Melanoma:
A PRIMER

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Melanoma is an increasingly common and potentially fatal form of skin cancer arising from the malignant transformation of melanocytes. Melanocytes are the cells that make the pigment melanin and are derived from the neural crest.

Although most melanomas arise in the skin, they may also arise from mucosal surfaces or at other sites to which neural crest cells migrate. Melanoma strikes more than 60,000 people in the United States annually.1 Substantial progress has been made in understanding the pathogenesis of melanoma at the cellular level, leading to the development of new agents in its treatment.

EPIDEMIOLOGY
For years, the incidence of melanoma has increased at a rate greater than any other form of cancer in the United States. Currently, melanoma is the sixth most common type of cancer and the second most common form of cancer for young adults ages 15 to 29.1,2 Trends in melanoma incidence in recent years, however, show largely an increase in thinner, less lethal tumors. Nonetheless, the death rate from melanoma has continued to increase, suggesting that high-risk primary melanomas are on the rise, too. Fortunately, the overall increases in melanoma incidence have begun to slow in Western Europe and North America.

ETIOLOGY, RISK FACTORS, AND RISK ASSESSMENT
Although the etiology of melanoma is not completely understood, case-control studies have identified a number of characteristics present in populations at high risk for developing melanoma. Risk factors for any malignancy can be subdivided into genetic and environmental with interaction between the two; this is no different for melanoma. Both the established and select hypothesized risk factors are listed in Table 1. The main risk factors are related to excessive sun exposure and tanning bed use, number of melanocytic nevi, cutaneous phenotype (pale Caucasian skin, red or blond hair with blue eyes), and family and personal history of melanoma (approximately 5% of all invasive cutaneous melanomas occur in a familial setting with two or more close relatives affected).
Nearly 70% of melanomas are discovered by patients or their family members secondary to a concern about a change in size or appearance of a lesion; a lesion associated with pain, pruritus, ulceration, or bleeding; or a lesion located in a cosmetically sensitive area. Approximately 25% of diagnosed melanomas are identified by a nurse or physician examining a patient for an unrelated condition or as part of a comprehensive workup.

An interactive tool has been developed by scientists at the National Cancer Institute, the University of Pennsylvania, and the University of California, San Francisco, that is designed to estimate a person’s absolute risk of developing invasive melanoma. The tool helps clinicians identify individuals at higher risk for melanoma to plan appropriate screening interventions with them.

### Table 1. Risk Factors for Cutaneous Melanoma

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Description</th>
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<tbody>
<tr>
<td>Excessive sun exposure</td>
<td>High solar exposure in early childhood (before age 10) Past history of one or more severe blistering sunburns Past tanning bed use (prior to age 30) Occupation (including airline crew)</td>
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<tr>
<td>Nevi-related risks</td>
<td>Multiple banal melanocytic nevi (&gt; 100) Three or more clinically atypical (dysplastic) nevi</td>
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<tr>
<td>Cutaneous phenotype</td>
<td>Pale Caucasian skin Red or blond hair with blue eyes</td>
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<tr>
<td>Personal or family history of invasive melanoma</td>
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<td>Past pesticide use</td>
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<td>Higher socioeconomic group</td>
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### PATHOPHYSIOLOGY

There are four main types of melanoma:
- **Superficial spreading melanoma** accounts for 60% to 70% of cases and occurs more frequently in younger adults.
- **Nodular melanoma** also occurs in younger adults, representing 10% to 15% of cases.
- **Lentigo maligna melanoma** occurs in older adults and accounts for only 15% of cases.
- **Acral or acral-lentiginous melanomas** are the least common form (less than 10% of cases) and appear on the palms, soles, and nail beds.

### PRESENTATION

Malignant melanoma usually appears as a changing or unusual mole with haphazard color variegation, including combinations of brown, black, blue, gray, white, and (rarely) pink. Most melanomas are larger than 5 millimeters in diameter at time of diagnosis. A number of clinical prediction rules have been developed to aid in the diagnosis, including the American Cancer Society’s ABCDE criteria (Figure 1) and the revised seven-point checklist developed in the United Kingdom.
STAGING AND WORKUP

The gold standard for diagnosis of all skin malignancies is a tissue biopsy. An excisional biopsy is standard, but an incisional biopsy of the most atypical portion is acceptable if the lesion is large or in a location for which the cosmetic result would be suboptimal in the face of a benign diagnosis. Melanoma has a particular predilection to metastasize even from a very small primary tumor to any organ; common sites of dissemination include the skin, subcutaneous tissues, lymph nodes, liver, bone, lung, brain, and visceral organs. Because of this metastatic potential, many physicians stage patients with a symptomatic localized (stage I and II) primary melanoma with extensive radiologic evaluations to search for distant metastases. However, in an asymptomatic patient with a clinical stage I or II lesion, imaging studies are not indicated since detection of distant metastases is rare.

