Guideline 8-7

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Follow-up of Patients with Cutaneous Melanoma who were Treated with Curative Intent


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# Table of Contents

Section 1: Recommendations .............................................................................. 1
Section 2: Guideline - Recommendations and Key Evidence.............................. 4
Section 3: Guideline Methods Overview ............................................................... 10
Section 4: Systematic Review ............................................................................. 13
Section 5: Internal and External Review ............................................................... 35
References ........................................................................................................... 40
Appendix 1: Members of the Melanoma Follow-up Guideline Development Group.. 43
Appendix 2: Literature Search Strategy ................................................................. 45
Appendix 3: AMSTAR Quality Assessment of Included Systematic Reviews ........... 47
Appendix 4: Quality Assessment of Included Studies ............................................ 48
Appendix 5: Summary of Published Melanoma Follow-up CPG Recommendations .... 50
Follow-up of Patients with Cutaneous Melanoma who were Treated with Curative Intent

Section 1: Recommendations

This section is a quick reference guide and provides the guideline recommendations only. For key evidence associated with each recommendation, see Section 2.

GUIDELINE OBJECTIVES
To recommend follow-up schedules involving appropriate evaluations and timing for early detection of local-regional recurrence, distant metastases and new primary melanomas for patients with melanoma after curative-intent treatment.

TARGET POPULATION
These recommendations apply to patients with cutaneous melanoma (hereafter referred to as melanoma) after treatment with curative intent.

INTENDED USERS
Intended users of this guideline are medical oncologists and surgical oncologists specializing in melanoma, as well as dermatologists, family doctors, and surgeons involved in the follow-up care of patients with melanoma, within the province of Ontario.

RECOMMENDATIONS
In patients who have received curative-intent treatment for melanoma:

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<thead>
<tr>
<th>Recommendation 1</th>
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<tr>
<td>• Routine shared follow-up care with an oncologist (surgical oncologist, medical oncologist, or radiation oncologist) and a dermatologist is recommended.</td>
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<th>Melanoma Stage</th>
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<td>High-risk Stage IIB/C and Stage IIIA</td>
<td>• Patients should receive clinical visits with an oncologist every six months in years 1 through 3, then annually until year 5. Patients may be discharged to care of dermatologist and family physician after five years if appropriate.</td>
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|                   | • Follow-up with a dermatologist should occur every six to 12
Guideline 8-7

Section 1: Recommendations - November 3, 2015

| Stage III B to C and resected stage IV | Patients should receive a clinical visit with an oncologist every three to six months in years 1 through 3 and every six months in years 4 to 5, or as clinically indicated. 
| | Follow-up with a dermatologist should occur every six to 12 months or as clinically indicated. |

**Qualifying Statements for Recommendation 1**

- Oncologists and dermatologists have distinct skill sets and training; thus, alternating follow-up visits with both specialists is recommended.
  - Clinical follow-up with a medical, radiation, or surgical oncologist/surgeon is recommended in order to detect a local, regional, or distant melanoma recurrence and is aided by the use of imaging modalities where appropriate.
  - Clinical follow-up with a dermatologist is recommended in order to detect new primary melanomas and local recurrences of resected melanoma with the aid of specialized dermatologic imaging, full skin examinations, and photo surveillance.
- Dermatologic follow-up may also occur when patients note a new pigmented lesion, as these patients are at a 6% to 8% increased risk for primary melanoma development.
- In patients with a high mitotic rate ($\geq$10 mitosis/mm$^2$), ulceration, or positive lymph node involvement, a more frequent schedule may be considered.
- Patients at low risk for recurrence or death should be discharged to care of a dermatologist alone after five years.

**Recommendation 2**

- For patients at high risk, the following diagnostic imaging may be appropriate.

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**Qualifying Statements for Recommendation 2**

- Diagnostic testing should only be ordered if that test will result in management decisions.
- Follow-up healthcare providers should consider the appropriateness of the diagnostic imaging coupled with the health of the patient, the potential risk of accumulated radiation exposure, and the available treatment options.
Guideline 8-7

- Diagnostic imaging modalities need to be evaluated in clinical trials to assess the actual survival rate benefit.
  - Radiologic identification does not necessarily translate to a better overall survival rate.
- Patients who are considered at high risk for recurrence or death include patients with stage III and resected stage IV melanomas, as well as patients with stage IIB/C cancers with high-risk pathologic features.

| Recommendation 3 | For high-risk patients, use of routine blood work (complete blood count [CBC] and blood chemistry, including liver function) and circulating lactate dehydrogenase (LDH) is not recommended. |

**Qualifying Statements for Recommendation 3**
- Patients who are considered at high risk for recurrence or death include patients with stage III and resected stage IV melanomas, as well as patients with stage IIB/C cancers with high-risk pathologic features.

| Recommendation 4 | In conjunction with routine follow-up, healthcare providers should provide patient education regarding skin self-examination and sun safety.  
  - In particular, patients should be instructed to inspect their melanoma incision(s) and the area between their scar and the lymph node basin monthly.  
  - Patients should also be instructed to watch for any new or persistent symptoms.  
  - New and persistent symptoms should be investigated by their healthcare provider. |

| Recommendation 5 | For patients with multiple nevi, photo surveillance, using prints or digital images, may be used by dermatologists.  
  - Photos may be kept by the patient or securely at the dermatologist’s office.  
  - If photos are kept at home, patients should bring the photos to scheduled follow-up visits with the dermatologist, or when visiting the patient’s family physician.  
  - Dermatologists, with proper training, may use dermoscopy to assess suspicious lesions. |
Follow-up of Patients with Cutaneous Melanoma who were Treated with Curative Intent

Section 2: Guideline - Recommendations and Key Evidence

GUIDELINE OBJECTIVES
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RECOMMENDATIONS, KEY EVIDENCE, AND INTERPRETATION OF EVIDENCE

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- Follow-up with a dermatologist should occur every six to 12 months or as clinically indicated.

**Qualifying Statements for Recommendation 1**
- Oncologists and dermatologists have distinct skill sets and training; thus, alternating follow-up visits with both specialists is recommended.
  - Clinical follow-up with a medical, radiation, or surgical oncologist/surgeon is recommended in order to detect a local, regional, or distant melanoma recurrence and is aided by the use of imaging modalities where appropriate.
  - Clinical follow-up with a dermatologist is recommended in order to detect new primary melanomas and local recurrences of resected melanoma with the aid of specialized dermatologic imaging, full skin examinations, and photo surveillance.
- Dermatologic follow-up may also occur when patients note a new pigmented lesion, as these patients are at a 6% to 8% increased risk for primary melanoma development.
- In patients with a high mitotic rate (≥10 mitosis/mm²), ulceration, or positive lymph node involvement, a more frequent schedule may be considered.
- Patients at low risk for recurrence or death should be discharged to care of a dermatologist alone after five years.

**Key Evidence for Recommendation 1**
Neither the search for existing systematic reviews nor the systematic review of the primary literature identified any studies that compared different surveillance schedules for survivors of melanoma. Identified studies instead focused on who detected the melanoma recurrence and the associated survival rate. Studies indicated that 47% to 67% of patients detected their own recurrence [1-5]. The remainder of recurrences were detected by the follow-up healthcare provider, either during a routine clinical visit or by scheduled diagnostic imaging [1-5]. When the studies compared patients who detected their own recurrence with those who had a recurrence detected by a physician, one mixed population (prospective and retrospective) study found no survival rate difference [4], and one retrospective study found that those that detected their own recurrence based on physical findings had an improved survival rate compared with those whose recurrence was detected by physician-performed physical examination, diagnostic imaging modality, or based on symptoms [3]. For patients with stage III melanoma, based on the time to first recurrence, a retrospective cohort study [2] calculated a ≤5% risk for initial relapse at a local/in-transit or lymph node site after three years for stage IIIA patients, a ≤5% risk for stage IIIB patients after two years, and a ≤5% risk for stage IIIC patients after seven months.

**Interpretation of Evidence for Recommendation 1**
It is well established that melanoma survivors who were originally diagnosed with stage IB and IIA melanoma have a 15% to 35% risk of recurrence, while patients diagnosed with stage IIB and IIC melanoma have a 40% to 70% risk of recurrence [6]. Additionally, patients diagnosed with stage IIIB and IIIC melanoma, and those who underwent resection for stage IV disease, are at a 70% to 85% risk for relapse [2]. Other studies have found that a high mitotic rate of ≥10 mitosis/mm² is associated with a lower probability of survival [7]. Due to the lack of identified evidence, a consensus approach was used to make a recommendation. The members of the Working Group considered other clinical practice guidelines and their clinical experience, taking into account the stage of the originally diagnosed melanoma, the known recurrence rate for that stage, and the presence of ulceration, lymph node status, and mitotic rate. The British Association of Dermatologists (BAD) recommends a multidisciplinary follow-up team [6]. Using reasoning similar to the current proposed schedule, the BAD [6], German [8], Australian Cancer Network [9], National Comprehensive Cancer Network (NCCN) [10], and Swiss Melanoma [11] guidelines all base the follow-up schedule on the melanoma...
stage. At first glance it appears that the current proposed schedule is less intensive than all the other clinical practice guidelines; however, if oncologist and dermatologist follow-up visits are combined, then the proposed follow-up schedule is in-line with BAD [6], Australian [9], and NCCN [10] guidelines.

**Recommendation 2**

- For patients at high risk, the following diagnostic imaging may be appropriate.

