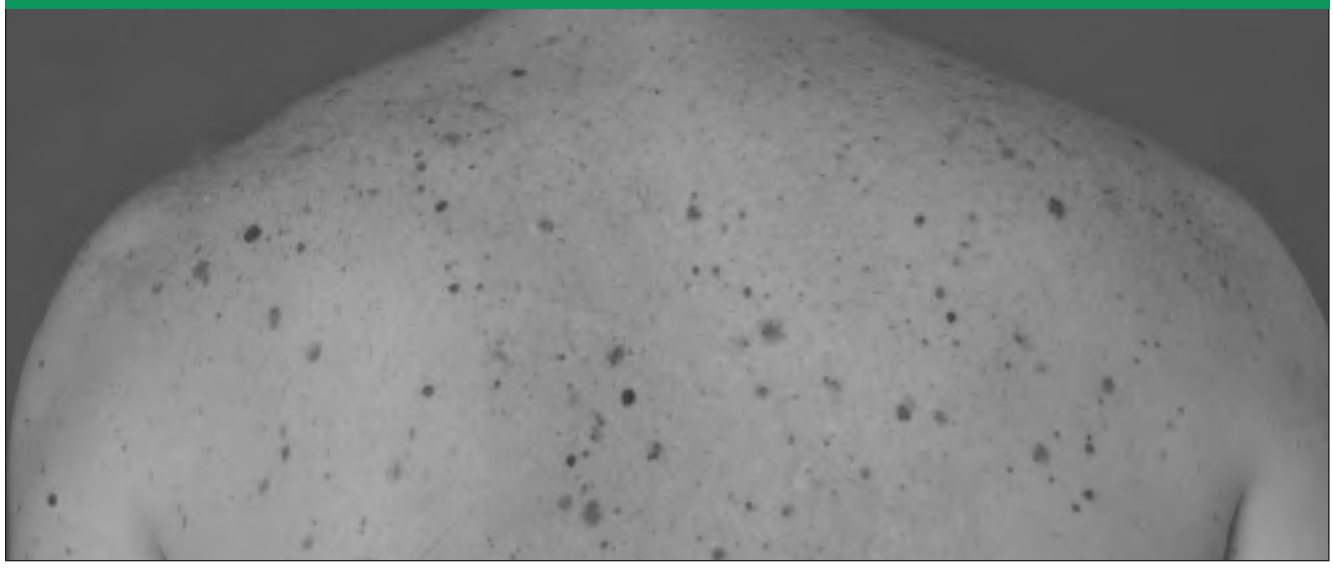
What would be your next step(s)?

1. Remove all clinically atypical nevi because they are precancerous
2. Remove several random clinically atypical nevi for pathologic evaluation
3. Obtain baseline total-body photographs (TBP)
4. Follow up in 6 months with interval monthly self-skin examinations

Reality of Risk

The authors recommend utilizing TBP for the reasons discussed below. However, a substantial proportion of melanomas are identified by

Figure 1. Multiple pigmented lesions on the back of a patient



Photograph courtesy of James M. Grichnik, MD, PhD.

patients or family members without additional techniques.[6] TBP and dermoscopy are ancillary techniques that can complement the screening process. Clinicians also use these techniques as surveillance tools.

The goal of screening is to detect early melanoma before it develops the ability to metastasize. Moles (melanocytic nevi) can represent both markers of increased risk of melanoma and they may on occasion be direct precursors to melanoma. But what is the risk for transformation? In patients younger than 40 years of age, it is estimated that less than 1 mole out of 200,000 will transform to melanoma on an annual basis.[7] However, this annual risk increases with age, particularly in men. For men older than 60 years of age, about 1 in 33,000 moles will turn malignant per year.[7] These findings suggest that nevi that persist into older age may be at higher risk for malignant degeneration.

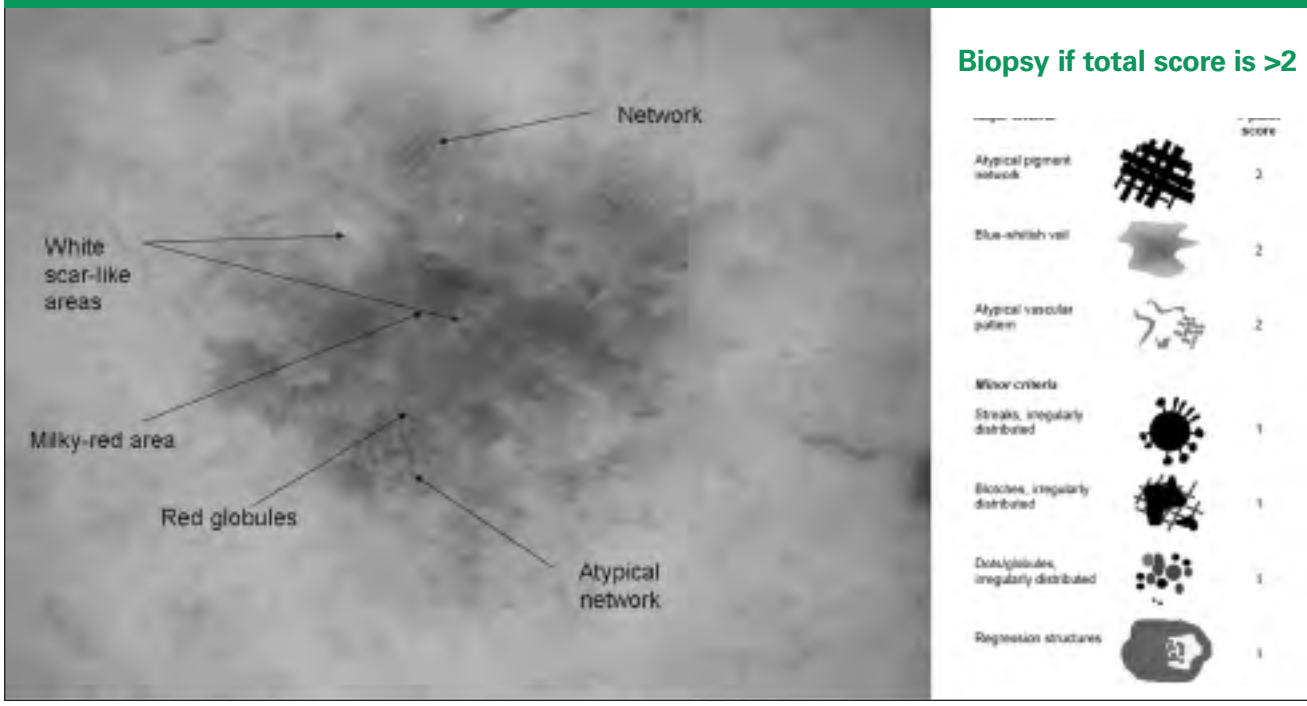
Gender and the persistence of the nevus influence the transformation rate. Based on the same model of malignant transformation, a single mole that persists for 60 years (eg, from age 20 to age 80) has a 1 in 3,164 chance to become melanoma in men, compared with a 1 in 10,800 chance in women.[7]

The presence and number of clinically atypical nevi correlates to melanoma risk. Having one clinically atypical nevus doubles the chance that a person will develop melanoma during his/her lifetime compared with the chance in patients without an atypical nevus. However, in melanoma patients, the presence of 10 or more atypical nevi increases the risk 12-fold ($P<.001$).[8] Thus, the case patient with multiple atypical nevi is at considerable risk of developing a melanoma.

However, in a series of more than 1,600 patients who were diagnosed with melanoma, only 26% of melanomas were histologically associated with precursor nevi, and the degree of histologic dysplasia did not necessarily correlate with risk of transformation.[9] Of those cases of melanoma associated with precursor nevi, 43% originated from dysplastic nevi, whereas 57% were associated with other nevi.[9] Note that the majority of melanomas do not derive from nevi, but rather appear to arise in apparently normal skin.[7] Thus, it is clear that dysplastic nevi are both markers that identify patients at high risk for developing melanoma and may also be potential precursors to melanoma.

Given the lack of absolute correlation between clinically atypical nevi and melanoma transformation, the need to excise clinically atypical nevi remains questionable.[10] The American Academy of Dermatology (AAD) recommends excising any clinically suspicious lesion with narrow (1 mm–3 mm) margins.[11] Most experts agree that prophylactic excision of a large number of clinically atypical nevi is not warranted,[7] suggesting that only those clinically suspicious for melanoma merit biopsy or excision. Some clinicians follow a standard practice of removing the 2 worst looking moles at the baseline visit. It is difficult to ascertain whether this practice is actually another way of selecting ugly duckling lesions or lesions that are clinically suspicious for melanoma. However, the reason for choosing 2 lesions is not clear, and to the author's knowledge, the benefit of this practice has not been studied in a

Figure 2. Representative features indicative of malignancy revealed by dermoscopy, including atypical networks, atypical globules, and changes in coloration. The pathologic diagnosis of this lesion revealed a 0.78 mm melanoma arising in association with a clinically atypical nevus. Papillary dermal regression was present.



Left side image courtesy of Ashfaq A. Marghoob, MD. Right side image used with permission. Malvehy J, Puig S, Braun SP, Maghoob AA, Kopf AW, *Handbook of Dermascopy*, Informal Healthcare, London, 2006.

formal study setting. Random removal of moles that are not considered suspicious is not warranted. Therefore, in the above decision section, Choice 1, Remove all clinically atypical nevi because they are precancerous, and Choice 2, Remove several random clinically atypical nevi for pathologic evaluation, are not appropriate. In addition, the large number of moles in this case suggest that clinically atypical nevi are best viewed as markers of increased risk in this patient, precluding the need for removal of some or all nevi if the moles are clinically stable, uniform in appearance, and do not represent the "ugly duckling" features wherein the nevus appears different from the rest. Removing all of these lesions would be costly and cause unnecessary morbidity. However, this patient should be followed closely, and this publication now turns to discussion of surveillance and follow-up strategies.

Total Body Skin Examination and Skin Self-Examination

Careful surveillance would be appropriate in this patient because of the presence of atypical nevi and a family history of melanoma. Indeed, regularly scheduled surveillance of high-risk patients results in detection of earlier disease and better survival outcomes for melanomas found during surveillance [incident melanomas] than for index lesions.[6] In this study, surveillance consisted of baseline photography, serial clinical examination, and patient education on recognition of early melanoma. These findings support the importance of involving the patient actively in melanoma surveillance. The authors recommend that all healthcare providers following high-risk patients perform regularly scheduled total body skin examinations. In addition, they should educate their patients about melanoma recognition and encourage them to perform regularly scheduled skin self-examinations.