One of the most significant advances in melanoma management over the last decade is the sentinel lymph node biopsy (SLNB). The procedure has been refined considerably over the years and is now standard care for melanomas greater than 1 millimeter in thickness at every major melanoma center in the United States. Reasons to consider performing SLNB include accurate staging and definition of prognosis, early therapeutic lymph node dissection, identification of well-defined patient populations for entry into clinical trials, and consideration of adjuvant treatment. Sentinel lymph node status is the most powerful independent prognostic factor predicting survival. The system most often used to stage melanoma is the American Joint Commission on Cancer (AJCC) TNM system (Table 2). The T category is based on the thickness of the melanoma seen in the skin biopsy using the Breslow measurement; N stands for nodal status; and the M category is based on whether the melanoma has metastasized (spread) to distant organs. The presence of microscopic ulceration, and more recently, the presence of dermal mitotic figures in melanoma cells are features of the primary melanoma that constitute a higher stage of disease. Previously, a widely employed staging system was based on the Clark level, which describes how far the melanoma has penetrated into the skin (e.g., within the epidermis, invading upper dermis, reached lower dermis, etc.) instead of actually measuring it. The future of melanoma staging will soon unfold at the molecular/genetic level (ultra-staging) using genetic messenger RNA and protein markers that relate to the underlying biology of metastasis. Preliminary results offer a glimpse of the power of gene-expression profiling to predict outcomes and response to treatment and to provide additional information for staging.10

Figure 1. American Cancer Society’s ABCDE Criteria8

The test is considered positive if a lesion exhibits one or more of the five criteria:

- Asymmetry – one half of the lesion is not identical to the other
- Border irregularity – lesion has an uneven or ragged border
- Color variegation – lesion has more than one color (i.e., black, blue, white, pink, or red)
- Diameter – lesion has a diameter greater than 6 millimeters
- Elevation or Enlargement – elevation of lesion above skin surface or enlargement by patient report
PROGNOSIS

Prognosis is affected by clinical and histological factors, as well as by anatomic location of the lesion. Patients who are younger, female, and have melanomas on the extremities generally have a better prognosis. The following factors also affect a patient’s prognosis: thickness and/or level of invasion of the melanoma, mitotic index, presence of tumor-infiltrating lymphocytes, number of regional lymph nodes involved, and ulceration or bleeding at the primary site. Clinical staging is based on whether the tumor has spread to regional lymph nodes or distant sites. With disease that is clinically confined to the primary site, the greater the thickness and depth of local invasion of the melanoma the higher the chance of synchronous or metachronous lymph node or systemic metastases – subsequently, the worse the prognosis.

TREATMENT

Surgery is the mainstay of treatment for localized or regionally advanced melanoma. Interferon and radiation therapy are considered as adjuncts in some cases. For metastatic disease, immunotherapy, chemotherapy, or experimental therapies are considered. For people with early stage, resectable (removable by surgery) melanoma, surgeons usually recommend surgery for the primary tumor alone or in combination with SLNB. The approach to melanoma that is localized is surgical excision with margins proportional to the microstage of the primary lesion. For most lesions 2 millimeters or less in thickness, this means margins at re-excision of 1 centimeter. For melanomas more than 2 millimeters to 4 millimeters in thickness, 2 centimeters to 3 centimeters radial re-excision margins are considered standard. As a result, skin grafting may be necessary to close the resulting defect. In addition, patients with melanomas more than 1 millimeter in thickness should be considered for SLNB followed by complete lymph node dissection if the sentinel node(s) are microscopically or macroscopically positive.

High-dose interferon-alfa-2b (20 mU/m² of body surface per day given intravenously for five days a week every week for four weeks, then 10 mU/m² of body surface per day given subcutaneously three times a week every week for 48 weeks) is the only FDA-approved adjuvant therapy for high-risk patients (patients with melanoma...
greater than 4 millimeters thick without involved lymph nodes, or patients with melanomas of any thickness with positive lymph nodes). Because high-dose regimens are associated with significant toxic effects, numerous trials have been undertaken or are ongoing exploring other adjuvant chemotherapy and/or adjuvant immunologic therapy.