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**Qualifying Statements for Recommendation 2**

- Diagnostic testing should only be ordered if that test will result in management decisions.
  - Follow-up healthcare providers should consider the appropriateness of the diagnostic imaging coupled with the health of the patient, the potential risk of accumulated radiation exposure, and the available treatment options.
- Diagnostic imaging modalities need to be evaluated in clinical trials to assess the actual survival rate benefit.
  - Radiologic identification does not necessarily translate to a better overall survival rate.
- Patients who are considered at high risk for recurrence or death include patients with stage III and resected stage IV melanomas, as well as patients with stage IIIB/C cancers with high-risk pathologic features.

**Key Evidence for Recommendation 2**

The limited identified evidence focused on CT, PET, PET/CT, ultrasound and chest x-ray for appropriate diagnostic imaging of melanoma recurrence or metastatic disease. An identified meta-analysis compared the diagnostic odds ratio for ultrasound, CT, PET, and PET/CT when used for surveillance of regional lymph nodes and distant metastatic sites and found that ultrasound had the highest diagnostic odds ratio for lymph node involvement and PET/CT performed best for surveillance of distant metastases [12]. Another systematic review demonstrated high sensitivity and specificity of PET for detection of relapse following curative treatment of patients with melanoma [13]. Three additional cohort studies found a diagnostic accuracy benefit for ultrasound in detection of lymph node metastases [14-16]. When comparing ultrasound with clinical examination, one study found that ultrasound had a higher sensitivity (89.2%) than clinical examination (71.4%), but this difference was not statistically investigated [15]. The second cohort study found that clinical examination plus ultrasound was significantly (p<0.0001) superior to clinical examination alone for detection of
lymph node metastases, based on an increase in both sensitivity and specificity [14]. Only two identified studies compared survival rates based on how the recurrence was detected. One found that the post-recurrence survival rate was higher for patients who self-detected their recurrence compared with those detected by diagnostic imaging modalities (p<0.001), but this was in a retrospective review that compared 109 patient detected recurrences with 41 routine chest x-ray-, CT- or PET-detected recurrences [3]. The second study found no difference in median survival rate when retrospectively comparing patients who had asymptomatic pulmonary metastases diagnosed by a routine chest x-ray, compared with those presenting with symptoms [17].

**Interpretation of Evidence for Recommendation 2**

Although ultrasound of the lymph node basin and PET/CT appear to provide some benefit, screening of the lymph node basin with ultrasound is not a routine practice in Canada. Additionally PET/CT is currently not recommended for screening purposes in Canada due to the lack of clinical evidence (PEBC PET Imaging in Melanoma Recommendation Report). However, with the rapidly changing availability of new systemic treatment modalities capable of prolonging survival in metastatic melanoma, PET/CT may play an increasingly important role in future melanoma surveillance. Of the studies identified by this systematic review, many reported on diagnostic accuracy, but only two studies investigated the survival rate benefit for recurrence and metastatic disease when detected by diagnostic imaging modalities compared with physical examination. The latest data from the Multicenter Selective Lymphadenectomy Trial (MSLT-I) indicates that early treatment following a positive sentinel lymph node biopsy, when burden of disease is low, is associated with improved survival rates [18]. Additionally, retrospective analysis of RCTs evaluating dabrafenib and trametinib combination therapy found that patients with less than 3 disease sites showed better survival [19]. Early radiologic identification may similarly translate into an overall survival rate benefit; however, without clinical trials assessing the survival rate benefit of treatment after early recurrence or progression identification by diagnostic imaging, this assumption cannot be made. A retrospective study from 2009 analyzed the radiation dose delivered by CT scans and estimated the number of number of patients that would develop a radiation-induced cancer [20]. For patients receiving routine chest CT scans at age 20, it was estimated that one in 390 women and one in 1040 men would develop a radiation-induced cancer, while for 40 year old patients, the estimates were one in 720 women and one in 1566 men [20]. When assessing patients receiving routine abdomen and pelvis CT scans, for patients at age 20, an estimated one in 500 women and one in 660 men will develop a radiation-induced cancer, and one in 930 women and one in 1002 men if receiving CT scans at 40 years of age [20]. In order to create a recommendation, members of the Working Group relied on a consensus process and weighed the ability of the test to inform the next stage of treatment and the availability of treatment options against the overuse of the test and the health of the patient.

**Recommendation 3**

- For high-risk patients, use of routine blood work (complete blood count [CBC] and blood chemistry, including liver function) and circulating lactate dehydrogenase (LDH) is not recommended.

**Qualifying Statement for Recommendation 3**

- Patients who are considered at high risk for recurrence or death include patients with stage III and resected stage IV melanomas, as well as patients with stage IIB/C cancers with high-risk pathologic features.

**Key Evidence for Recommendation 3**

A longitudinal study that enrolled high-risk patients with melanoma on adjuvant treatment...
found that for detection accuracy LDH has a low overall sensitivity of 17%, but a high specificity of 98% [21]. A second cohort study that compared LDH levels in patients with positive versus negative sentinel lymph node involvement found that LDH has no prognostic impact on overall survival rate, disease-free survival rate or distant metastasis-free survival rate and no correlation with sentinel node status [22]. There were no studies identified that reported on the use of routine blood work during follow-up care.

**Interpretation of Evidence for Recommendation 3**

The members of the Working Group are aware that the American Joint Committee on Cancer (AJCC) Melanoma Staging Database demonstrated that elevated serum LDH was a predictor of survival rate outcomes with stage IV disease, and that measurements of LDH level should be used to delineate the M1 stage into its subcategories [23]. Additionally, the monitoring of circulating LDH levels for melanoma surveillance is common practice in Ontario; however, due to the lack of data to support this decision, the Working Group is unable to recommend routine testing of circulating LDH for high-risk patients.

**Recommendation 4**

- In conjunction with routine follow-up, healthcare providers should provide patient education regarding skin self-examination and sun safety.
  - In particular, patients should be instructed to inspect their melanoma incision(s) and the area between their scar and the lymph node basin monthly.
  - Patients should also be instructed to watch for any new or persistent symptoms.
- New and persistent symptoms should be investigated by their healthcare provider.

**Key Evidence for Recommendation 4**

The literature search did not identify any studies that evaluated the benefit of skin self-examination. Identified studies focused on the percentage of survivors that were practising sun safety. A survey study reported that only 17% of survivors were conducting deliberate and systematic skin self-examinations and 23% were adherent to sun protection practices [24]. A second survey study found that 84% of survivors reported conducting a skin self-examination in the preceding year, but only 13.7% performed a thorough examination [25]. This survey also reported that 80.3% of the survivors indicated that their physician recommended skin self-examination, but only 46.1% of those physicians demonstrated how to perform a self-examination. The literature search designed to identify the signs and symptoms of melanoma recurrence, metastatic disease, and new primary melanomas also did not return any systematic reviews or studies.

**Interpretation of Evidence for Recommendation 4**

The data in these survey studies need to be considered with caution as all survey studies carry a high risk of recall bias; however, they do indicate that patient education is important in ensuring melanoma survivors practise skin self-examination and sun safety practices. With no regulated literature available to provide to patients, healthcare professionals should provide patient education regarding skin self-examination and sun safety. There are a myriad of signs and symptoms of melanoma recurrence given the numerous organ systems that may become involved with metastatic disease. The members of Working Group believe physicians in clinical practice are well versed in conducting a functional enquiry to elicit symptoms of recurrence/metastatic disease. Also, the mole examination criteria of “ABCDE” (asymmetry, border, colour, diameter, evolution), is well established in clinical practice. For these reasons and due to the lack of data in the literature, the Working Group members deemed it inappropriate to provide a list of potential signs and symptoms.

**Recommendation 5**

- For patients with multiple nevi, photo surveillance, using prints or digital images, may be
used by dermatologists.
  - Photos may be kept by the patient or securely at the dermatologist’s office.
  - If photos are kept at home, patients should bring the photos to scheduled follow-up visits with the dermatologist, or when visiting the patient’s family physician.
- Dermatologists, with proper training, may use dermoscopy to assess suspicious lesions.

Key Evidence for Recommendation 5
A cohort study, which assessed the use of dermoscopy and photo surveillance and consisting of 87% patients previously diagnosed with invasive melanoma and 13% melanoma-naïve patients, found that 38% of new melanomas were detected with the aid of photo surveillance, and 39% were detected with the aid of sequential digital dermoscopy imaging [26]. A meta-analysis of primary setting studies calculated that 348 (range, 31 to 1008) lesions needed to be monitored by dermoscopy to detect one melanoma [27]. An additional cohort study, published after the meta-analysis, followed patients who were undergoing surveillance with dermoscopy and found that of 38 lesions excised based on dermatoscopic findings, seven were melanomas in situ, four were thin invasive melanomas, and 27 were melanocytic nevi [28].

Interpretation of Evidence for Recommendation 5
The literature search did not identify any studies that assessed specifically the value of photo-surveillance or specialized dermatological imaging devices/examinations for detection of new primary melanomas in patient populations after curative treatment. When the search was extended to include patients not previously treated for melanoma, a limited number of studies were identified. Identified studies indicate that dermoscopy may be a beneficial tool for assessing pigmented lesions; however, dermatologists on the Working Group caution that use of dermoscopes requires specific training. Although the value of photo surveillance was only assessed by one identified study, the use of whole body photographs as a baseline for skin examination comparisons is a common practice among dermatologists.

RELATED GUIDELINES
Follow-up of Patients with Cutaneous Melanoma who were Treated with Curative Intent

Section 3: Guideline Methods Overview

This section summarizes the methods used to create the guideline. For the systematic review, see Section 4.

THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO). The PEBC mandate is to improve the lives of Ontarians affected by cancer through the development, dissemination, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer control.

The PEBC supports the work of Guideline Development Groups (GDGs) in the development of various PEBC products. The GDGs are comprised of clinicians, other health care providers and decision makers, methodologists, and community representatives from across the province.