Role of Dermoscopy

Dermoscopy, also known as digital epiluminescence microscopy (DELM), is a noninvasive method that allows for the evaluation of colors and microstructures of the epidermis, the dermoepidermal junction, and papillary dermis, which are not visible to the naked eye. It extends the traditional clinical examination of suspicious lesions by the ABCDE criteria (asymmetry, irregular borders, multiple colors, diameter >6 mm, evolving lesion) and Glasgow 7-point checklist criteria (change in size, jagged shape, irregular color, diameter greater than 7 mm, inflammation, oozing or bleeding, and change in sensation).[12] The features of melanoma revealed by dermoscopy include atypical or

Figure 3. The use of TBP (and dermoscopy) in identifying potential melanoma. Left: baseline TBP; Middle: lesion on follow-up clinical examination reveals a change; Right: dermoscopy reveals an asymmetric and disorganized pattern with a peripheral blotch, features often seen in melanoma.

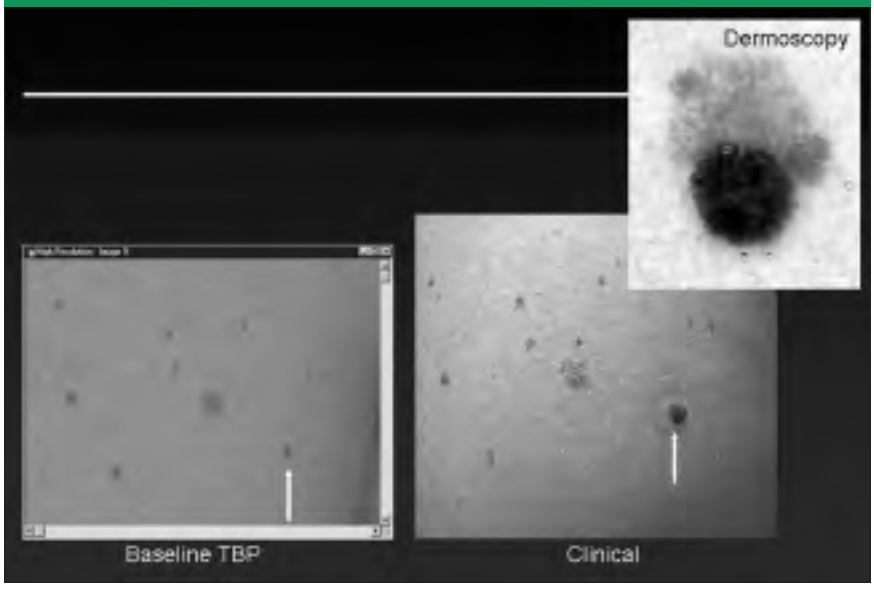


Image courtesy of James M. Grichnik, MD, PhD.

negative network, atypical dots or globules, streaks, off-center blotches, the blue-white veil, regression structures, and other vascular structures indicative of malignancy (Figure 2).

Dermoscopy has many advantages for assessing patients. Dermoscopy helps differentiate melanocytic from non-melanocytic lesions as well as distinguishing benign from malignant lesions; improves diagnostic accuracy and the observer's confidence in his/her clinical diagnosis; confirms the diagnosis made using the naked eye, thereby providing a clinical-dermoscopy correlation; and may help reassure patients who have concerns about a particular lesion.[13]

Dermoscopy has a high sensitivity (75%-96%) and specificity (79%-98%) for diagnosis.[14] Specificity and sensitivity of the technique improves with experience. Experts in the use of dermoscopy make accurate diagnoses at a rate that far exceeds the rate made with clinical examination alone.[15]

Despite its benefits, barely half of physicians in US dermatology residency programs use dermoscopy in the analysis of pigmented lesions.[16] In part, lack of training, a perception of non-utility, and the belief that the process is too time consuming limit the use of dermoscopy despite its proven benefits.[16] With dermoscopy widely used in Europe, increased training could be a first step toward the more widespread acceptance of the role of dermoscopy in the diagnosis of and surveillance for melanoma in the United States. Until such training and more widespread adoption of dermoscopy is accomplished, all healthcare providers following patients at high-risk for melanoma should continue focusing on regularly scheduled total body skin examinations and skin self-examinations, which should be cornerstones of all surveillance strategies, regardless of the use of additional supportive surveillance techniques.

Short term mole monitoring of nevi by utilizing baseline dermoscopic images has been shown to be helpful to physicians in detecting clinically featureless melanoma.

As performed by the case author [AAM], short-term follow-up involves examining lesions that are of slight concern such as those that appear banal but are of concern to the patient or are new. Such lesions are imaged dermoscopically with a repeat image 3 months later. If any dermoscopic changes are found, the lesion is removed. Otherwise the lesion can be monitored at each follow-up examination as per routine. Such short-term monitoring has documented efficacy. Menzies and colleagues studied dermoscopic changes in suspicious lesions using short-term monitoring (2.5- to 4.5-month follow-up periods). The group found that of the 318 lesions, 81% of lesions did not change. Of the 61 that did change, 7 were melanomas, including 5 in situ and 2 invasive (Breslow thicknesses of 0.25 mm and 0.28 mm, respectively) melanomas. Note that in this series, none of the melanomas developed any classic clinical or dermoscopic features, they just exhibited morphologic change in such parameters as shape, size, interior architecture, and color.[17] The authors reported that dermoscopy had a specificity of 83% for melanoma diagnosis.

Role of Photography

Mole mapping using digital photography is emerging as an important aid in surveillance of

high-risk patients who may develop melanoma. In this procedure, a series of high-resolution digital overview photos of the entire cutaneous surface are taken at baseline. Subsequent follow-up examinations are performed by comparing the patient's presentation with his/her baseline images to help visualize new or changing lesions that may be indicative of melanoma.[18]

No specific guidelines for selecting appropriate patients for mole mapping exist; however several patient populations may benefit from the procedure. Patients with a personal or family history of melanoma; atypical mole syndrome; positive *p16* genetic test results; multiple nevi of different size, shape, and color; patients with a heightened anxiety about developing melanoma, and patients with large congenital nevi can be considered suitable candidates for mole mapping.[19,20,21] The case patient meets multiple criteria; therefore, TBP should be considered. TBP has many merits, including helping in the detection of new or changing lesions, documenting change, aiding in self-screening, encouraging patient participation in monitoring or detecting suspicious lesions, reducing biopsy rates for benign nevi, and reassuring patients that stable lesions are benign.

Clinicians may use different approaches for TBP. Some physicians first examine the patient clinically, find a suspicious area, and then refer back to the baseline images to determine if the lesion is new or has changed. Other healthcare providers use a side-by-side comparison technique, whereby they compare the current examination with the baseline images. By looking at the array of moles and how they change over time, new and evolving lesions can be relatively easy to identify and monitor via TBP.

The efficacy of mole mapping has been documented in clinical studies. In a study of 576 patients who underwent TBP, 93 lesions were identified as suspicious enough to warrant biopsy. Of these, 35% were diagnosed as melanoma. Lesions found to be melanoma included 74% that revealed changes in existing lesions and 19% that developed as new lesions. Most of these melanomas had subtle characteristics that fell outside the classic clinical criteria for melanoma.[18]

TBP also appears to increase the efficiency of biopsy. Banky and colleagues followed 309 patients with risk factors for melanoma (including personal or family history, 100 or more nevi, or 4 or more clinically atypical nevi) who underwent TBP and dermoscopy. In the study, 573 suspicious changes were identified. Of these, only 71 (12.4% of the new or changed lesions) were excised, yielding a rate of 0.09 biopsies per patient per year.[19] Of the excised lesions, nearly 1 in 3 biopsies revealed melanoma, which compares favorably to the 1 in 12 to 1 in 30 biopsies ordered by clinicians assessing suspicious lesions without the aid of photography and dermoscopy.[19]

TBP may save lives as well by allowing for earlier detection. In a large study conducted by the National Institutes of Health, 844 melanoma-prone family members who had a lifetime risk of developing melanoma approaching 80% to 100% were followed by photographic mole mapping. None of the patients, who were followed for up to 25 years, died from melanoma-related causes.[22] Serial photography helped clinicians rapidly identify new and changing lesions. In addition, high-resolution images were able to capture the subtle changes indicative of malignant transformation into cutaneous melanoma.

Combination Approaches

The combination of TBP and short-term mole monitoring has the potential to increase the sensitivity of detecting malignant melanoma, while at the same time maintaining a high specificity of diagnosis. Determining the changes that should prompt biopsy requires a judgment on the part of the healthcare provider. A stable lesion is most often benign. New lesions or a change in an existing lesion should raise suspicion and prompt further assessment. Yet, at some point, clinically atypical and common acquired nevi are new and enlarging, indicative of a normal growth phase. In patients younger than 50, less than 3% of changing or new lesions prove to be malignant.[19] The key to the "E" in evaluating the clinical evolution is that melanomas tend to be unusual compared with surrounding nevi, grow disproportionately faster than surrounding nevi, and become progressively more nonuniform. The clinician will often recognize this suspicious nevus as an "ugly duckling," because it does not resemble the other nevus on the patient, which often share common features. Dermoscopy may assist in this evaluation (**Figure 3**).

Related Case Presentation

The patient's son presents at age 13. He already has multiple clinically atypical nevi in addition to his family history of melanoma.

What would be your next step(s)?

1. Remove all clinically atypical nevi because they are precancerous
2. Remove several clinically atypical nevi to see what the pathologist thinks
3. Obtain TBP
4. Follow up in 6 months with interval monthly self-skin examinations

Clearly, an adolescent who already has many moles will develop many more moles over his lifetime. Removing all atypical nevi would be costly, physically challenging, and medically unnecessary. TBP will help identify both benign growth of existing nevi and new nevi. Using TBP in children remains a challenge because both patients and practitioners need to be comfortable sorting out which changing nevi should be removed. In this case, TBP and dermoscopy of moles of the child were performed because of his family history. When the patient was 16, the photographs helped the clinician find a melanoma. On a subsequent visit, the patient presented with a new black dot-like lesion, which was excised and recorded as an early melanoma. Thus, TBP may be useful in younger mole-laden individuals (particularly those with personal or family history of melanoma) but must be used with caution to prevent anxiety and removal of benign lesions undergoing normal changes.

Obstacles to the Use of Mole Mapping

No national guidelines exist regarding the use of TBP. Fear about repercussions on the part of some providers (Sidebar 1), lack of reimbursement, and follow-up challenges confound the use of this cost-effective and evidence-based management strategy.

Insurance companies differ on reimbursement for these procedures. According to Patricia K. Long, MSN, FNP, some companies (eg, BlueCross BlueShield, Cigna) do not cover surveillance technologies, including TBP, dermoscopy, or ultrasonography for the early detection of malignant melanoma because they are considered experimental, investigational, or unproven (see (http://www.cigna.com/customer_care/healthcare_professional/coverage_positions/medical/mm_0240_coveragepositioncriteria_photo_surveil_early_detect_melanoma.pdf AND http://www.bcbsnc.com/services/medicalpolicy/pdf/whole_body_integumentary_photography_dermatoscopy.pdf). Other insurers (eg, Aetna) consider TBP and dermoscopy medically necessary in some cases (see http://www.aetna.com/ cpb/medical/data/100_199/0188.html).