Advanced melanoma is refractory to most standard systemic therapies, and because of this, all newly diagnosed patients should be considered as candidates for clinical trials evaluating novel approaches. Several biologic response modifiers and cytotoxic agents have been reported to produce objective responses; however, rarely have these investigational attempts yielded a positive effect on survival for the entire population treated. Several randomized trials have evaluated combinations of chemotherapy agents or chemotherapy combined with immunotherapy compared with single-agent dacarbazine. Frequently, higher response rates have been reported, but never an improvement in overall survival.

Promising results have been observed in clinical trials employing therapies that are based on a deeper molecular understanding of melanoma and immunologic recognition of cancer. The discovery of activating mutations in the BRAF signal transduction enzyme (50% of all melanoma) have led to the development of selective inhibitors that are associated with high response rates and apparent improvement in control of metastatic disease. A small subset of melanoma (2%) harbors the same activating mutations in the c-kit receptor tyrosine kinase that are found in gastrointestinal stromal tumors. Early results from trials using these inhibitors in patients whose melanomas contain these mutations have produced clear evidence of tumor regression in some patients. Simultaneously, advances have been made in the development of therapies that specifically activate the type of lymphocytes that can recognize melanoma. A monoclonal antibody that blocks an inhibitory mechanism in lymphocytes, resulting in their activation, has produced dramatic and durable responses in a subset of patients. Ongoing trials are seeking to produce evidence sufficient to gain FDA approval and establish these therapies as new standard approaches.

Inhibition of tumor angiogenesis is a validated treatment strategy in several cancer subtypes and has recently been investigated in melanoma.

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<tr>
<th>Table 3. Bevacizumab in Melanoma: Ongoing Clinical Trials</th>
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<tr>
<td>Bevacizumab plus sorafenib (phase 2) (closed)</td>
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<tr>
<td>Bevacizumab plus temsirolimus (phase 2) (closed)</td>
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<td>Erlotinib plus bevacizumab (phase 2) (closed)</td>
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<td>Bevacizumab plus nanoparticle bound paclitaxel (phase 2)</td>
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<td>Bevacizumab plus temozolomide (phase 2)</td>
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<tr>
<td>Bevacizumab, dacarbazine, and interferon-alfa (phase 2) (closed)</td>
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<td>Sorafenib, bevacizumab, and oxaliplatin (phase 1/2)</td>
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<tr>
<td>Bevacizumab +/- low- or high-dose interferon-alfa (randomized phase 2)</td>
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<td>Paclitaxel (conventional), carboplatin, and bevacizumab (phase 2) (closed, 1; open, 1)</td>
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<td>Paclitaxel (nanoparticle), carboplatin, and bevacizumab versus temozolomide (randomized phase 2)</td>
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<tr>
<td>Paclitaxel (conventional), carboplatin, and bevacizumab +/- everolimus (randomized phase 2)</td>
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Encouraging data from a randomized phase 2 trial investigating bevacizumab, an anti-angiogenesis inhibitor, in combination with chemotherapy versus chemotherapy alone were presented recently in a joint meeting of the European Cancer Organization and the European Society for Medical Oncology. Median survival was 12.3 months for the chemotherapy-plus-bevacizumab–treated patients, compared with 8.6 months for patients who received chemotherapy alone. The results warrant confirmation in a phase 3 trial as the primary endpoint; a statistically significant delay in disease progression was not achieved despite a 22% improvement in progression-free survival favoring the bevacizumab arm. A triple combination of bevacizumab, paclitaxel, and carboplatin was reported earlier in 2009 by the North Central Cancer Treatment Group to be well tolerated with clinical benefit. Based on the excitement generated from these data, a number of ongoing trials are incorporating bevacizumab into the treatment of malignant melanoma (Table 3).

Most feel the key to unlocking the mystery of why melanoma is so refractory to therapies studied to date is in answering two pivotal questions: 1) Are common features shared by responders to a given therapy?; and 2) if so, could such markers be useful in identifying patients who are likely to respond to a given treatment? The application of genomic technology holds promise for improved outcomes in the treatment of melanoma. Molecular profiling will help better identify resistance and sensitivity patterns, serve as predictive markers for both sensitivity and resistance, and help identify novel drug targets for treating melanoma.

References