The PEBC is a provincial initiative of CCO supported by the Ontario Ministry of Health and Long-Term Care (OMHLTC). All work produced by the PEBC is editorially independent from the OMHLTC.

JUSTIFICATION FOR GUIDELINE

There is substantial variability in the care provided to patients with melanoma after receiving treatment with curative intent.

GUIDELINE DEVELOPERS

This guideline was developed by the Melanoma Follow-up GDG (Appendix 1), which was convened at the request of the Melanoma Disease Site Group.

The project was led by a small Working Group of the Melanoma Follow-up GDG, which was responsible for reviewing the evidence base, drafting the guideline recommendations and responding to comments received during the document review process. The members of the Working Group had expertise in medical oncology, dermatology, radiation oncology, surgical oncology, and health research methodology. Other members of the Melanoma Follow-up GDG served as the Expert Panel and were responsible for the review and approval of the draft document produced by the Working Group. Conflict of interest declarations for all GDG members are summarized in Appendix 1, and were managed in accordance with the PEBC Conflict of Interest Policy.

GUIDELINE DEVELOPMENT METHODS

The PEBC produces evidence-based and evidence-informed guidance documents using the methods of the Practice Guidelines Development Cycle [29,30]. This process includes a systematic review, interpretation of the evidence by the members of the Working Group and draft recommendations, internal review by content and methodology experts, and external review by Ontario clinicians and other stakeholders.

The PEBC uses the AGREE II framework [31] as a methodological strategy for guideline development. AGREE II is a 23-item validated tool that is designed to assess the methodological rigour and transparency of guideline development.
The currency of each document is ensured through periodic review and evaluation of the scientific literature and, where appropriate, the addition of newer literature to the original evidence-base. This is described in the PEBC Document Assessment and Review Protocol.

PEBC guideline recommendations are based on clinical evidence, and not on feasibility of implementation; however, a list of implementation considerations such as cost, human resources, and unique requirements for special or disadvantaged populations is provided along with the recommendations for information purposes. PEBC guideline development methods are described in more detail in the PEBC Handbook and the PEBC Methods Handbook.

Search for Existing Guidelines

A search for existing guidelines is generally undertaken prior to searching for existing systematic reviews or primary literature. This is done with the goal of identifying existing guidelines for adaptation, using the ADAPTE framework [32], or endorsement in order to avoid the duplication of guideline development efforts across jurisdictions. For this project, the following sources were searched for existing guidelines that addressed the research questions:

- Guideline developer websites: European Society of Clinical Oncology (ESMO), National Institute for Health and Care Excellence (NICE), Scottish Intercollegiate Guidelines Network (SIGN), American Society of Clinical Oncology (ASCO), British Association of Dermatologists (BAD), and National Health and Medical Research Council - Australia.

The following criteria were used to select potentially relevant guidelines:

- Guidelines published after the year 2010.
- Guidelines that included a systematic review of the literature that covered at least one of the outcomes of interest.

Guidelines that were considered relevant to the objectives and the research questions were then evaluated for quality using the AGREE II instrument [31].

- A search for existing guidelines for adaptation or endorsement did not yield an appropriate source document. A search of the primary literature was required (see Section 4: Evidence Review).
- Although no identified guidelines were incorporated into the systematic review of this guideline, the recommendations for follow-up from all identified guidelines are summarized in Appendix 5 for reference. Recommendations from the National Comprehensive Cancer Network (NCCN) are also included in Appendix 5. The NCCN guideline for melanoma care is not based on a systematic review; however, the Melanoma Follow-Up GDG is aware that some physicians make use of this guideline, so recommendations were included for the sake of completeness.

Process for Consensus Recommendations

Due to a lack of evidence, members of the Working Group used a consensus process to recommend the timing of follow-up care for patients with melanoma after treatment with curative intent. The following consensus process used a modified Delphi approach for both clinical follow-up schedules in Recommendation 1, and the timing of computed tomography (CT) scan in Recommendation 2.

1. The Working Group drafted recommendations as a group at an in-person meeting.
2. The methodologist created a consensus voting form that was emailed out to all Working Group members. Each recommendation was broken into individual
Statements and members were asked to agree or disagree with each statement. The form also included a comments section for additional suggestions.

3. All statements that received 75% approval were incorporated into the consensus recommendation. Statements that did not receive 75% approval were altered based on the provided comments and were sent back out for approval.

4. Once all statements within a recommendation were approved by the group, a final voting form was emailed to the Working Group members. The voting form sought approval for each recommendation in its entirety and additional comment sections were not provided.

5. Complete recommendations that received 75% approval became final recommendations.

GUIDELINE REVIEW AND APPROVAL

Internal Review
For the guideline document to be approved, 75% of the content experts who comprise the GDG Expert Panel must cast a vote indicating whether or not they approve the document, or abstain from voting for a specified reason, and of those that vote, 75% must approve the document. In addition, the PEBC Report Approval Panel (RAP), a three-person panel with methodology expertise, must unanimously approve the document. The Expert Panel and RAP members may specify that approval is conditional, and that changes to the document are required. If substantial changes are subsequently made to the recommendations during external review, then the revised draft must be resubmitted for approval by the RAP and the GDG Expert Panel.

External Review
Feedback on the approved draft guideline is obtained from content experts and the target users through two processes. Through the Targeted Peer Review, several individuals with content expertise are identified by the GDG and asked to review and provide feedback on the guideline document. Through Professional Consultation, relevant care providers and other potential users of the guideline are contacted and asked to provide feedback on the guideline recommendations through a brief online survey. This consultation is intended to facilitate the dissemination of the final guidance report to Ontario practitioners.

ACKNOWLEDGEMENTS
The Melanoma Follow-up GDG would like to thank the following individuals for their assistance in developing this report:
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Follow-up of Patients with Cutaneous Melanoma who were Treated with Curative Intent

Section 4: Systematic Review

INTRODUCTION

Skin cancer is the most common type of cancer diagnosed in Canada [33]. Among skin cancers, melanoma has the highest mortality rate, and is the seventh most common malignancy in Canada for both men and women [33]. It is estimated that there will be 6800 new cases of melanoma in 2015 and 1150 deaths [33]. Initial curative treatment for melanoma involves surgical resection [34]. Subsequent adjuvant treatment is based on tumour stage with a focus on tumour depth of invasion, lymph node involvement, ulceration and mitotic rate [35].

While surgery and adjuvant therapy are undertaken with curative intent, there is a substantial risk of both locoregional recurrence and metastatic disease. Patients diagnosed with stage IIB and IIC melanoma have a 40% to 70% risk of recurrence [6]. Additionally, patients with curatively resected metastatic disease and those diagnosed with stage IIIB and IIIC disease are at a 70% to 85% risk for relapse [2]. Thus, melanoma survivors should be offered routine follow-up care to address three needs: detection of melanoma recurrence, detection of further primary melanomas, and to provide support, information, and education.

There is no high-quality evidence to support one surveillance schedule for follow-up care of melanoma survivors, which results in great variability in guideline recommendations from different organizations. The current authors sought to create an evidence-based follow-up protocol for survivors who have received curative-intent treatment following a diagnosis of melanoma. In order to make recommendations as part of a clinical practice guideline, the Working Group of the Melanoma Disease Site Group (DSG) developed this evidentiary base upon which those recommendations are founded. Based on the objectives of the guideline, the Working Group derived the research questions outlined below.

RESEARCH QUESTIONS

In survivors who have received curative-intent treatment for melanoma:

1. Which evaluations should be performed for surveillance of local-regional recurrence and distant metastases?
   a. At what frequency/interval should these evaluations be performed?
   b. What are the signs and symptoms of melanoma recurrence?

2. Which evaluations should be performed for detection of a new melanoma?
   a. At what frequency/interval should these evaluations be performed?
   b. Is there a value to photo-surveillance or specialized dermatological imaging devices/examinations for detection of new primary melanomas?
   c. What are the signs and symptoms of a new melanoma?

METHODS

This evidence review was conducted in two planned stages, including a search for systematic reviews followed by a search for primary literature. These stages are described in subsequent sections.

Search for Existing Systematic Reviews

A search was conducted for existing systematic reviews. Systematic reviews published as a component of practice guidelines were also considered eligible for inclusion. An
electronic search employing OVID was used to systematically search the MEDLINE and EMBASE databases for systematic reviews on the follow-up care of curatively treated patients with melanoma. OVID was searched from 2000 to week 8 of 2015 using the following keywords: “melanoma,” “malignant melanoma,” “surveillance,” “follow up,” “after care,” “survivor” and “recurrence”. In addition, websites/databases of specific guideline developers that used systematic reviews as their evidentiary base, and websites of systematic review producers, were also searched, using the same keywords and for the same time period. These websites/databases included: British Association of Dermatologists (BAD), German Cancer Society (GCS), German Dermatologic Society (GDS), French Society of Dermatology (SFD), Gruppo Italiano di Dermatologia Oncologica (GIODO), Swiss Group for Clinical Cancer Research (SAKK), Cochrane Database of Systematic Reviews (CDSR), Scottish Intercollegiate Guideline Network (SIGN), American Society of Clinical Oncology (ASCO), European Society of Clinical Oncology (ESMO) and National Comprehensive Cancer Network (NCCN). When multiple reviews were found with overlapping outcomes, only the most recent systematic review was chosen for further evaluation.

Identified systematic reviews were evaluated based on their clinical content and relevance. Relevant systematic reviews were assessed using the 11-item Assessment of Multiple Systematic Reviews (AMSTAR) tool [36] to determine whether or not existing systematic reviews met a minimum threshold for methodological quality and could be considered for inclusion in the evidence base.