Another potential barrier to successful implementation of TBP is suboptimal follow-up. Some patients who have baseline TBP images taken may not return for a follow-up visit. In one study, 12% of patients offered monitoring did not return for follow-up imaging.[17]

SUMMARY

Mole mapping can play an important role in the screening of patients for melanoma. TBP can help identify lesions that are abnormal by virtue of their new or changing appearance. Once a suspicious lesion is identified, dermoscopy can help determine if a biopsy is necessary. These practices can reduce the number of unnecessary biopsies and improve the early detection of malignant melanoma.

Sidebar 1

Are There Legal Pitfalls of Mole Mapping?

Total body photography (TBP) is widely used by academic dermatologists, with 63% employing the technique as part of their screening process.[63] Some clinicians may hesitate to employ TBP or dermoscopy for fear that it may be used in a lawsuit should they miss a diagnosis. In fact, a survey of dermatology residency programs that did not use dermoscopy cited increased anxiety and fear of litigation as reasons precluding its use.[16] This fear may be unfounded, as it has no historical merit. In fact, these practices could help support the physician's case. Chart documentation is enhanced when the clinician indicates that new or changing lesions with features suggestive of melanoma on clinical or dermoscopic examination warrant biopsy. Lesions that do not meet these criteria can be documented as well, indicating that they do not require biopsy. Furthermore, fear of litigation should not be a barrier to delivering excellent healthcare. In fact, the use of TBP in very high-risk patients may reduce development of malignant disease by allowing for the rapid identification of suspicious lesions, some of which may be evolving toward melanoma.[22]

Most patients view TBP as a comforting procedure that is part of a thorough examination. Because the examining physician is referring back to the images on every visit, he or she is able to filter through the array of moles on the images and identify changes. The repetition of the process over time decreases the chance of missing a superficial spreading melanoma.

It is important to remind patients that the physician's examination and patient monthly skin examinations are complementary processes. Patients can use TBP as part of their self-examination. When using this approach, 30% of melanomas were first identified by the patient[18] and skin self-examination reduced mortality of melanoma by 63%.[64] In addition, 26% of the lesions that concerned patients were not deemed worthy of biopsy by the examining physician, thereby reducing the number of unnecessary biopsies.[18] Thus, TBP serves the dual purposes of finding early melanoma and minimizing the total number of biopies performed. The efficacy of the procedure, the engagement of patients in their own healthcare, and the reassurance patients find in the thoroughness of the process argues against TBP being used as the basis for a lawsuit.

CASE 2 GENETIC TESTING

By Sancy Leachman, MD, PhD

CASE PRESENTATION

A 64-year-old nurse practitioner presents to her dermatologist with atypical mole syndrome. The patient, who has no children, reports a personal history of melanoma. She is not aware of a diagnosis of melanoma or pancreatic cancer in any of her family members. The dermatologist consults a genetic counseling group to discuss genetic testing for this patient because the patient wishes to have *p16* genetic testing performed on a self-pay basis. The patient is interested in participating in available research protocols for melanoma.

The Reality of the Risk

Should clinical genetic testing be offered to this patient outside of the context of a clinical trial involving IRB review and written informed consent?

1. Yes
2. No

Based on the criteria for genetic testing that will be discussed, the consensus of the faculty is not to offer genetic testing to this patient. However, the faculty recognizes that this patient is motivated to pursue genetic testing and that she wishes to participate in available research protocols. This should be taken into consideration when counseling and educating this patient.

Melanoma has a genetic component, but the vast majority of cases are not due to a single inherited factor. Rather, exposure to ultraviolet rays (through a lifetime of sun exposure, tanning beds, or other means) typically causes genetic lesions, reflected as disturbances in gene copy numbers, amplifications, or mutations.

The genetics of melanoma is an area of intense research. Many targeted therapy strategies are being investigated that address specific components of the melanoma cell-signalling cascade. In addition, investigators are studying the correlation of mutational status with histologic or clinical features of melanoma. Unfortunately, a review of this intriguing research is outside the scope of this publication, which focuses only on commercially available genetic testing.

Among the best known predisposing factors for melanoma is mutation in the *p16* (cyclin-dependent kinase inhibitor 2A [CDKN2A]) gene.[23] Commercially available molecular assays can determine whether a person harbors mutation of the *p16* gene, which is present in 20% to 40% of patients with hereditary melanoma.[21]

The *p16* gene, located on the short arm of chromosome 9, helps control the growth and cycling or proliferation—processes altered during the transformation from normalcy to malignancy. Specifically, *p16* encodes a protein that inhibits the CDK4 cell-cycle protein kinase, an important enzyme in the regulation of cell growth.[20] Known carriers of *p16* mutations are at extremely high risk for melanoma development. A person with a *p16* mutation who is living in the United States has a 50% chance of developing melanoma by age 50 and a 76% chance by age 80.[24]

Increased risk of pancreatic cancer also correlates with carriage of *p16* mutation. Pancreatic cancer risk in patients with *p16* mutations is 11% to 17% greater than in patients with unaltered *p16* genes.[21] Yet, the clinical usefulness of *p16* testing remains an area of considerable debate, in part because a negative result does not exclude a patient from being at high risk for melanoma development. Even in families who carry *p16*

Figure 4. Rule of 3s for identifying individuals at increased risk for having a *p16* mutation (personal communication, Sancy Leachman, MD, PhD).

Proposed Rule of 3s

Rule	Probability of *p16* Mutation
• 3 or more family members with melanoma	20%-40%[21]
• 3 primary melanomas in an individual	20%-40%
• 3 melanoma or pancreatic cancer events	45%[21]

mutations, 9% of cases of melanoma occur in family members without a *p16* mutation.[20] This rate of melanoma development in non-carriers within the *p16* mutation-carrying families is about 2-fold, on the same order as the risk experienced by a patient with red hair.[21]

Based on typical criteria used to evaluate a patient for genetic testing, this patient is unlikely to benefit from *p16* testing. The suggested guideline termed the "Rule of 3s," provides a rationale for criteria that could warrant genetic testing for melanoma (**Figure 4**). This algorithm identifies families at high risk of having a *p16* mutation[21] and provides a potential rationale for testing based on one of the following criteria: **3** confirmed melanomas in a family, **3** primary melanomas in an individual, or **3** cancer events in a family (ie, 2 melanomas plus 1 pancreatic cancer or 2 pancreatic cancer plus 1 melanoma) (personal communication, Sancy Leachman, MD, PhD).

In this patient, the lack of family history of melanoma suggests she is not a carrier of the mutation. Individuals with non-familial melanoma have an extremely low chance (0.2%-2.0%) of having abnormal *p16* status.[23,25] This patient has not experienced multiple primary lesions, nor does she have a personal or family history of pancreatic cancer. Thus, she does not fit the "red flag" criteria for genetic testing suggested by the Rule of 3s.

Having numerous or atypical moles does not predict whether someone has a *p16* mutation. Indeed, the *p16* mutation does not cosegregate with the presence of atypical/dysplastic nevi.[26] In addition, recommendations of the American Society of Clinical Oncology (ASCO) regarding genetic testing suggest that genetic testing not be performed unless it has the potential to alter the medical management of the patient or the patient's family members.[21] Because the patient has already been diagnosed with melanoma and has no children, there is little chance that a positive or negative test result will alter prevention, early detection, management, or follow-up recommendations.

The Testing Process

In contrast to the case presented, if a person has been identified as an appropriate candidate for genetic counseling, the clinician should first attempt to refer the candidate to a research protocol, and the patient should receive genetic counseling and informed consent to determine if testing might be helpful. In the event of a positive *p16* finding, enrollment of patients in a research protocol involving *p16*-mutation carriers is preferable whenever possible,[21] though patients should be made aware that not all research protocols report back genetic test results. First-degree relatives of individuals carrying a *p16* mutation are candidates for genetic testing and should receive meticulous follow up regardless of whether they choose to be tested or not.

Prior to and following genetic testing, patients should receive genetic counseling. Genetic counseling involves documenting personal and family history of cancers to accurately assess personal risk, educating the patient on inheritance and familial melanoma, and discussing medical and psychological aspects of genetic testing. Genetic counseling can also highlight the interplay of medical, social, and financial issues that may arise from a positive test. Some patients may have concerns about the impact of the results of the tests on their health, insurability, or other issues. Informed consent answers many of these questions, addressing the risks, benefits, and limitations of genetic testing. Despite the perception that the results of genetic testing can influence a person's candidacy for medical insurance, the Federal Health Insurance Portability and Accountability Act of 1996, as well as state legislation in most states, protects patient privacy and prohibits health insurance discrimination based on genetic information.[27]

Genetic testing may impact rates and eligibility for life insurance. A positive test for melanoma susceptibility genes may reveal a predisposition to the development of melanoma that might not be evident from other underwriting information. Thus, the applicant may be deemed a higher risk than would have been presumed otherwise, which could translate into higher rates or loss of eligibility for a particular policy. However, negative results by genetic testing may improve the assessment of an applicant with a strong family history of melanoma. In a patient who already had melanoma, rates are primarily determined by that person's cancer status, not by genetic testing.

In the average outpatient setting, the healthcare provider is likely to have difficulty performing clinical genetic testing. Local centers can be found using a searchable database on a Web Site maintained by the National Society of Genetic Counselors (http://www.nsgc.org/resourcelink.cfm). The Family Cancer Assessment Clinic at the Huntsman Cancer Institute in Salt Lake City, Utah, also provides genetic testing for some families with a strong family history of certain types of cancer.

Currently 4 genetic testing laboratories in the United States are

Clinical Laboratory Improvement Amendments (CLIA)-certified to offer *p16* genetic testing: Creighton University Medical Center (Omaha, NE); GeneDX, Inc. (Gaithersburg, MD); Myriad Genetic Laboratories (Salt Lake City, UT); and Yale University School of Medicine (New Haven, CT) (www.genetests.org). The cost of full-gene testing exceeds several hundred dollars, although some laboratories will assist with obtaining insurance approvals for appropriate candidates.[28]

Management Direction

A patient's results following genetic testing may not alter the management strategy substantially. Regardless of genetic test results, *everyone* should be educated on photoprotection and how to recognize early changes of melanoma. For patients at high risk, regardless of their *p16* mutation status, current treatment guidelines recommend screening via a thorough full-body skin evaluation, monthly self-skin examinations, and a regular full-body skin examination by a physician.[3] As discussed, both photography and dermoscopy enhance mole features, and can facilitate screening and surveillance processes. Clinicians might consider a lower threshold for removal of a suspicious mole in patients with *p16* abnormalities.

The issue of *p16* testing in children has not been addressed in the literature to date. Within families carrying a *p16* mutation, children found to carry the mutation should begin skin surveillance including an interval total-body skin exam by a physician by around age 10.[21] Non-carriers within a *p16* family may choose to defer physician performed total-body skin examinations during this sometimes sensitive adolescent period. If genetic testing is not performed on the children in the family, all children of a *p16*-mutation carrier should be treated as carriers with respect to screening and follow-up procedures. An additional consideration for *p16* mutation carriers (which does not apply to non-carriers in the same family or families shown not to have a *p16* mutation) is possible referral to a pancreatic cancer surveillance program. Because screening for pancreatic cancer is still in its infancy, *p16*-mutation carriers should be referred to institutions specializing in pancreatic cancer screening or offering research protocols.[21]

SUMMARY

Genetic testing offers the primary advantage of providing an enhanced knowledge of an individual's melanoma risk. Yet, melanoma genetic testing is not appropriate for the vast majority of melanoma patients, and proper selection for candidacy is crucial to garner the optimal physical, emotional, and economic value. A healthcare specialist can provide accurate, up-to-date information on whether melanoma genetic testing is helpful based on individual circumstances and personall family history of melanoma.