Search for Primary Literature

The Working Group’s methods for locating and evaluating primary literature, if no existing systematic review were identified or if identified reviews were incomplete in some fashion, are described below. If the identified systematic reviews were incomplete, then the primary literature review might be reduced in scope (e.g. in subject areas covered, in time frames covered).

Literature Search Strategy

OVID was used to systematically search the MEDLINE and EMBASE databases for articles related to follow-up care of curatively treated patients with melanoma, published between 2000 and week 8 of 2015. A complete literature search strategy for each research question can be found in Appendix 2. In addition to the MEDLINE and EMBASE databases searches, reference lists of included systematic reviews and primary literature were scanned for potentially useful studies.

Study Selection Criteria and Process

All hits from the OVID literature search were input into reference management software (EndNote X6), where the citations underwent deduplication. Due to the limited amount of data that was expected to be found and the inability to conduct randomized trials for some of the outcomes of interest, the Working Group members searched for randomized controlled trials (RCTs), as well as non-randomized studies. However, cohort studies that enrolled less than 30 patients, as well as case series, letters, editorials, and studies not published in English were excluded from the evidentiary base. Additionally all studies, except for those that evaluated the detection accuracy of dermoscopy, had to enrol only patients with melanoma after curative-intent treatment. Since it was anticipated that very little data on dermoscopy outside of dermatologic practice would be available, while the current systematic review sought to assess its role in detection of new primary melanomas, dermoscopy studies that enrolled melanoma-naïve patients were included.
A review of the titles and abstracts that resulted from the search was done by one reviewer (LS) and verified by a second (SR). For those items that warranted full text review, one reviewer (LS) determined if the inclusion and exclusion criteria were met. The list of proposed studies was verified by a second reviewer (SR) then a final list was approved by the entire Working Group.

**Data Extraction and Assessment of Study Quality and Potential for Bias**

Data were extracted from all studies that passed full text review by one reviewer (LS) and were checked by a second reviewer (SR). All extracted data and information was audited by an independent auditor.

Important quality features, such as study design, comparison type, group allocation method, recruitment method, sources of bias, and sources of funding, were extracted for each study. Since non-randomized and diagnostic cohort studies were included in this review, no specific quality assessment tool was used. Instead the quality features listed above were extracted. For diagnostic studies, the quality features extracted were based on a modified form from the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy. For non-randomized studies, the study designs were defined by the Cochrane Collaborations schema ([Cochrane Handbook](https://www.cochrane-handbook.org) - Table 13.2a).

**Synthesizing the Evidence**

Due to the anticipated large variation in study quality and outcomes measured, a meta-analysis was not planned.

**RESULTS**

**Search for Existing Systematic Reviews**

The search for existing systematic reviews identified 35 reviews on the follow-up care of curatively treated patients with melanoma. Of the 34 systematic reviews identified by the literature search, only four [12,13,27,37] met the inclusion criteria (passed full text review). These four were assessed with the AMSTAR tool and are included in this evidence summary. The AMSTAR tool assesses 11 important features of systematic review methodology. The assessment of the four included systematic reviews with the AMSTAR tool can be found in Appendix 3. Apart from the assessment of publication bias domain, all four systematic reviews scored highly with the AMSTAR tool. The Danielsen et al systematic review [13] indicated that a formal assessment of publication could not be performed due to the small number of studies included (n=7) and a high level of heterogeneity among these studies; however, the authors elaborated on sources of bias within the discussion section of the review. Mocellin et al. [37] did not report on conflict of interest, but met all other AMSTAR criteria. Danielsen et al. [13], Salerni et al. [27], and Xing et al. [12] did not indicate that duplicate study selection and data extraction were employed, but met all other criteria. It is also worth mentioning however that the AMSTAR tool was designed to assess systematic reviews of RCTs and that all four of the assessed reviews included studies of a lower design quality.

**Search for Primary Literature**

The primary literature systematic review was used to address outcomes of interest not covered by the included systematic reviews. Additionally, where systematic reviews existed, a search of the primary literature was conducted from the end date of the search in the reviews.
**Literature Search Results**

Nineteen studies were identified that met inclusion criteria (Figure 1). Table 1 summarizes the number and types of studies included per research question for each intervention of interest. Both systematic reviews and primary studies were identified for all research questions (Table 1). For Research Question 1, systematic reviews that evaluated measurement of S100 calcium-binding protein B (S100B) [37] and diagnostic imaging modalities [12,13] for recurrence detection accuracy were identified, so the primary literature was searched for studies using these modalities after the search dates of the Mocellin et al. [37], Xing et al. [12], and Danielsen et al. [13] systematic reviews. For Research Question 2, one systematic review which assessed the detection accuracy of dermoscopy for primary melanomas was identified [27], so the primary literature was searched for studies involving dermoscopy after the search dates of the Salerni et al. systematic review. For Research Questions 1 and 2, primary studies over the entire planned search period (2000 to present) constituted the evidentiary base for the remaining outcomes of interest (Table 1).
Potentially relevant citations identified by initial electronic search: 
n=3393

Citations excluded after title review: 
n=2621

Citations included in abstract review: 
n=772

Citations excluded after abstract review: 
n=632

Studies included in full text review: 
n=140

Studies excluded after full-text review: 
n=117

29 - Inappropriate methodology ¥
28 - Narrative review
9 - Study outcome covered by existing systematic review
36 - Outcomes of interest not addressed
15 - Studies with quality of life as main outcome

Studies included in evidentiary base: 
n=23

Existing Systematic Review, n=4
Primary Literature, n=19
4 - Before-and-after comparisons
3 - Comparative cohort studies
10 - Retrospective studies
2 - Surveys

Figure 4-1. Selection of systematic reviews and primary literature from the search results of MEDLINE and EMBASE. Note: ¥ indicates studies of inappropriate methodology including preliminary reports, histological studies, studies that were non-comparative and non-longitudinal, and studies enrolling fewer than 30 patients.

Table 4-1. Studies selected for inclusion.

<table>
<thead>
<tr>
<th>Research Question</th>
<th>Intervention</th>
<th>Number of systematic reviews and studies by type [ref]</th>
</tr>
</thead>
</table>
| Q1. Evaluations for detection of local-regional recurrence and distant metastases | Clinical follow-up | 2 - Comparative study [15]* [14]*
| | | 5 - Retrospective study [1-5]
| | Imaging modalities (US, CT, PET, PET/CT) | 2 - Systematic review (SR) [12,13]
| | | 2 - Comparative study [15]* [14]*
| | | 4 - Retrospective study [16,17,38,39]
| | Laboratory tests (LDH and S100B) | 1 - SR [37]
| | | 1 - Comparative study [22]
| | | 2 - Before-and-after comparison [21,40]
| | | 1 - Retrospective study [41]
| | Skin self-examination | 2 - Survey [24]* [25]*
Study Design and Quality

The primary literature returned 19 studies that met the inclusion and exclusion criteria. A description of the study design and quality of the studies can be found in Appendix 4. The evidentiary base was comprised of moderate to low quality study designs and no randomized controlled trials. Of the 19 included studies, seven used a prospective design [14,15,21,22,26,28,40] and 10 relied on a retrospective design [1-5,16,17,38,39,41] (Figure 1, Table 1). The remaining two studies used a survey design [24,25] (Figure 1, Table 1). When evaluating the quality of diagnostic studies, the Program in Evidence-based Care (PEBC) endorses the methods described in the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy. The six prospective non-randomized studies were further defined using the Cochrane Collaborations schema (Handbook Table 13.2a) as before-and-after comparisons [21,28,40] and comparative cohort studies [14,15,22] (Table 1, Appendix 4). It is well recognized that prospective data collection studies are of better methodological quality than retrospective studies (considered low quality) and as such, the prospective studies will carry more weight when developing recommendations. In addition to using prospective data collection, the before-and-after comparisons collected data longitudinally and compared data across time within the cohort, while the comparative cohort studies compared the survivor group with a control group. It is still worth noting however that all non-randomized studies carry an unclear risk of bias and are of moderate methodological quality, which was considered when drafting the recommendations. Lastly, the two survey studies [24,25] used questionnaires answered in the home, which result in an increased risk of recall bias, as survivors were required to recall actions performed over a period of time. They are also considered to be of low quality (Appendix 4). All seven prospective cohort studies, 10 retrospective studies, and two survey studies were included in the evidentiary base.

Interventions and Outcomes

The results are organized by intervention category within each research question. For interventions where all study types were identified, meta-analyses will be presented first, followed by prospective cohort studies, then diagnostic studies, retrospective cohort studies, and finally, survey studies. For interventions where only some study types were identified, those types not identified will be omitted. When meta-analyses have been identified, the additional primary literature only contains studies published since the search date of the meta-analysis. All included studies are detailed fully in text and summarized in tables where appropriate. Outcomes of interest included recurrence detection accuracy, new primary detection accuracy, survival rate (overall survival rate, recurrence-free survival rate, disease free survival rate, and distant metastasis-free survival rate), quality of life (QoL), signs and/or symptoms of recurrence or new primary disease, and change in treatment or treatment plan.

<table>
<thead>
<tr>
<th>Research Question</th>
<th>Intervention</th>
<th>Number of systematic reviews and studies by type [ref]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q2. Evaluations for detection of new melanomas</td>
<td>Dermoscopy/Dermatoscope</td>
<td>1 - SR [27]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 - Before-and-after comparison [26,28]</td>
</tr>
<tr>
<td></td>
<td>Skin self-examination</td>
<td>2 - Survey [24]* [25]*</td>
</tr>
</tbody>
</table>

Abbreviations: CT, computed tomography; LDH, lactate dehydrogenase; PET, positron emission tomography; S100B, S100B calcium-binding protein B; SR, systematic review; US, ultrasound.

*Denotes studies that appear under more than one intervention.
Question 1: Which evaluations should be performed for surveillance of local-regional recurrence and distant metastases? At what frequency/interval should these evaluations be performed? What are the signs and symptoms of melanoma recurrence?

Three systematic reviews with meta-analyses were identified to inform this research question. One meta-analysis assessed the detection accuracy of ultrasound, computed tomography (CT), positron emission tomography (PET), and PET/CT [12], while the second focused on PET [13], and the third assessed the prognostic value of S100B [37]. The systematic review of the primary literature identified 18 studies; five focused on clinical follow-up [1-5], three assessed diagnostic imaging modalities [17,38,39], two compared clinical follow-up with imaging modalities [14,15], four assessed the prognostic value of S100B or lactate dehydrogenase (LDH) [21,22,40,41], and the final two focused on the prevalence of skin self-examination among melanoma survivors [24,25]. Although included in the design of the literature search, the search did not identify any studies that assessed any of the outcomes of interest for brain scan with magnetic resonance imaging (MRI), blood work, electrolyte levels or liver function. Additionally, the literature search was designed to identify signs and symptoms of local-regional recurrence and distant metastases, but no studies were identified.

**Clinical Follow-up**

A cohort study with a mixed retrospective and prospective design compared frequency of first melanoma recurrence detected by patient with first melanoma recurrence detected by physician [4]. The study included 211 patients that were originally diagnosed with stage I, II or III melanoma and presented with a first melanoma recurrence. For the prospectively enrolled patients, information regarding who detected both the original primary melanoma and the first recurrence was collected over the telephone, while medical records were used for the retrospectively enrolled patients. Of the 211 patients, 67% (n=141) of patients detected the first melanoma recurrence themselves and 6% (n=13) had their recurrence detected by their spouse, while 27% (n=57) of patients had their recurrence detected by their physician (Table 2). Almost 75% of the cohort (n=157) experienced symptoms of the recurrence, with 61 of the patients detecting their recurrences based on the symptoms. Of the 57 patients with a physician-detected recurrence, 50 were found during a scheduled follow-up visit. There was no statistically significant survival rate difference between the patient-detected melanoma recurrence group and the physician-detected melanoma recurrence group.

A retrospective review of a prospective database study also focused on method of recurrence detection [3]. The study reviewed the records of 1062 patients who had been diagnosed with stage I or II melanoma and who had undergone sentinel lymph node biopsy (SLNB). After curative-intent surgery, patients were followed with physical examination every three or four months in year 1, every three to six months in year 2 and every six to 12 months thereafter. Patients also received a chest x-ray every six to 12 months in years 1 to 3, as well as serum LDH and a complete blood count annually in years 1 to 3, and CT and PET scans on a selection basis as clinically indicated. Of the 1062 enrolled patients, 203 (19%) patients recurred with 230 recurrences. Only 198 were followed long-term and could be included in the data analysis. Just over half the patients (55%; n=109/198) detected their own recurrence, with the majority noticing physical findings and not symptoms (Table 2). Of the 109 patients with self-detected recurrence, 75 (69%) of them were seen by their physician prior to their scheduled visit due to recurrence suspicion. The remaining 89 (45%) patients had their recurrence detected by their physician (Table 2). Of the 89 recurrences detected by a physician, 52% were detected by a physical examination, while the remaining were detected by scheduled chest x-ray (n=14; 16%), CT (n=26; 29%), or PET (n=1; 1%). An
additional 2% (n=2/89) of recurrences by physicians were detected by an abnormal blood test. When analysing sites of recurrence, 58% (n=56/97) of local, in-transit and nodal recurrences were patient detected compared with physician detected, while 52% (n=53/101) of systemic recurrences were patient detected. Patients with self-detected recurrences based on physical findings had improved survival rates (median, 37 months) compared with those detected by symptoms only (median, 7 months), those detected by physician physical examination (median, 29 months) or those detected by diagnostic imaging modalities (median, 9 months; p<0.001).

A second retrospective review of a prospective database analysed the method of recurrence detection in 83 patients with stage II and 35 patients with stage III melanoma who were followed for at least two years [5]. All patients were treated within one institution and were followed by a surgical oncologist, dermatologist or surgical nurse practitioner every three months in years 1 through 3, then every six months in years 3 to 5, then at least annually until year 10. At scheduled follow-up visits, patients received full-body examination of the skin and lymph node basins. Additionally, patients received annual routine blood work, including LDH, as well as annual chest x-ray in patients with stage II melanoma and annual routine body and brain imaging in years 1 to 3 with CT, PET/CT, or MRI for patients with stage III melanoma. A recurrence was defined as patient detected if the survivor sought care outside of the scheduled follow-up due to new symptoms. Recurrences were defined as either local (within 3 cm), in-transit, regional lymph node basin, or distant. After 14 months (median), 43 patients developed recurrences, four with local recurrence, 17 with in-transit recurrence, seven with regional lymph node recurrence, and 15 with distant recurrence. Of the 43 recurrences, 29 (67%) recurrences were patient detected or symptomatic, while 11 (26%) were detected by a physician at a routine follow-up visit (Table 2). The remaining three were detected by a diagnostic imaging modality, two with chest x-ray and one with a brain MRI in asymptomatic patients (Table 2).

A third retrospective cohort study reviewed the pathology records of patients to determine who identified melanoma recurrence [1]. The study reviewed the records of 94 patients who were diagnosed with any type of recurrence. No data on clinical follow-up interval or type of follow-up healthcare provider was included in the study. Almost half of the recurrences were detected by the patient (n=45; 47.9%), while 31.9% (n=30) were detected by the healthcare provider during the clinical follow-up visit, and 11.7% (n=11) of recurrences were diagnosed when patients were admitted to emergency facilities with metastatic disease.

The final retrospective cohort study evaluated the timing and method of first relapse detection in patients with stage III melanoma [2]. The study reviewed the records of 340 patients, 95 (28%) of whom were diagnosed with stage IIIA, 155 (46%) with stage IIIB, and 90 (26%) with stage IIIC disease. Patients received scheduled follow-up clinical visits with a medical oncologist every three months for the first two years after curative-intent treatment, then every six months. CT scans, complete blood counts, comprehensive panels, and LDH tests were completed prior to the clinical follow-up visit. Patients also received visits with a surgical oncologist and a dermatologist, but the schedule was not reported. For all patients, the first site of relapse was most likely to occur at systemic sites (51%), followed by local/in-transit (28%) and within the nodal basin (21%). For patients with stage IIIA melanoma, almost all local/in-transit and modal recurrences occurred by 40 months, while systemic recurrences occurred up to 71 months following treatment. For stage IIIB patients, the majority of first recurrences occurred by 36 months post-treatment irrespective of site. Finally, for patients with stage IIIC melanoma, almost all recurrences occurred by 24 months. These values translated into a ≤5% risk for initial relapse at a local/in-transit or lymph node site after three years for stage IIIA patients, a ≤5% risk for stage IIIB patients after two years, and a ≤5% risk
for stage IIIC patients after seven months. The study also assessed the method of first relapse detection and found that patients and/or family members discovered 62.5% of local and in-transit recurrences, while 36.5% were detected by a physician during the scheduled follow-up visit, and 1% were detected by imaging. For nodal recurrences, 48.6% were detected by the patient and/or a family member, 26.4% by a physician, and 25% by imaging. When first relapse occurred at systemic sites, it was self-detected by 37.4% of patients, detected 9.2% of the time by physicians, and 53.4% of the time by imaging.

Table 4-2. Method of recurrence detection

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design</th>
<th>Sample Size</th>
<th>Stage of Primary Melanoma</th>
<th>Method of Recurrence Detection</th>
</tr>
</thead>
</table>
| Auckland et al, 2014 [1]| Retrospective review of patient records           | n = 94      | Not reported              | • 47.9% (n=45) self-detected  
• 31.9% (n=30) physician-detected during clinical visit  
• 11.7% (n=11) admitted to emergency with metastatic disease  
• 8.5% (n=8) detected by other means (mostly incidental findings) |
| Francken et al, 2007 [4]| Mixed prospective and retrospective cohort       | n = 211     | Stage I, II or III        | • 67% (n=141) self-detected  
• 6% (n=13) detected by spouse  
• 27% (n=57) physician-detected during clinical visit |
| Dalal et al, 2008 [3]   | Retrospective review of prospective database      | n = 198     | Stage I or II             | • 55% (n=109) self-detected  
• 45% (n=89) physician-detected  
  o 52% (n=46) by physical exam  
  o 16% (n=14) by scheduled chest x-ray  
  o 29% (n=26) by scheduled CT  
  o 1% (n=1) by scheduled PET  
  o 2% (n=2) by abnormal blood test |
| Meyers et al, 2009 [5]  | Retrospective review of prospective database      | n = 118     | Stage II (n=74), stage III (n=35), or unknown (n=9) | • 67% (n=29/43) self-detected or symptomatic  
• 26% (n=11/43) physician-detected with clinical exam  
• 7% (n=3/43) with scheduled chest x-ray or brain MRI |
| Romano et al, 2010 [2]  | Retrospective review of patient records           | n = 340     | Stage IIIA (n=95), stage IIIB (n=155), stage IIIC (n=90) | • Local/in-transit recurrence  
  o 62.5% (n=62/99) self-detected or detected by a family member  
  o 36.5% (n=36/99) detected by physician with physical exam  
  o 1% (n=1/99) detected by scheduled imaging  
• Nodal recurrence  
  o 48.6% (n=48/78) self-detected or detected by a family member  
  o 26.4% (n=26/78) detected by physician with physical exam  
  o 25.0% (n=25/78) detected by scheduled imaging  
• Systemic recurrence  
  o 37.4% (n=37/163) self-detected or |
Study Design
Sample Size
Stage of Primary Melanoma
Method of Recurrence Detection

- detected by a family member
  - 9.2% (n=15/163) detected by physician with physical exam
  - 53.4% (n=87/163) detected by scheduled imaging

Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography.