CASE 3 MARKERS OF HIGH-RISK LOCALIZED MELANOMA

By Vernon K. Sondak, MD and Jane L. Messina, MD

Based On A Case By: David E. Elder, MB, ChB, FRCPA

CASE PRESENTATION

A 55-year-old man presents with 0.78 mm, Clark level II, superficial spreading melanoma on the back, with vertical growth phase (VGP) and a dermal mitosis. The pathology report indicates no ulceration and negative but narrow biopsy margins.

What would you talk with the patient about?

1. Nothing further (employ a negative margin biopsy as only treatment)
2. 1-cm wide local excision, no nodal staging
3. 2-cm wide local excision, no nodal staging
4. 1-cm wide local excision, sentinel lymph node (SLN) biopsy
5. 2-cm wide local excision, SLN biopsy
6. PET/CT scan and, if negative, only wide excision

Author Opinions Vary

The case author [VKS] would recommend a 1-cm wide local excision and would discuss an SLN biopsy with the patient because of the depth of the lesion (>0.75 mm). However, not all of the faculty would agree. The editor, Sancy Leachman, MD, PhD, would not recommend an SLN biopsy. At her institution, The University of Utah, her surgical colleagues do not routinely perform SLN biopsies in melanomas thinner than 1 mm unless they are Clark level IV

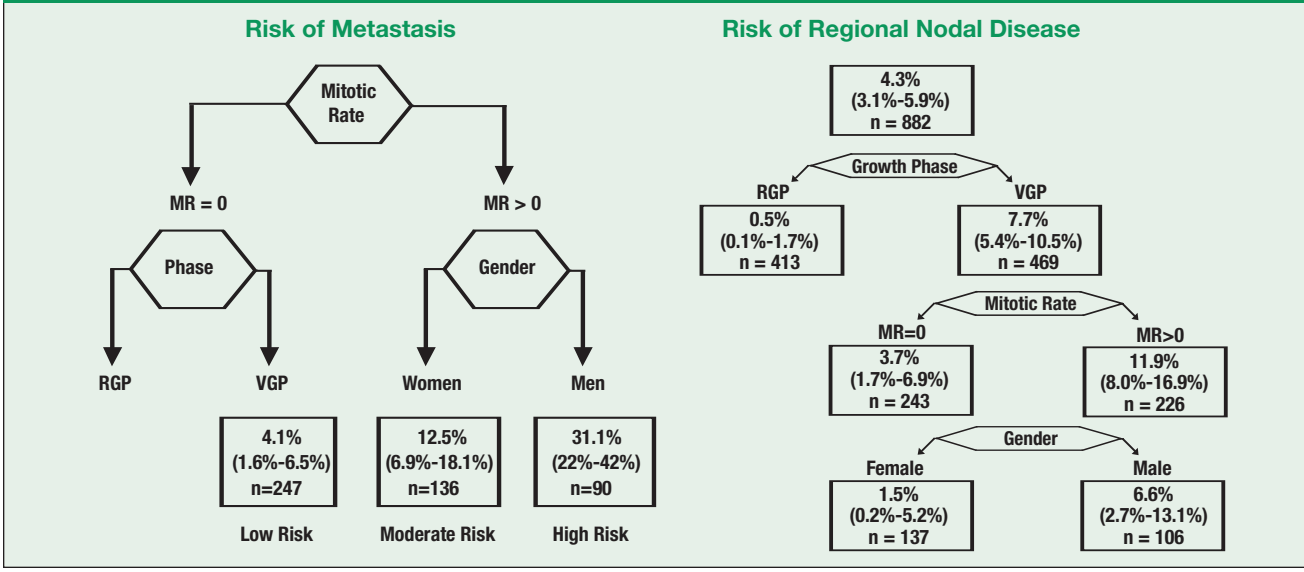
or V or ulcerated. However, the decision to undergo SLN biopsy ultimately should be made by the patient following a balanced presentation of the procedures benefits and limitations.

David E. Elder, MB, ChB, FRCPA, the case contributor, acknowledged the challenge in evaluating the role of SLN biopsy in such lesions. He would recommend that a patient with a melanoma with these attributes be offered a discussion of the pros and cons of SLN sampling, because of the presence of 3 risk factors that are not considered in the present tumor-node-metastasis (TNM) staging system: a thickness greater than 0.75 mm; the presence of VGP; and the presence of a dermal mitosis. This means that the melanoma is both "tumorigenic" and "mitogenic". As discussed more extensively in the section below, recent data have demonstrated that patients with "thin" American Joint Commission on Cancer (AJCC) Stage IA melanomas with these risk factors are at increased risk for metastasis when compared with patients who lack these factors.[4,29-32] In addition, the majority of positive lymph nodes in this thickness subset (a Breslow thickness of less than 1 mm) occur in melanomas in the range of 0.75 to 1.0 mm. Interestingly, the cutoff of 0.75 mm was the one originally proposed by Alexander Breslow in his seminal publication, which advocated the use of thickness measurement for determination of prognosis in melanoma.[33] The Breslow thickness measurement remains the single most powerful prognostic attribute for melanomas to this day, almost 40 years after his original observation. Finally, the patient is an older male and the lesion is on the back. Paradoxically, although the incidence of SLN positivity may be higher in younger patients,[32] the mortality from melanoma tends to be highest in older males. According to Dr Elder, the purpose of SLN sampling is to more accurately stage the melanoma. There may be a slight survival benefit, but this is unknown, especially in this thickness subset. Patients with positive sentinel nodes should have a complete lymph node dissection, although this may be controversial in the setting of isolated tumor cells or "submicroscopic metastases."[34] Node-positive patients should also be considered for adjuvant therapy.

Discussion of Individual Prognostic Factors

According to the AJCC classification system, which is the standard staging method for melanoma,[35] Breslow thickness, lack of ulceration, and Clark level classifies this tumor as T1a. If node-negative and non-metastatic, this tumor would be considered Stage IA disease, which is associated with a 95.3% 5-year survival rate and an 87.9% 10-year survival rate.[35] Thus, by current AJCC criteria, this represents low-risk melanoma. However, as mentioned previously, thin melanoma lesions can metastasize and contribute substantially to overall population-based melanoma mortality. Since SLN

Figure 5. Prognostic trees using other pathologic variables for AJCC Stage 1 melanoma (Breslow thickness <1 mm). Left: male patients with a mitotic rate greater than 0 exhibit the highest risk of metastasis within 10 years. Right: melanomas exhibiting a VGP and mitotic rate greater than 0 have the highest risk of regional nodal disease.[29,30]



MR indicates mitotic rate, RGP indicates radial growth phase, and VGP indicates vertical growth phase. Left: From Gimotty et al, 2004.[29] Reprinted with permission from the American Society of Clinical Oncology. Right: From Karakousis et al, 2006.[30] Adapted with permission from the Society of Surgical Oncology.

status is the most important predictor of recurrence and survival in patients with clinically node-negative melanoma,[36,37] this procedure may provide important information and identify node-positive patients who might benefit from additional therapy, such as complete lymph node dissection or adjuvant therapy with standard high-dose interferon alfa-2b (IFN alfa-2b) per protocol or another agent in a clinical trial.

The criteria for performing SLN biopsy in thin melanomas are very controversial. Although SLN status provides important prognostic information, the cost to identify a single positive SLN in thin melanomas is prohibitive for routine screening because of the relatively low rate of SLN positivity in patients with thin melanomas.[38] Cutoffs for SLN biopsy were initially derived from eligibility criteria for elective lymph node dissection (ELND) trials. Most of these trials evaluated intermediate thickness category patients (1-4 mm) for pathologic nodal staging. However, newer information has expanded the use of SLN biopsy to include some patients with thinner tumors with histologic ulceration or a high mitotic rate.[3]

Based on the tumor-node-metastases (TNM) system employed by the AJCC staging system, this melanoma requires a 1-cm excision with no SLN biopsy.[3] However, in thin melanomas, other pathologic factors predict metastasis, and these factors help supplement the information provided by the TNM system.[29] This case demonstrates some of the prognostic features of concern for thin melanomas that are being considered when making therapeutic decisions.[39] According to published prognostic trees for thin melanomas, male gender, the presence of a VGP, and a mitotic rate greater than zero gives this patient between an 11.9% and 31.1% chance for nodal involvement within 10 years (**Figure 5**).[29,30] However, as discussed more extensively below, the cutoff points for mitotic rate that are associated with higher-risk lesions are a matter of debate and would impact decision making in this case.

Importance of Considering Features of the Pathology Report

As discussed, key prognostic information may be contained in the pathology report, making its examination important for assessing risk. Pathology reporting practices vary widely. At the minimum, the report should include essential patient and gross pathology information, including specimen identification and date of procedure, anatomic site of tumor, diameter of lesion, and diameter and type of biopsy (ie, incisional or excisional). In addition, important microscopic information should be included, including the diagnosis as primary melanoma, Breslow thickness, Clark level of invasion, presence or absence of ulceration, and the presence or absence of satellites. Although there are no formal recommendations to measure or evaluate margin widths in the excision specimens of cutaneous melanoma, the pathologist should report whether the margin is negative or positive and can comment on the width (pathologically clear margins).[35,40-42]

Current staging guidelines reflect the consensus opinion that Breslow thickness is the most useful prognostic factor in patients with localized cutaneous melanoma.[40] Thus, SLN biopsy may be recommended based on the T classification of the AJCC International Union of Cancer Commission staging system. Currently, this system designates a thickness of 1.01 to 2.0 mm as T2 melanoma, and tumors of this thickness or greater are generally considered appropriate for pathologic staging of the regional nodal basin with SLN biopsy. However, some melanoma centers extend the lower limit cutoff point for SLN biopsy, to 0.75 mm, recognizing that there is gradient of risk of SLN involvement that increases toward the upper end of the 0 to 1.00 mm thickness range.[43,44] As discussed, there is no uniform consensus on this point among melanoma specialists. Although Clark level IV or V or the presence of ulceration are frequently used to select patients with melanomas less than 1 mm in thickness for SLN biopsy, there is substantial evidence against this approach. Clark level is not a good predictor of nodal status for thin melanomas when other pathologic factors (described below) are taken into consideration,[29-32,44] and ulceration is infrequent in thin melanomas and is of very limited use.[45]

Other types of microscopic information have been demonstrated to have additional prognostic significance in some databases. Phase of progression represents one such category. The VGP describes the presence of melanoma cells capable of surviving and proliferating in the dermis. VGP correlates with poorer prognosis, because tumors with a VGP have acquired the capability to metastasize. If the tumor is limited to only the radial growth phase, whereby cancerous melanocytes grow in a horizontal array as single cells or small clusters confined to the epidermis, the prognosis is extremely favorable, with survival rates exceeding 98%.[41,46]

For any melanoma that exhibits a VGP, the dermal mitotic rate should also be reported. This index, measured as the number of mitoses in the VGP per square millimeter per high-powered field, potentially mirrors the tumor

growth rate. Mitotic rate associates with tumor thickness but may serve as an independent prognostic variable, with higher rates correlating to worse prognosis.[41] However, in thin melanomas, groups have found variable results in terms of the breakpoint in number of mitoses per high-powered field that is associated with poorer outcomes such as nodal progression and decreased survival.[32,46,47] Indeed, a small series did not find suggestion of a correlation between mitotic rate and nodal progression.[44] Although some groups propose that any degree of mitogenicity represents a high-risk-lesion, the case author [VKS] suggests that more work needs to be done to define the cutoffs for this mitotic rate before this biomarker can be used broadly to select patients who should be counseled about SLN biopsy.