**Diagnostic Imaging Modalities**

One systematic review evaluated studies assessing the diagnostic value of PET for detecting of relapse during melanoma follow-up [13]. The systematic review pooled seven studies that were published between 1999 and 2013 and specifically employed PET with a fluorodeoxyglucose (FDG) tracer. Review authors constructed a 2x2 contingency table of summed values for true positive, true negative, false positive, and false negative results across six studies to calculate pooled sensitivity and specificity values. The pooled mean sensitivity for the studies was 96% (95% confidence interval [CI], 92-98%) and the pooled mean specificity was 92% (95%CI, 87-95%) for discriminating relapse from no relapse.

An identified systematic review with meta-analysis evaluated the detection accuracy of ultrasonography, CT, PET and PET/CT when used for staging and surveillance of regional lymph nodes and distant metastatic sites [12]. The meta-analysis pooled 74 studies that were published between 1990 and 2009 and assessed ultrasonography (n=21), CT (n=13), PET (n=45), and/or PET/CT (n=13). For staging of regional lymph nodes, ultrasound demonstrated the highest sensitivity (60%; 95% credible interval [CrI], 33-83%), specificity (97%; 95%CrI, 88-99%), and diagnostic odds ratio (OR, 42; 95%CrI, 8.08-249.8). When analysing staging of distant metastases, PET/CT had the highest sensitivity (80%; 95%CrI, 53-93%), specificity (87%; 95%CrI, 54-97%), and diagnostic OR (25; 95%CrI, 3.58-198.7). Similar findings were calculated when analysing melanoma surveillance of lymph node involvement, with ultrasonography having the highest sensitivity (96%; 95%CrI, 85-99%), specificity (99%; 95%CrI, 95-100%), and diagnostic OR (1675; 95%CrI, 226.6-15,920). Similar findings appear when analyzing surveillance of distant metastases, with PET/CT once again having the highest sensitivity (86%; 95%CrI, 76-93%), specificity (91%; 95%CrI, 79-97%) and diagnostic OR (67; 95%CrI, 20.42-229.7).

A retrospective review of a prospective database evaluated the accuracy of surveillance chest x-ray for detection of asymptomatic pulmonary metastases in melanoma patients with a positive SLNB [17]. The study reviewed the records of 108 high risk patients, who had been diagnosed with stage IIIA/B melanoma and a positive SLNB and had been prospectively enrolled into a chest x-ray monitoring program. The study excluded patients who were previously treated with chemotherapy or radiotherapy for melanoma. Patients received a scheduled chest x-ray every six months for five years, then annually for an additional five years. On the same day, patients also received a physical examination before the chest x-ray was conducted. The physical examination included a medical history, inspection of the primary melanoma site, inspection of the lymph node dissection sites and palpation of any relevant lymph node fields. The reference standard for pulmonary metastases was a positive histopathology diagnosis from a fine needle aspirate (FNA) of the lung lesion. If the chest x-ray found a suspicious lesion, a chest CT was arranged within seven days, while PET imaging and FNA was arranged within one month. Of the 108 patients, 23 (21%) developed pulmonary metastases, which were detected 48% (n=11/23) of the time by surveillance chest x-ray and led to resection of three (13%; n=3/23) asymptomatic patients.
Based on 19 false positives and 12 false-negatives, the sensitivity of chest x-ray for detection of pulmonary metastases was 48% (95%CI, 0.27-0.68) and the specificity was 78% (95%CI, 0.77-0.79). The study found no significant difference in the median time to detection of pulmonary metastases when comparing chest x-ray (24 months [m]; 95%CI, 12-41m) with clinical follow-up detection of symptomatic disease (16m; 95%CI, 10-30m; p=0.3). There was also no significant difference in median survival for symptomatic (36m; 95%CI, 18-46m) compared with asymptomatic (42m; 95%CI, 24-84m; p=0.53) patients. Pulmonary metastases most often occurred in the first three years.

A retrospective review assessed the utility of restaging patients with stage IIB to IIIC melanoma at year 3 of follow-up care [38]. Patients (n=52) who had undergone routine restaging head CT or MRI and torso CT scans three years after completion of local-regional therapy or initiation of adjuvant therapy were identified from a larger database. Of the 52 patients who received head CT or MRI, there was one false positive and no true positive scans, while torso CT scans resulted in three false positives and two true positives. True positives were verified by symptomatic recurrence within one week of positive imaging.

Another retrospective study evaluated the impact of FDG PET/CT on restaging and management of patients with melanoma [39]. The study reviewed medical records of 78 patients and compared treatment planning before and after restaging with FDG PET/CT. All 78 patients were restaged before PET/CT and then again after, with histology and clinical follow-up used to verify the findings. Before PET/CT imaging, 14.1% of the patients (n=11/78) were restaged as having local recurrence, 29.5% (n=23/78) as locoregional recurrence and 56.4% (n=44/78) as distant recurrence. Following PET/CT, two patients were upstaging from local recurrence; however, both of these were false-positives. False negative images occurred in two different patients. Change in patient management occurred in 24.4% (n=19/78) of patients.

A final retrospective study evaluated the diagnostic accuracy of ultrasound compared with ultrasound-guided fine-needle aspiration biopsy (FNAB) in the assessment of suspicious recurrent lymph nodes [16]. The study reviewed the medical records of 480 patients who underwent ultrasound-guided FNAB to verify ultrasound imaging. Compared with FNAB results, ultrasound demonstrated a sensitivity of 95% and a specificity of 55.7%.

**Clinical Follow-up Compared with Imaging Modality**

A comparative cohort study evaluated the diagnostic accuracy of ultrasonography for regional lymph node metastases when compared with clinical exam [15]. The study enrolled 1288 patients who had been diagnosed with histologically confirmed melanoma. Patients received regular follow-up, consisting of medical history and physical examination every three months for five years, followed by every six months until year 10. Additionally, patients received ultrasound of the resection scar, lymphatic drainage area and regional lymph node regions once a year for low-risk melanoma patients and every three to six months for patients who had a resected local, in-transit or lymph node metastasis. All ultrasound appointments were preceded by clinical examination and included inspection and palpation of the same areas that were to be imaged with ultrasound. For the clinical examination, enlarged and/or firm lymph nodes or subcutaneous nodules were considered potential metastases. Findings for both clinical examination and ultrasound imaging were verified by histology. Of the total population, there were 263 positive findings, which were verified by surgery in 154 patients. Clinical examination had a false negative rate of 28.6% (n=68/238), with a sensitivity of 71.4% and a specificity of 99.7%. Ultrasound imaging demonstrated a sensitivity of 89.2% and a specificity of 99.7%.

A second prospective study compared clinical examination plus ultrasound with clinical examination alone for detection of lymph node metastases [14]. The study enrolled 433
survivors who were originally diagnosed with melanoma in situ, stage IA or IB, stages IIA to IIC, stages IIIA to IIB or stage IV melanoma. Survivors received follow-up care at intervals based on the stage of their original melanoma, but in general, patients received a clinical visit every three or six months. However, if suspicious findings were reported by the patient or noticed by the attending physician, the clinical examination and ultrasound were conducted earlier than the next scheduled follow-up appointment. The clinical visit included a medical history, clinical examination, and ultrasound. The clinical examination consisted of inspection and palpation of the scar, lymphatic draining area, and regional lymph nodes and always occurred before the ultrasound. All findings were verified by histology of an entirely removed lymph node or a FNA sample. For the clinical examination, findings were defined as false negative when lymph node metastases were detected by the ultrasound only and verified by histology and findings were defined as false positive when clinically suspicious lesions were clearly benign on the ultrasound. For ultrasound, findings were defined as false negative when histologically confirmed metastases were diagnosed within one follow-up visit following a negative combined clinical examination and ultrasound visit, while false positive were defined as lesions deemed suspicious by clinical examination and ultrasound but not confirmed by histology. A total of 23 patients and 33 lymph node metastases were diagnosed. Clinical examination alone had a sensitivity of 33.33% (95%CI, 17.96-51.83%), and a specificity of 96.07% (95%CI, 94.87-97.06%), with a positive predictive value of 17.74% and a negative predictive value of 98.27%. Clinical examination plus ultrasound raised (p<0.0001) the sensitivity to 93.94% (95%CI, 79.77-99.26%) and specificity to 98.08% (95%CI, 97.17-98.75%), with a positive predictive value of 55.36% and a negative predictive value of 99.84%, indicating that clinical examination plus ultrasound is superior to clinical examination alone for detection of lymph node metastases. When stages were analysed separately, it appeared that added ultrasound is advantageous for patients with stage I (p=0.0389), stage III (p=0.0101) and stage IV (p=0.0016) melanoma.

Table 4-3. Diagnostic accuracy of imaging modalities and clinical examination

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design</th>
<th>Sample Size</th>
<th>Imaging Modality</th>
<th>Diagnostic Accuracy</th>
</tr>
</thead>
</table>
| Danielsen et al, 2014 [13] | Systematic review             | n = 415 across six studies | FDG PET, FDG PET/CT | • Pooled mean sensitivity of 96% (95%CI, 92-98%)  
                          |                                |                       |                                   | • Pooled mean specificity of 92% (95%CI, 87-95%)                                    |
| Xing et al, 2011 [12] | Meta-analysis                 | n = 10,528 across 74 studies | Ultrasound, CT, PET, and PET/CT | • Regional lymph nodes:  
                          |                                |                       |                                   | o Highest diagnostic OR for ultrasound (1675; 95%Crl, 226.6-15,920)               |
|                 |                                |                       |                                   | • Distant metastases:  
                          |                                |                       |                                   | o Highest diagnostic OR for PET/CT (67; 95%Crl, 20.42-229.7)                     |
| Morton et al, 2009 [17] | Retrospective review of prospective database | n = 108 high-risk patients | Scheduled chest x-ray | • Sensitivity of 48% (95%CI, 0.27-0.68)  
                          |                                |                       |                                   | • Specificity of 78% (95%CI, 0.77-0.79)                                           |
|                 |                                |                       |                                   | • 48% (n=11/23) of pulmonary metastases detected by scheduled chest x-ray in asymptomatic patients |
|                 |                                |                       |                                   | • No difference in median survival rate for asymptomatic compared with symptomatic patients |
| DeRose et al, 2011 [38] | Retrospective review of patient records | n = 52 | CT or MRI of head and torso CT | • Head CT: 4% false-positive rate and sample size too small to calculate true-positive  
                          |                                |                       |                                   | • Head MRI: sample size too small to calculate false-positive and true-positive     |
## Laboratory Tests

A systematic review with meta-analysis assessed the ability of S100B level to predict survival rate in patients with melanoma [37]. The meta-analysis pooled 22 studies with a total of 3,393 patients who had been diagnosed with stage I through stage IV melanoma. Analysis determined that patients that tested positive for S100B had a significantly poorer survival rate (hazard ratio (HR), 2.23; 95%CI, 1.92-2.58; p<0.0001). However, the included studies were significantly heterogeneous ($I^2$, 99%; p<0.0001) with no single study being responsible for heterogeneity. In order to find a hazard ratio based on non-homogeneous studies, Mocellin et al conducted a subgroup analysis of only patients with stage I to III melanoma and calculated a hazard ratio of 2.28 (95%CI, 1.8-2.89; p<0.0001).

A before-and-after comparison followed 670 high risk-patients on adjuvant radiation therapy (RT) treatment to determine the overall survival rate and recurrence-free survival rate as a consequence of S100B [40]. Patients were enrolled in the E1694 adjuvant trial and had sera collected at baseline (before treatment) and after initiation of adjuvant RT during specific week ranges (weeks: 4-6, 12-14, 48-52). The median follow-up time was 7.8 years (range, 1.4-10.6 years). When analysing the entire group, the median overall survival (OS) rate was 7.2 years (95%CI, 6.0 years -not reached), while the recurrence-free survival (RFS) rate was 3.1 years (95%CI, 2.4-3.7 years), based on assessment of 667 patients, 408 of whom experienced relapse before publication of the study. At baseline, the median serum S100B level was 0.08µg/L (range, 0.02-1.54µg/L; n=670). Based on a univariate analysis, a baseline S100B of ≥0.15µg/L was significantly correlated with OS (p=0.01) but not significantly associated with RFS (p=0.062). A multivariate analysis (Cox model) was also conducted and accounted for baseline S100B level, node involvement, ulceration and treatment. The multivariate analysis found that a S100B baseline level above 0.15µg/L was significantly

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<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design</th>
<th>Sample Size</th>
<th>Imaging Modality</th>
<th>Diagnostic Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blum et al, 2000 [15]</td>
<td>Comparative cohort n = 1,288 cohort n = 154 developed lymph node metastases</td>
<td>Ultrasound compared with clinical examination</td>
<td>• Clinical examination:  o Sensitivity of 71.4%  o Specificity of 99.7%  • Ultrasound:  o Sensitivity of 89.2%  o Specificity of 99.7%</td>
<td></td>
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<tr>
<td>Kruger et al, 2011 [14]</td>
<td>Comparative cohort n = 433 cohort n = 23 developed lymph node metastases</td>
<td>Clinical examination compared with clinical examination plus ultrasound</td>
<td>• Clinical examination:  o Sensitivity of 33.33% (95%CI, 17.96-51.83%)  o Specificity of 96.07% (95%CI, 94.87-97.06%)  • Clinical examination plus ultrasound:  o Sensitivity of 93.94% (95%CI, 79.77-99.26%)  o Specificity of 98.08% (95%CI, 97.17-98.75%)</td>
<td></td>
</tr>
<tr>
<td>Solivetti et al, 2014 [16]</td>
<td>Retrospective cohort n = 340</td>
<td>Ultrasound</td>
<td>• Sensitivity of 95%  • Specificity of 55.7%</td>
<td></td>
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</tbody>
</table>

Abbreviations: CI, confidence interval; Crl, credible interval; CT, computed tomography; FDG, fluorodeoxyglucose; MRI, magnetic resonance imaging; n, sample size; OR, odds ratio; PET, positron emission tomography.
associated with OS (HR, 1.39; 95%CI, 1.01-1.92; p=0.043), but not RFS. Additionally, the study conductors separated the population into three groups based on S100B levels and conducted subgroup analyses. Patients in group A had S100B levels that were below 0.15µg/L at baseline and any later time points (n=378), group B included patients with S100B levels of ≥0.15µg/L at any time (n=71), and group C included patients with S100B levels of <0.15µg/L at baseline and then an increase above 0.15µg/L at any time point (n=162). Group A had a median OS that was not reached (95%CI, 7 years - not reached) and a median RFS of 4.6 years (95%CI, 3.5-6.0 years). Group B had a median OS of 7.8 years (95%CI, 4.7-not reached) and median RFS of 4.3 years (95%CI, 1.5-7.0 years). Finally, group C had a median OS of 7.0 years (95%CI, 4.5 years - not reached) and a median RFS of 2.4 years (95%CI, 1.7-5.0 years). When looking at only OS, there was a significant difference between groups A and C (p=0.048) but not across all three groups. When looking at only RFS, there was again a significant difference between groups A and C (p=0.017), but not across all three groups. A Cox regression model, which adjusted for node involvement, ulceration, and treatment, indicated that S100B is a significant predictor of death (HR, 1.44; 95%CI, 1.06-1.95; p=0.0210) and relapse (HR, 1.70; 95%CI, 1.21-1.92; p<0.001).

A second before-and-after comparison assessed the usefulness of LDH and S100B assessment in high risk patients [21]. The study enrolled 97 patients with stage II or III melanoma who were participating in adjuvant treatment clinical trials. The study population was divided into three groups; group A included patients with a tumour thickness greater than 1.5mm and clinically negative lymph nodes, group B included patients with in-transit skin metastases and/or recurrent lymph node metastases, and group C included patients with clinically detectable lymph node metastases. Patients in group A received follow-up care that consisted of physical examination and blood evaluations every three months for the first three years, then every six months until the end of study, plus chest x-ray and abdomen ultrasound once a year. In contrast, patients in groups B and C received physical examination and blood evaluations every three months through year 5, plus CT of chest and abdomen, MRI of brain and bone scan twice a year for five years. The overall median follow-up time was 30 months and 52 (53.6%) patients developed locoregional and/or distant metastases. When analysing the detection accuracy of S100B, overall it demonstrated a sensitivity of 37% (95%CI, 23-50%) and a specificity of 98% (95%CI, 97-100%), with a positive predictive value of 73% (95%CI, 56-90%). Analysis of LDH indicated that LDH has an overall sensitivity of 17% (95%CI, 7-28%) and specificity of 98% (95%CI, 97-100%), with a positive predictive value of 64% (95%CI, 39-80%). Although both low, the sensitivity of S100B was significantly higher than LDH for detection of metastases (p=0.006) and this was most pronounced in patients who had progressed to stage IV (S100B sensitivity, 53.8% vs. LDH sensitivity, 23.1%; p=0.008).

A comparative cohort study evaluated the value of serum S100B and LDH when comparing patients with positive and negative sentinel lymph node status [22]. The study enrolled 259 patients prior to sentinel lymph node dissection and assessed OS, disease-free survival (DFS) rate and distant metastasis-free survival (DMFS) rate. Mean follow-up time was 27.1 months. Of the total population, 17% (n=44/259) had micrometastases of the sentinel node, with 31 patients (12%) having only one sentinel node involved, and 13 patients (5%) with two or more sentinel nodes containing melanoma cells. Univariate analysis determined that neither S100B nor LDH had a prognostic impact on OS, DFS or DMFS. Additionally, there was no correlation between sentinel node status and pre-dissection S100B or LDH levels. A retrospective review of 127 patients with recurrence compared S100B with diagnostic imaging modalities to assess recurrence detection [41]. The included patients had undergone S100B level evaluations in parallel with imaging. Upon melanoma recurrence detection, the patients had received ultrasound of lymph node and abdomen plus chest x-ray for melanomas smaller than 4mm and PET for melanoma larger than 4mm. Before PET was
available at the treatment centre, patients underwent CT scans for melanomas larger than 4mm. At the time of recurrence, 37% of patients (n=47/127) had elevated S100B levels. Of the 127 with recurrence, 15 had local recurrence and 27% of those (n=4/15) had increased S100B levels, while 10 had in-transit melanomas with 40% (n=4/10) also having increased S100B. An additional 60 patients had progressed to stage III with nodal metastases and 32% (n=19/60) of these patients had increased S100B. Finally, 42 patients had developed distant metastases, with 48% of them (n=20/42) having increased S100B. S100B was the first indicator of recurrence in 5.5% of the cases. Diagnostic imaging modalities detected recurrence in 26.8% (n=34/127) of the patients (ultrasound: 6; PET: 12; CT: 13; PET/CT: 3; chest x-ray: 0).