The presence of tumor-infiltrating lymphocytes (TILs) indicates an inflammatory response to the presence of melanoma cells. Defined as absent, brisk (diffuse infiltrate throughout the VGP or the presence of TILs along 90% of the circumference of the lesion), and nonbrisk (limited to focal infiltration), the description of the TIL has significant impact on survival. Patients with primary cutaneous melanomas (AJCC Stage I and II) with brisk infiltration demonstrated a 77% 8-year survival rate, compared with 53% for nonbrisk TILs, and 37% for those categorized with absent TILs.[41,48] If validated in an independent data set, these results might support the role of TILs as a biomarker.

Regression describes an area of absent melanocytic growth in the epidermis and dermis bordered on one or both sides by melanoma. In some studies, tumor regression correlates with worse prognosis, but in most other studies this is not a significant prognostic indicator.[41] However, the conflicting results of studies suggest that regression should not be used to select patients for SLN biopsy.

The presence of tumor within the blood or lymphatic vessels (angiolymphatic invasion) correlates with poor prognosis. Thus, the presence or absence of vascular/lymphatic invasion represents another pathologic feature of melanoma that should be reported.[41] As discussed in other portions of this publication, the histogenetic type and associated precursor lesions can also provide valuable information.

Clinical Prognostic Factors

Patient and other factors may also influence the choice for performing an SLN biopsy. As discussed previously, some prognostic models have found a relationship between gender and metastasis or nodal involvement of thin lesions (with a greater propensity for metastases among men than women).[29,30] Note that other series have not found a significant correlation of gender with sentinel node involvement in thin lesions.[31,44,47] Thus, it appears that gender must be considered in the context of other information.

As mentioned previously, older individuals with melanoma generally have a worse prognosis than younger individuals (although trends among pediatric patient subgroups differ and will be discussed later).[40] Some studies suggest that age inversely correlates with the likelihood of positive node involvement. In an analysis of 429 consecutively treated melanoma patients who underwent sentinel node biopsy, younger age significantly predicted an increased likelihood of nodal involvement.[32] In this study, the rate of nodal progression decreased steadily as patient age increased, with 26.3% positivity observed in the age 35-and-under subset, compared with an 11.8% positivity rate in patients over age 60. Other data series suggest that, compared with older age, younger age significantly portends nodal involvement.[49,50] However, SLN involvement has not been directly correlated with age as a continuous variable. Therefore, the author [VKS] does not consider age a validated criterion for recommending or avoiding SLN biopsy in thin melanoma patients.

The site of the primary lesion may also correlate with prognosis, with axial tumors having lower 10-year survival rates than tumors on the extremities.[51] In an analysis of 1,130 patients undergoing SLN biopsy for tumors 1 mm or thicker, lesions located on the trunk or lower extremity were more predictive of SLN involvement than upper extremity and head and neck locations.[50] Less is known about the influence of tumor location on SLN involvement for thinner melanomas, but substantially lower 10-year survival rates have been reported for patients with tumor thickness 0.76 mm to 1.69 mm when the tumor presents in an axial location.[51]

Taken together, these results suggest the importance of assessing pathologic features and patient factors when making treatment decisions in thin melanomas. These lesions may metastasize, and the challenge for the healthcare team and for melanoma researchers is to develop a cost-effective methodology for identifying these thin lesions that are high risk and that warrant further evaluation or treatment through SLN biopsy and potentially adjuvant therapy if the nodes are positive. This recommendation hinges on the belief that complete lymph node dissection and adjuvant therapy with microscopic-positive SLNs is beneficial. The benefit is a topic of debate, with some experts agreeing, some declining, and others feeling that the answer is yet to be determined.

CASE 4

Pediatric Melanoma

By Ashfaq A. Marghoob, MD, FAAD

Based On A Case By: Clara Curiel-Lewandrowski, MD

CASE PRESENTATION

A 10-year-old boy presents for a follow-up dermatologic examination. He has a substantially increased number of nevi on his back. His father was diagnosed with clinically atypical nevi and malignant melanoma at age 38. On examination, an atypical pigmented lesion is identified on his back. When compared with its presentation in baseline images, the lesion appears to be rapidly increasing in size. In addition, by dermoscopy, an atypical pigment network is observed. A skin biopsy was performed and the diagnosis of primary cutaneous melanoma, superficial spreading type was confirmed. The pathology report indicated the lesion was 0.70 mm in thickness, Clark level IV, without evidence of ulceration, and a mitotic rate of 1 per 10 high-powered fields.

What would you do?

1. Perform a wide excision with a 1-cm margin
2. Perform a wide excision with a 1-cm margin and an SLN biopsy
3. Perform the wide excision and postpone the SLN biopsy until the patient is older and can agree to the procedure
4. Perform a wide excision with a 0.5-cm margin

According to AJCC Staging guidelines, the melanoma in this pediatric case is classified as a T1b, which, in the absence of positive nodes or metastasis, represents Stage IB disease and has a good prognosis.[35] The author [AAM] would recommend excision with 1-cm margin. There are some who may consider performing an SLN biopsy for thin melanomas with a Clark level of IV and presence of mitoses; however, this remains controversial for reasons discussed earlier.[3]

Epidemiology

Melanoma of childhood is rare, accounting for only 1% to 3% of all childhood malignancies.[52] In the United States, only 1% to 2% of melanomas occur in individuals younger than 20 years of age. As children enter adolescence, the incidence increases. Melanoma is 7 times more frequent in the second decade of life than in the first, with only 0.4% of melanomas occurring in prepubertal children.[53,54]

In contrast to the situation in adults, the incidence of melanoma in children younger than 14 to 15 years appears unchanged over time. Although reports demonstrated that the incidence rate of melanoma in adolescence increased by 2.5% to 4% per year for the past 20 to 25 years, these data may be skewed because of increased reporting and changes in diagnostic criteria.[52,54]

Differences In Melanoma Characteristics By Age

Several features differ in the melanomas of pediatric and adult patients, and these features differ even among different age cohorts of pediatric patients. The Table

Table. Differences Between Pediatric and Adult Melanomas[52,56]

	Adult Cases	Pediatric Cases
Risk Profile	Red hair, freckling, skin prone to sunburn, history of sunburn, strong family history of melanoma	Frequently non-white, primary lesion on the head, face, or neck; prior history of non skin-cancer (particularly in the younger subset of children)
Gender	M>F	F>M (overall, but differences in age subsets exist)
Appearance/Histologic type	Frequently melanotic/predominantly superficial spreading	Often amelanotic, nodular lesions more common
Melanoma depth at diagnosis	Generally thinner	Generally thicker

summarizes key general differences between melanoma of adulthood and melanoma of childhood. In clinical practice, pediatric melanomas (particularly those in younger children) frequently do not present with the generally identifiable risk factors associated with melanoma in adults, such as red hair and freckling, a history of sunburn, or a strong family history of melanoma.[55] Risk factors such as large congenital nevi, familial atypical mole and melanoma (FAMM) syndrome, atypical mole syndrome (AMS), an increased number of atypical nevi, xeroderma pigmentosum, immunosuppression, or a family history of melanoma have been studied.[54] However, the relative contribution of these risk factors to the overall presentation of pediatric melanoma is difficult to ascertain—for example, even the magnitude of risk of melanoma arising in congenital nevi remains a controversial issue.[55] Melanomas arising in childhood are often amelanotic, and their depth at diagnosis is typically thicker than for those diagnosed in adults.[55,56] As such, children are diagnosed with lesions that would be expected to have a worse prognosis. Delay in clinical diagnosis has been reported in up to 60% of children.[53]

In part, the delay in diagnosis is due to the rarity of the disease in children. In addition, there may be reluctance on the part of the clinician to render the diagnosis of melanoma in borderline lesions in pediatric cases. Furthermore, a problem area encountered by the clinician examining children is the difficulty in recognizing these melanomas, which often do not exhibit the classic "ABCDE" features of melanoma found in adults as suspect lesions. Another problem area in children is encountered by the pathologist when evaluating benign atypical Spitz nevi. These lesions are relatively common in children and must be distinguished from melanoma. In one multicenter European study conducted in patients up to 16 years of age at diagnosis, of 102 lesions that were originally diagnosed as melanoma, more than 1 in 3 were reclassified as benign upon review.[56] Because of the nuances involved with evaluating the dermatopathology of pigmented lesions in children, the faculty recommends that providers evaluating suspicious pigmented lesions in children seek a consultation with a dermatopathologist with expertise in pigmented lesions, and more specifically with the histopathologic appearance of benign moles and other lesions in children and teenagers.[55] Molecular techniques may aid in the diagnostic process—as discussed in **Sidebar 2**, comparative genomic hybridization (CGH) has been employed as a means of distinguishing Spitz nevi from melanoma.[57,58]

Sidebar 2

Use of Comparative Genomic Hybridization for Differential Diagnosis

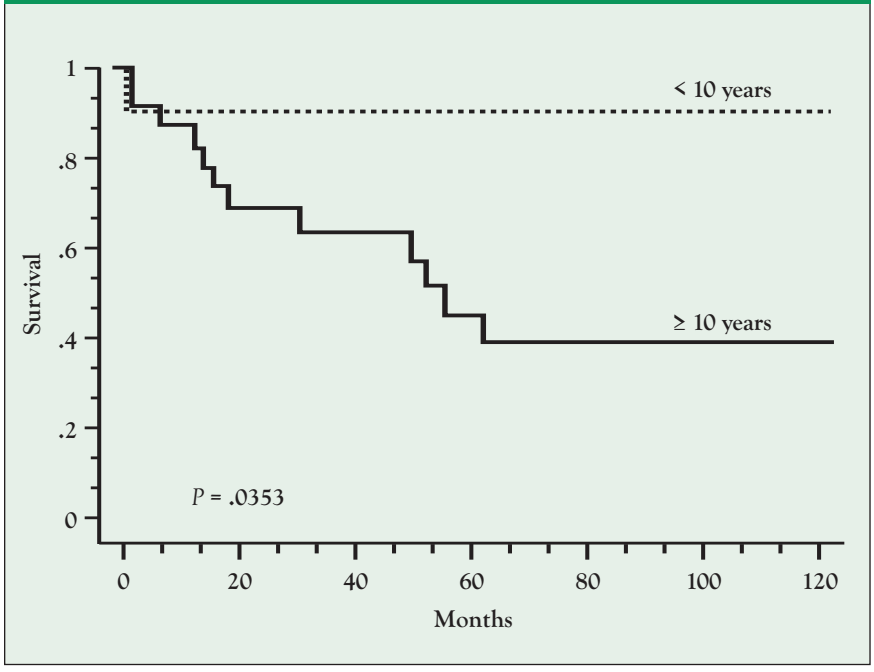
Comparative genomic hybridization (CGH) is a molecular cytogenetic method used to screen a tumor for genetic changes. It assesses changes in the copy numbers of genes (losses, gains, or amplifications) within the tumor compared with another reference sample. CGH begins by labeling the genetic material of the tumor with a fluorescent dye (eg, FITC, which emits green fluorescence) and the genetic material of its comparator with another fluorescent dye (eg, Texas red, which emits red fluorescence). After mixing the DNA pools along with unlabeled human DNA that binds to repetitive DNA sequences (Cot-1), the mixture is hybridized to either metaphase chromosomes or to a slide containing an array of hundreds or thousands of defined DNA probes.[58]

During the hybridization, the 2 populations compete for their corresponding sequences on the substrate chromosomes or array. The ratio of the fluorescence at each point on the array is used to evaluate regions of DNA gain or loss in the tumor sample. If the relative abundances of the tumor DNA and the reference DNA are equal, the relative ratio of tumor-to-reference fluorescence intensity for the respective genomic region equals 1. If the tumor has increases in copy number of a given region, the ratio of tumor-to-reference fluorescence intensity exceeds 1. The degree of increase determines whether it is a copy number gain or an amplification, with the latter exhibiting a substantial increase in the ratio. If the ratio is less than 1, a loss has occurred.[58]

CGH analysis may be able to help distinguish between melanoma and benign nevi. About 96% of melanomas exhibit numerous copy number changes.[66] In contrast, benign nevi typically show no chromosomal aberrations, or, in the case of Spitz nevi, have a restricted set of alterations that do not overlap with the ones observed in melanoma. Thus, changes revealed by CGH may someday be able to classify melanocytic tumors better than histopathologic assessment alone.[57,58]

Routine use of CGH may be compromised by the fact that it is currently an experimental diagnostic test, with a cost that is generally not covered by insurers. Some clinicians, including some of the faculty, feel uncomfortable recommending that patients pay out of pocket for an unproved research test, such as CGH.

Figure 6. Event-free survival (EFS) according to age: EFS was significantly better for children who were younger than 10 years (5-year EFS: 90.0%) than for older patients (5-year EFS: 46.7%).[56]



From Ferrari et al, 2005.[56] Reprinted with permission from the American Academy of Pediatrics.

As is also the case with adults, the most important melanoma prognostic predictor of survival for pediatric melanoma is the stage at diagnosis. In general, better prognoses have been observed in female patients than in male patients.[59] In the experience of many melanoma care providers, children with melanoma generally fare better than adults. The relationship between age of onset and outcomes remains unclear, especially when factors such as depth and clinical stage are controlled for.[55] Survival rates vary across studies. **Figure 6** summarizes one report of survival rates in pediatric melanomas. In this study, according to the revised AJCC Staging System, the 5-year overall survival for pediatric patients with melanoma was 85.7% for Stage I, 83.6% for Stage II, 49.9% for Stage III, and 0% for Stage IV.[56] In the recent report by Lange and colleagues, which evaluated data from 3,158 pediatric patients (ages 1 through 19) in the National Cancer Database, 5-year survival rates were slightly higher, with rates of 98.7% for in situ melanomas, 93.6% for localized invasive disease, 68.0% for regional metastatic disease, and 11.8% for distant disease.[59] In this study, children aged 1 to 9 had significantly poorer 5-year survival than other age groups[59] but other studies have shown just the opposite.

Experience in adults primarily dictates the treatment protocols for pediatric melanoma. No precise consensus exists for the best approach to care for children with melanoma because of the lack of large-scale studies of therapies in this patient population. Several studies suggest that SLN biopsy can be effectively employed in children.[60-62] This procedure may have a role in evaluating cases such as atypical melanocytic lesions with spitzoid features or melanocytic tumors of uncertain malignant potential (MELTUMP); however, this remains highly controversial and there are no well-designed studies to document the merits of SLN biopsy for Spitzoid tumors.[60-62] In addition, preliminary data on the use of IFN alfa 2b (intravenous induction and subcutaneous maintenance phase) suggest that IFN has good tolerability in children,[60-63] although this drug's use and benefits in childhood melanoma has not yet been documented in any controlled studies. Bruce Averbook, MD, of Metro Health Medical Center/Case Western Reserve University, has led the development of a national pediatric melanoma and melanocytic neoplasms database, and preliminary analyses of the registry are planned. Individuals interested in learning more about the database or joining the registry can contact Dr Averbook at 216-778-4795 or John Kirkwood, MD, who is involved with the registry at the University of Pittsburg Medical Center (1-412-623-7707).

SUMMARY

Childhood melanoma is a rare disease, accounting for approximately 2% of all melanomas diagnosed in the United States. Melanomas in children often lack the clinical ABCDE features, are amelanotic, nodular, and grow rapidly. Melanomas in prepubertal children appear to act very differently than melanomas arising in older children and adults, suggesting that the biology of these tumors may be different. Clinicians need to be aware of these findings when evaluating children in the clinic and should make use of specialized dermatopathologic resources in addressing these challenging lesions. Genomic hybridization technology holds great promise for better characterization of melanoma in general and may be particularly useful in correctly classifying histologically atypical spitzoid tumors as benign or malignant.

References of Clinical Content

1. Howe HL, Wu X, Ries LAG, et al. Annual report to the nation on the status of cancer, 1975-2003, featuring cancer among U.S. hispanic/latino populations. *Cancer.* 2006;107: 1711-1742.
2. American Cancer Society. *Cancer facts & figures 2007.* 2007.
3. *National Comprehensive Cancer Network: clinical practice guidelines in oncology.* 2007.
4. Gimotty PA, Botbyl J, Soong S, Guerry D. A population-based validation of the American Joint Committee on Cancer melanoma staging system. *J Clin Oncol.* 2005;23:8065-8075.
5. Gimotty PA, Elder DE, Fraker DL, et al. Identification of high-risk patients among those diagnosed with thin cutaneous melanomas. *J Clin Oncol.* 2007;25:1129-1134.
6. Masri GD, Clark WH Jr, Guerry D4 IV, et al. Screening and surveillance of patients at high risk for malignant melanoma result in detection of earlier disease. *J Am Acad Dermatol.* 1990;22(6 pt 1):1042-1048.
7. Tsao H, Bevona C, Goggins W, Quinn T. The transformation rate of moles (melanocytic nevi) into cutaneous melanoma: a population-based estimate. *Arch Dermatol.* 2003;139:282-288.
8. Tucker MA, Halpern A, Holly EA, et al. Clinically recognized dysplastic nevi: a central risk factor for cutaneous melanoma. *JAMA.* 1997;277:1439-1444.
9. Bevona C, Goggins W, Quinn T, Fullerton J, Tsao H. Cutaneous melanomas associated with nevi. *Arch Dermatol.* 2003;139:1620-1624.
10. Piepkorn M, Meyer LJ, Goldgar D, et al. The dysplastic melanocytic nevus: a prevalent lesion that correlates poorly with clinical phenotype. *J Am Acad Dermatol.* 1989;20: 407-415.
11. Sober AJ, Chuang TY, Duvic M, et al. Guidelines of care for primary cutaneous melanoma. *J Am Acad Dermatol.* 2001;45:579-586.
12. Abbasi NR, Shaw HM, Rigel DS, et al. Early diagnosis of cutaneous melanoma: revisiting the ABCD criteria. *JAMA.* 2004;292:2771-2776.
13. Benvenuto C MA. Ten reasons why dermoscopy is beneficial for the evaluation of skin lesions. *Expert Rev Dermatol.* 2006;1:1-6.
14. Bafounta M, Beauchet A, Aegerter P, Saiag P. Is dermoscopy (epiluminescence microscopy) useful for the diagnosis of melanoma? *Arch Dermatol.* 2001;137:1343-1350.
15. Kittler H, Binder M. Risks and benefits of sequential imaging of melanocytic skin lesions in patients with multiple atypical nevi. *Arch Dermatol.* 2001;137:1590-1595.
16. Nehal KS, Oliveria SA, Marghoob AA, et al. Use of and beliefs about dermoscopy in the management of patients with pigmented lesions: a survey of dermatology residency programmes in the United States. *Melanoma Res.* 2002;12:601-605.
17. Menzies SW, Gutenev A, Avramidis M, Batrac A, McCarthy WH. Short-term digital surface microscopic monitoring of atypical or changing melanocytic lesions. *Arch Dermatol.* 2001;137:1583-1589.
18. Feit NE, Dusza SW, Marghoob A. Clinical and laboratory investigations melanomas detected with the aid of total cutaneous photography. *Br J Dermatol.* 2004;150:706-714.
19. Banky JP, Kelly JW, English DR, Yeatman JM, Dowling JP. Incidence of new and changed nevi and melanomas detected using baseline images and dermoscopy in patients at high risk for melanoma. *Arch Dermatol.* 2005;141:998-1006.
20. Kefford R, Bishop JN, Tucker M, et al. Genetic testing for melanoma. *Lancet Oncol.* 2002;3:653-654.
21. Hansen CB, Wadge LM, Lowstuter K, Boucher K, Leachman SA. Clinical germline genetic testing for melanoma. *Lancet Oncol.* 2004;5:314-319.
22. Tucker M, Fraser MC, Goldstein AM, et al. A natural history of melanomas and dysplastic nevi: an atlas of lesions in melanoma-prone families. *Cancer.* 2002;94:3192-3209.
23. Aitken J, Welch J, Duffy D, et al. CDKN2A variants in a population-based sample of Queensland families with melanoma. *J Natl Cancer Inst.* 1999;91:446-452.
24. Bishop DT, Demenais F, Goldstein AM, et al, and The Melanoma Genetics Consortium. Geographical variation in the penetrance of CDKN2A mutations for melanoma. *J Natl Cancer Inst.* 2002;94:894-903.
25. Begg CB, Orlow I, Hummer AJ, et al. Lifetime risk of melanoma in CDKN2A mutation carriers in a population-based sample. *J Natl Cancer Inst.* 2005;97:1507-1515.
26. Goldstein AM, Martinez M, Tucker MA, Demenais F. Gene-covariate interaction between dysplastic nevi and the CDKN2A gene in American melanoma-prone families. *Cancer Epidemiol Biomarkers Prev.* 2000;9:889-894.
27. HIPAA. Prohibiting discrimination against individual participants and beneficiaries based on health status. 1996;29/18/1/b/7/a:1182.
28. Hereditary Melanoma. 2007; Massachusetts General Hospital Cancer Center; Center for Cancer Risk Analysis: Cancer Genetics.
29. Gimotty PA, Guerry D, Ming ME, et al. Thin primary cutaneous malignant melanoma: a prognostic tree for 10-year metastasis is more accurate than American Joint Committee on Cancer staging. *J Clin Oncol.* 2004;22:3668-3676.
30. Karakousis GC, Gimotty PA, Botbyl JD, et al. Predictors of regional nodal disease in patients with thin melanomas. *Ann Surg Oncol.* 2006;13:533-541.
31. Kesmodel SB, Karakousis GC, Botbyl JD, et al. Mitotic rate as a predictor of sentinel lymph node positivity in patients with thin melanomas. *Ann Surg Oncol.* 2005;12:449-458.
32. Sondak VK, Taylor JMG, Sabel MS, et al. Mitotic rate and younger age are predictors of sentinel lymph node positivity: lessons learned from the generation of a probabilistic model. *Ann Surg Oncol.* 2004;11:247-258.
33. Breslow A. Thickness, cross-sectional areas and depth of invasion in the prognosis of cutaneous melanoma. *Ann Surg.* 1970;172:902-908.
34. van Akkooi A, de Wilt J, Verhoef C, et al. Clinical relevance of melanoma micrometastases (<0.1 mm) in sentinel nodes: are these nodes to be considered negative? *Ann Oncol.* 2006;17:1578-1585.
35. Balch CM, Buzaid AC, Soong S-J, et al. Final version of the American Joint Committee on Cancer staging system for cutaneous melanoma. *J Clin Oncol.* 2001;19:3635-3648.
36. Gershenwald JE, Thompson W, Mansfield PF, et al. Multi-institutional melanoma lymphatic mapping experience: the prognostic value of sentinel lymph node status in 612 stage I or II melanoma patients. *J Clin Oncol.* 1999;17:976-983.
37. Morton DL, Thompson JF, Cochran AJ, et al, for the MSLT Group. Sentinel-node biopsy or nodal observation in melanoma. *N Engl J Med.* 2006;355:1307-1317.
38. Agnese DM, Abdessalam SF, Burak WE Jr, et al. Cost-effectiveness of sentinel lymph node biopsy in thin melanomas. *Surgery.* 2003;134:542-547.
39. Markovic SN, Erickson LA, Rao RD, et al. Malignant melanoma in the 21st century, part 2: staging, prognosis, and treatment. *Mayo Clin Proc.* 2007;82:490-513.
40. Balch CM, Soong S-J, Gershenwald JE, et al. Prognostic factors analysis of 17,600 melanoma patients: validation of the American Joint Committee on Cancer melanoma staging system. *J Clin Oncol.* 2001;19:3622-3634.
41. Crowson AN, Magro CM, Mihm MC Jr. Prognosticators of melanoma, the melanoma report, and the sentinel lymph node. *Mod Pathol.* 2006;19(suppl 2):S71-S87.
42. Harrist TJ, Rigel DS, Day CJ, et al. "Microscopic satellites" are more highly associated with regional lymph node metastases than is primary melanoma thickness. *Cancer.* 1984;53:2183-2187.
43. Bleicher RJ, Essner R, Foshag LJ, Wanek LA, Morton DL. Role of sentinel lymphadenectomy in thin invasive cutaneous melanomas. *J Clin Oncol.* 2003;21:1326-1331.
44. Stitzenberg KB, Groben PA, Stern SL, et al. Indications for lymphatic mapping and sentinel lymphadenectomy in patients with thin melanoma (Breslow thickness ≤1.0 mm). *Ann Surg Oncol.* 2004;11:900-906.
45. Puleo CA, Messina JL, Riker AI, et al. Sentinel node biopsy for thin melanomas: Which patients should be considered? *Cancer Control.* 2005;12:230-235.
46. Elder DE, Gimotty PA, Guerry D. Cutaneous melanoma: estimating survival and recurrence risk based on histopathologic features. *Dermatol Ther.* 2005;18:369-385.
47. Ranieri JM, Wagner JD, Wenck S, Johnson CS, Coleman JJ. The prognostic importance of sentinel lymph node biopsy in thin melanoma. *Ann Surg Oncol.* 2006;13:927-932.
48. Clemente CG, Mihm MC Jr, Bufalino R, et al. Prognostic value of tumor infiltrating lymphocytes in the vertical growth phase of primary cutaneous melanoma. *Cancer.* 1996;77:1303-1310.
49. Chao C, Martin RCG II, Ross MI, et al. Correlation between prognostic factors and increasing age in melanoma. *Ann Surg Oncol.* 2004;11:259-264.
50. Paek SC, Griffith KA, Johnson TM, et al. The impact of factors beyond Breslow depth on predicting sentinel lymph node positivity in melanoma. *Cancer.* 2007;109:100-108.
51. Schuchter L, Schultz DJ, Synnestvedt M, et al. A prognostic model for predicting 10-year survival in patients with primary melanoma. *Ann Intern Med.* 1996;125:369-375.
52. Pappo AS. Melanoma in children and adolescents. *Eur J Cancer.* 2003;39:2651-2661.
53. Ceballos PI, Ruiz-Maldonado R, Mihm MC Jr. Melanoma in children. *N Engl J Med.* 1995;332:656-662.
54. Huynh PM, Grant-Kels JM, Grin CM. Childhood melanoma: update and treatment. *Int J Dermatol.* 2005;44:715-723.
55. Orlow SJ. Melanoma in children: rare but dangerous. *The Melanoma Letter.* 2007;25:3-4.
56. Ferrari A, Bono A, Baldi M, et al. Does melanoma behave differently in younger children than in adults? A retrospective study of 33 cases of childhood melanoma from a single institution. *Pediatrics.* 2005;115:649-654.
57. Bastian BC. Molecular cytogenetics as a diagnostic tool for typing melanocytic tumors. *Recent Results Cancer Res.* 2002;160:92-99.
58. Bauer J, Bastian B. Distinguishing melanocytic nevi from melanoma by DNA copy number changes: comparative genomic hybridization as a research and diagnostic tool. *Dermatol Ther.* 2006;19:40-49.
59. Lange JR, Palis BE, Chang DC, Soong S-J, Balch CM. Melanoma in children and teenagers: an analysis of patients from the National Cancer Data Base. *J Clin Oncol.* 2007;25:1363-1368.
60. Gamblin TC, Edington H, Kirkwood JM, Rao UN. Sentinel lymph node biopsy for atypical melanocytic lesions with spitzoid features. *Ann Surg Oncol.* 2006;13:1664-1670.
61. French JC, Rowe MR, Lee TJ, Zwart JE. Pediatric melanoma of the head and neck: a single institutions experience. *Laryngoscope.* 2006;116:2216-2220.
62. Shah N, Gerstle JT, Stuart M, Winter C, Pappo A. Use of sentinel lymph node biopsy and high-dose interferon in pediatric patients with high-risk melanoma: the Hospital for Sick Children experience. *J Pediatr Hematol Oncol.* 2006;28:496-500.
63. Navid F, Furman WL, Fleming M, et al. The feasibility of adjuvant interferon alpha-2b in children with high-risk melanoma. *Cancer.* 2005;103:780-787.
64. Menzies SW. Cutaneous melanoma: making a clinical diagnosis, present and future. *Dermatol Ther.* 2006;19:32-39.
65. Berwick M, Begg CB, Fine JA, Roush GC, Barnhill RL. Screening for cutaneous melanoma by skin self-examination. *J Natl Cancer Inst.* 1996;88:17-23.
66. Carlson JA, Ross JS, Slominski A, et al. Molecular diagnostics in melanoma. *J Am Acad Dermatol.* 2005;52:743-775.

Barriers-to-Care for Patients with Melanoma: Medicolegal Aspects of Early Detection

(continued from page 4)

Malpractice Lawsuits Due to Misdiagnosis of Melanomas

In a presentation at the 2006 annual meeting of the American Academy of Dermatology, Marghoob recommended that a high level of suspicion, listening to your patients, and consistent follow-up of lesions would help dermatologists avoid lawsuits related to missed melanoma diagnoses. Marghoob outlined seven major reasons for misdiagnosis of melanoma and provided some recommendations for their prevention.

1. Nodular melanoma missed-clinically. Noting that nodular melanoma often lacks the typical ABCD changes and may be aggressive and rapidly growing, Marghoob recommends biopsy for nodular lesions that a patient says is evolving, including change in symptoms, appearance, and the presence of bleeding or ulceration.

2. Nodular melanoma misdiagnosed as a nevus by a pathologist. Dermatologists need to be aware that even though a pathologist made the incorrect diagnosis, the dermatologist may still be seen as having clinical responsibility and would be at risk of a lawsuit. Dermatologists should reconcile their clinical diagnosis with the pathology report and, if concerned, request additional stains and sectioning.

3. Partial biopsies (shave & punch) leading to an inaccurate diagnosis. Because a partial biopsy may sample a nondiagnostic area or miss the prognostically worst portion of the lesion, Marghoob recommends an excisional biopsy for all melanocytic lesions in which the differential diagnosis includes melanoma.

4. Melanoma misdiagnosed as a "dysplastic nevus involving margins". Marghoob recommends a re-excision if "nevus" margins are positive and a review of original pathology slides for any "recurrent nevus."

5. Melanoma misdiagnosed as a Spitz nevus. Gelbard and colleagues noted that there is a lack of certainty in the histologic differentiation of Spitz nevi from melanomas, which is also reflected in the medical literature.[6] Because of this concern about melanoma, the authors said that, "it is usually recommended that Spitz nevi be completely excised."

6. Unrecognized desmoplastic melanoma. A high index of suspicion is warranted for some patients, including older men with banal appearing or scar-like lesions on chronically sun-damaged skin of the head and neck, especially if the lesion is symptomatic or growing. Additional clues include lesions with unexpected presence of irregular vessels under dermoscopy, unexplained scars, and lentigo maligna in which one can palpate a firm area.

7. Patients presenting with metastatic melanoma with an unknown primary. Marghoob cautions that when removing skin growths, dermatologists should not discard what appear to be clinically benign lesions, and be selective with the use of liquid nitrogen treatment on lesions not biopsied.

Strategies for Avoiding Errors

- Document as much as possible. If it is not written down, it did not occur.
- Consider the use of photography to document the appearance and location of lesions.
- Have patients actively participate in decision making and in their health care. Stress the importance of self skin examinations.
- Make sure that patients understand that lesions may change—patients should watch for changes and follow up with their physicians periodically and whenever they see a new or changing lesion.
- Follow-up on lesions that a patient brings to your attention.
- Follow-up on Spitz nevi, even if margins are clear.
- Follow-up on lesions treated with liquid nitrogen.
- Review the original pathology and excise recurrent nevi.
- Excise pigmented lesions completely if the differential diagnosis includes melanoma and a complete excision is feasible.
- Question yourself and your pathologist always regarding the diagnosis and reconcile your clinical suspicion with the pathology diagnosis.

References

1. Troxel DB. Pitfalls in the diagnosis of malignant melanoma: findings of a risk management panel study. *Am J Surg Path.* 2003;27:1278-1283.
2. Troxel DB. Medicolegal aspects of error in pathology. *Arch Path Lab Med.* 2006;130:617-619.
3. Weinstock MA. Progress and prospects on melanoma: the way forward for early detection and reduced mortality. *Clin Cancer Res.* 2006;12:2297S-2300S.
4. Baade PD, English DR, Youl PH, et al. The relationship between melanoma thickness and time to diagnosis in a large population-based study. *Arch Dermatol.* 2006;142:1422-1427.
5. Berwick M. Evaluating early detection in the diagnosis of melanoma. *Arch Dermatol.* 2006;142:1485-1486.
6. Gelbard SN, Tripp JM, Marghoob AA, et al. Management of spitz nevi: a survey of dermatologists in the United States. *J Am Acad Dermatol.* 2002; 47:224-230.

Barriers-to-Care for Patients With Melanoma: Lack of Effective Web Sites, Advocacy Groups

(continued from page 4)

including breast cancer (23.8%), prostate cancer (11.5%), and skin cancer (11.3%).[3]

Searching for Health Information

Of the 80% of Americans who have searched for health information online, most start their search using a general search engine.[4] And, according to Pew, 75% of online health information seekers do not consistently examine quality indicators (such as the source and date) for the information they find.

The most commonly used search engine in this country is Google™. A recent search for the topic "melanoma" on Google™ documented more than 10 million hits [accessed April 21, 2007]. Further, Google™ allows users to refine their results into several categories, including treatment, tests and diagnosis, symptoms, causes and risk factors, and alternative medicine. These overlapping categories and the amount of information available can be confusing and misleading for some people seeking information about melanoma.

Dermatologists Can Help Patients Find Credible Information

For dermatologists who treat patients with early stages of melanoma, information on the Internet can provide a powerful tool for helping patients understand their condition. To ensure that patients are reviewing appropriate information, dermatologists need to be aware of available melanoma-related information and reliable sources.

Bichakjian and colleagues assessed melanoma information on the Internet by evaluating 74 Web sites.[5] Independent reviewers evaluated the sites on general melanoma information, risk factors, diagnosis, treatment, prevention, and prognosis. The majority of sites failed to include complete information and 10 sites (14%) contained inaccuracies. Although accurate at the time of publication, many of the sites listed in the article no longer exist, including three sites that the authors concluded had the most accurate and complete information.

In another article the University of Michigan group also investigated the use of the Internet and its effect on patients with melanoma.[6] Among the patients studied, almost 40% indicated that they had used the Internet to research melanoma. Of these, 94% thought the Internet was useful and 67% believed it helped them better understand their conditions. About a third of the patients indicated that the information from the Internet made them more anxious about their disease.

Although dermatologists might not all agree on which sites are the most credible, their patients will continue to go online when seeking information about diagnosis, treatment and access to clinical trials. Based on the stage of their disease, dermatologists can identify and make available to their patients with melanoma and their caregivers, a list of appropriate online resources.

Melanoma Advocacy

The Internet has fostered an explosion in the number of cancer-related advocacy groups and foundations, many of them started by cancer survivors or the families of people who have died of cancer. For some cancers, most notably breast cancer, these advocacy groups have had a significant effect on public awareness, raising money for research and programs, fostering screening and early diagnosis and treatment, and affecting legislation at the state and federal levels.

In March 2006, 19 melanoma advocacy groups and foundations met to discuss the needs of melanoma patients and explore the possibility of unifying to increase the effect of the melanoma community on a national level. Most of the meeting participants supported the idea of forming a coalition to focus on concerns that organizations working on their own were not meeting.

National Melanoma Alliance

Despite knowing that individual groups would have limited time and

Recommended Melanoma Information Web Sites for Patients

American Cancer Society www.cancer.org
MEDLINEplus: Melanoma Home Page www.nlm.nih.gov/medlineplus/melanoma.html
Melanoma Center www.melanomacenter.org
National Cancer Institute: Melanoma Home Page www.cancer.gov/cancertopics/types/melanoma
National Comprehensive Cancer Network: Melanoma Treatment Guidelines www.nccn.org
Oncolink www.oncolink.com
People Living with Cancer (ASCO) www.plwc.org
The Skin Cancer Foundation www.skincancer.org

resources, the melanoma organizations established a steering committee to recommend ways to unify melanoma organizations. During the past year, the committee engaged in a thorough process to develop a proposal to form the National Melanoma Alliance including melanoma organizations, researchers, and health professionals.

The alliance's strategy will be to leverage the combined strength of its participants to promote a national agenda that will include increasing funding for melanoma research and ensuring that research aligns with the needs of melanoma patients and those at risk for melanoma. Although the alliance has not yet been formally launched, the melanoma organizations have begun working on public policy issues.

More information about the National Melanoma Alliance is available at 877.877.1594.

References

1. Pew Internet & American Life Project. Finding Answers Online in Sickness and in Health. http://www.pewinternet.org/pdfs/PIP_Health_Decisions_2006.pdf [Accessed April 2007]
2. Bass SB, Ruzek SB, Gordon TF, et al. Relationship of internet health information use with patient behavior and eelf-efficacy: experiences of newly diagnosed cancer patients who contact the national cancer institute's cancer information service. *J Health Commun.* 2006;18:219-36.
3. Rutten LJ, Squiers L, Hesse B. Cancer-related information seeking: hints from the 2003 Health Information National Trends Survey (HINTS). *J Health Commun.* 2006; 11 Suppl 1:147-56.
4. Pew Internet & American Life Project. Online Health Search 2006. http://www.pewinternet.org/pdfs/PIP_Online_Health_2006.pdf [Accessed April 2007]
5. Bichakjian CK, Schwartz JL, Wang TS, et al. Melanoma information on the internet: often incomplete—a public health opportunity? *J Clin Oncol.* 2001;20:134-41.
6. Sabel M, Strecher VJ, Schwartz JL, et al. Patterns of internet use and impact on patients with melanoma. *J Am Acad Dermatol.* 2005;52:779-85

CE Posttest Questions

Please answer each question in the space provided on the back cover.

1. The majority of melanomas in adults arise:
- A. In apparently normal skin
- B. In clinically atypical nevi
- C. In giant congenital nevi
- D. In melanocytic nevi

2. When determining if a lesion has clinically evolved to melanoma, what factors should be considered?
- A. Unusual appearance compared with other nevi
- B. Growing
- C. Progressive non-uniform appearance
- D. All of the above

3. Which of the following would not be supportive of genetic testing for melanoma?
- A. 3 primary melanomas in an individual
- B. 3 cancer events (melanoma in a family member plus pancreatic cancer)
- C. 3 confirmed melanomas in a family
- D. 3 prior months of cancer therapy

4. ASCO guidelines suggest that genetic testing be limited to patients:
- A. Who have had at least 2 family members with confirmed invasive melanoma
- B. In patients under the age of 20
- C. In times when it might alter the management of the patient or his or her family members
- D. In the setting of metastatic disease

5. Patients with "low-risk" melanomas account for what proportion of melanoma deaths?
- A. 1%
- B. 5%
- C. 10%
- D. 15%

6. A delay in diagnosis of pediatric melanoma has been reported to occur in ___ of cases.
- A. 20%
- B. 40%
- C. 60%
- D. 80%

7. Compared with adult melanoma, which of the following is true regarding pediatric melanoma?
- A. Pediatric melanoma is less likely to be nodular
- B. Pediatric melanoma depth at diagnosis is thinner
- C. Pediatric melanoma more often is amelanotic and lacks the ABCDE features of melanoma
- D. All of the above

8. According to research for the Pew Internet & American Life Project, what percent of e-caregivers say that the most important source of information they use is something they have found online?
- A. 24%
- B. 38%
- C. 45%
- D. 58%
- E. 75%

9. Independent reviewers, including faculty members from the University of Michigan Multidisciplinary Melanoma Clinic, evaluated Web sites on general melanoma information, risk factors, diagnosis, treatment, prevention, and prognosis. How many of the sites contained inaccuracies?
- A. 5
- B. 10
- C. 15
- D. 20
- E. 25

10. In a study by researchers at the University of Michigan on the use of the Internet and its effect on patients with melanoma, what percentage of patients said they used the Internet to research melanoma?
- A. 20%
- B. 30%
- C. 40%
- D. 50%
- E. 60%

Evaluation Form

Please use the scale below in answering these questions. Fill in the circle completely. You may use pen or pencil.

Very Low Low Moderate High Very High

1. To what extent were the following objectives of the educational activity achieved?

   A. List the benefits of mole mapping and dermoscopy in the early recognition of melanoma
   ❍ ❍ ❍ ❍ ❍

   B. Describe the role of genetic testing in melanoma
   ❍ ❍ ❍ ❍ ❍

   C. Compare and contrast pathologic markers of high-risk cutaneous melanoma
   ❍ ❍ ❍ ❍ ❍

   D. Describe the differential diagnosis of pediatric melanoma
   ❍ ❍ ❍ ❍ ❍

2. To what extent were you satisfied with the overall quality of the educational activity?
   ❍ ❍ ❍ ❍ ❍

3. To what extent was the content of the program relevant to your practice or professional responsibilities?
   ❍ ❍ ❍ ❍ ❍

4. To what extent did the program enhance your knowledge of the subject area?
   ❍ ❍ ❍ ❍ ❍

5. To what extent did the program change the way you think about clinical care and/or professional responsibilities?
   ❍ ❍ ❍ ❍ ❍

6. To what extent will you make a change in your practice and/or professional responsibilities as a result of your participation in this educational activity?
   ❍ ❍ ❍ ❍ ❍

7. To what extent did the activity present scientifically rigorous, unbiased, and balanced information?
   ❍ ❍ ❍ ❍ ❍

8. To what extent was the presentation free of commercial bias?
   ❍ ❍ ❍ ❍ ❍

Posttest Answer Sheet

1. ☐ 2. ☐ 3. ☐ 4. ☐ 5. ☐ 6. ☐ 7. ☐ 8. ☐ 9. ☐ 10. ☐

If you wish to receive credit for this activity, please fill in your name and address and fax to:

University of Pittsburgh Center for Continuing Education at 412-647-8222 or mail to:
UPMC Center for Continuing Education, Medical Arts Building, Suite 220, 200 Lothrop Street, Pittsburgh, PA 15213

❑ I have completed the activity and claim _____ credit hours

Request for Credit

Name: Degree:

Address: City, State, ZIP:

Organization: Specialty: Last 5 Digits of SSN:

Telephone Number: Fax: E-mail:

MELANOMA CARE OPTIONS™

JUNE 2007

Issue 1: Dermatology Edition

PharmAdura, LLC
523 Route 303
Orangeburg, NY 10962