**Skin Self-Examination**

A survey study invited 148 melanoma survivors to participate in a 30 minute telephone interview to determine the percentage of survivors that complete skin self-examination [24]. The interview was designed to assess if survivors were performing deliberate and systematic skin self-examination at least once every two months on their arms and face, front of legs, side of body, back of legs, side of legs, bottom of feet, back of thighs, upper back and shoulders, and middle and lower back. The telephone interview was conducted between nine and 30 months after melanoma diagnosis. The interview additionally assessed sun protection strategies, including frequency of sunscreen use on sunny summer days, sun protection factor (SPF) of sunscreen (if used), wearing a hat, shade seeking and use of protective clothing when outside on sunny summer days for more than one hour. Of the 148 survivors invited, 78% completed the interview. Of those that participated, 17% conducted deliberate and systematic skin self-examinations and 23% were adherent to sun protection practices. A slim majority of survivors (57%) were always or nearly always using sunscreen on sunny summer days, with an average SPF of 25.

A second survey also sought to determine skin self-examination and sun protection practice, knowledge and attitude among melanoma survivors [25]. The study enrolled 229 survivors at a follow-up visit. Survivors were asked to fill in the questionnaire and return it by mail. The questionnaire was designed to assess both non-psychological measures, such as demographics, health history and access to care, melanoma knowledge (based on a 23-item melanoma knowledge scale), skin self-examination guideline knowledge, and whether their doctor recommended skin self-examination and sun protection, as well as psychological measures, including perceived melanoma risk for recurrence, distress, skin self-examination benefits and barriers, sun protection benefits and barriers, perceived melanoma severity and sun protection practice norms for family and friends. Outcomes measured included frequency and thoroughness of skin self-examination, stage of adoption for skin self-examination (precontemplation, contemplation, relapse risk, action), sun protection practice, and sun protection stage of adoption. Of the 229 patients enrolled, 84.3% reported conducting a skin self-examination at least once in the past year, but only 13.7% performed a thorough exam. The majority of survivors used sunscreen (59.4%), made a conscious effort to seek shade (53.2%) and wore sunglasses (70.7%), while slightly less than the majority wore a hat (44.5%) or long-sleeved shirt (44.9%). When the study conductors evaluated physician recommendations, the questionnaire indicated that 80.3% of physicians recommended that survivors perform skin self-examination, but only 46.1% demonstrated how to perform a self-examination and only 70.2% showed the survivor what a lesion looks like. Additionally, 81.5% of physicians recommended sunscreen use, while only 72.2% suggested sun avoidance, and 70.0% suggested wearing a hat or long sleeves.
Signs and Symptoms of Recurrence
The literature search did not return any systematic reviews or studies that evaluated common signs or symptoms of melanoma recurrence.

Ongoing Studies
Ongoing studies were searched through https://clinicaltrial.gov with no studies identified.

Question 2: Which evaluations should be performed for detection of a new melanoma? At what frequency/interval should these evaluations be performed? Is there a value to photo-surveillance of specialized dermatological imaging devices/examinations for detection of new primary melanomas? What are the signs and symptoms of a new melanoma?

One systematic review with meta-analyses, which assessed the detection accuracy of dermoscopy for new primary melanomas, was identified to inform this research question [27]. Two additional studies assessed the detection accuracy of digital dermoscopy [26,28] and two surveys focused on the prevalence of skin self-examination among melanoma survivors [24,25]. Although included in the design of the literature search, the search did not identify any studies involving clinical follow-up frequency, circulating S100B and LDH, electrolyte levels, or liver function in the detection of new primary melanomas. Additionally, the literature search was designed to identify signs and symptoms of new melanomas, but no studies apart from changes on dermoscopy were identified.

Dermoscopy
A systematic review with meta-analysis evaluated the number of lesions needed to be monitored (NNM) to detect one melanoma with dermoscopy [27]. The meta-analysis pooled data from 14 studies that enrolled a total of 5,787 patients with 52,739 lesions. The majority of studies enrolled patients being followed with dermoscopy following a diagnosis of atypical mole syndrome. Data extracted from the studies included number of patients enrolled, number of lesions monitored, mean number of lesions monitored per patient, length of follow-up, number of lesions excised, histopathology diagnosis of excised lesions, benign/malignant ratio, and number of patients diagnosed with melanoma. When all studies were pooled, 12 lesions (mean, range 1-35) were monitored per patient. Studies used either devices that allowed for recording of both total body photography and digital dermoscopy images for comparative analysis of sequential images (five studies with MoleMax, one study with Fotofinder), or devices that allowed for recording and comparison of dermoscopic images, locating lesions in diagrams of the human body, but with no body photos (two studies with SolarScan, one study with Dermogenius Ultra, one study with Hikoscope), or both types of devices (three studies used Fotofinder and Hikoscope, one study used MoleMax and Videocap). The mean NNM across all studies was 348 (range, 31-1008) with less than 1 lesion excised per patient. A regression analysis indicated that the number of melanomas detected during follow-up with dermoscopy correlated with the median length of follow-up (p=0.002), where the longer the length of follow-up, the more melanomas that were detected.

A before-and-after comparison evaluated the frequency of characteristics of dermatologic changes using digital dermatoscope [28]. The study enrolled and followed 121 patients with a total of 1,027 melanocytic nevi. To be included in the study, patients needed to have 50 or more melanocytic nevi on the trunk and/or the proximal parts of extremities and five or more clinically atypical nevi, plus at least one additional risk factor. Risk factors could be personal or family history of melanoma, phototype I skin, repeated sunburns, immunosuppression, and/or presence of melanocytic nevi in double-ultraviolet-protected
body area (areas covered by underwear). Enrolled patients were divided into melanoma positive and melanoma negative subgroups based on prior melanoma diagnosis, but the two groups were not compared. Patients were monitored clinically and dermatoscopically with the microDERM digital dermatoscopic system, at baseline, every six months (±1 month) for the first year, then every six to 12 months (±1 month). A total of 38 monitored lesions were excised due to dermatoscopic findings. Seven of the lesions were melanomas in situ, four were thin invasive melanomas and 27 were melanocytic nevi.

A prospective cohort study followed individuals at high risk for primary melanomas with dermoscopy and photo surveillance [26]. The study enrolled 311 patients, 271 of whom had been diagnosed with a previous invasive melanoma. Each patient underwent a full skin examination and dermoscopy evaluation at baseline and then was followed every six months by the dermatologist using the same full-body examination schedule with the aid of the baseline images. The photographs were both stored at the dermatologist’s office and provided to the patient to take home. There were 75 new primary melanomas detected during follow-up. Of the newly diagnosed melanomas, 38% were detected with the aid of the total-body photography and 39% were detected with the aid of sequential digital dermoscopy imaging.

**Skin Self-Examination**

The two survey studies that assessed skin self-examination practice among melanoma survivors were fully described under Research Question 1. In brief, one survey found that 17% of enrolled survivors conducted deliberate and systematic skin self-examinations and 23% were adherent to sun protection practices [24]. The second survey demonstrated that of the 229 enrolled survivors, 84.3% reported conducting a skin self-examination at least once in the past year, but only 13.7% performed a thorough examination [25].

**Signs and Symptoms of New Primary Melanoma**

The literature search did not return any systematic reviews or studies that evaluated common signs or symptoms of a new primary melanoma.

**Ongoing Studies**

Ongoing studies were searched through https://clinicaltrial.gov with no studies identified.

**DISCUSSION**

**Clinical Follow-up**

The original literature search was designed to identify studies that compared different surveillance schedules for survivors of melanoma. Unfortunately, both the search for existing systematic reviews and the systematic review of the primary literature did not identify any such evidence. Due to this lack of evidence, surveillance protocols must necessarily be based on individual risk of recurrence and established best practice. It is well established that melanoma survivors who were originally diagnosed with stage IB and IIA melanoma have a 15% to 35% risk of recurrence, while those diagnosed with stage IIB and IIC melanoma have a 40% to 70% risk of recurrence [6]. Furthermore, patients with melanoma who were diagnosed with stage IIIB or IIIC disease, and those who have undergone resection for stage IV disease, are all at high risk of developing recurrent metastatic disease [6]. Additionally, a study that assessed mitotic rate in patients with melanoma has indicated that a high mitotic rate (≥20 mitosis/mm²) is associated with a lower probability of survival [7]. Other known risk factors
for increased risk of developing melanoma recurrence include positive lymph node involvement and the presence of ulceration [42].

Studies that were identified by the systematic review of the primary literature indicated that 47% to 67% [1-5] of patients detected their own recurrence. The remaining recurrences were detected by the follow-up healthcare provider, either during a routine clinical visit or by scheduled diagnostic imaging [1-5]. When the studies compared patients who detected their own recurrence with those who had a recurrence detected by a physician, one mixed population (prospective and retrospective) study found no difference in survival rate [4], and one retrospective study found that those who detected their own recurrence based on physical findings had an improved survival rate compared with those whose recurrence was detected by physician-performed physical examination, diagnostic imaging modality, or based on symptoms [3]. Based on the time to first recurrence, the Romano et al retrospective cohort study [2] calculated a ≤5% risk for initial relapse at a local/in-transit or lymph node site after three years for patients with stage IIIA melanoma, a ≤5% risk for patients with stage IIIB melanoma after two years, and a ≤5% risk for patients with stage IIC melanoma after seven months. Additional retrospective research out of the scope of the systematic review, but which may help frame the recommendations has indicated that for patients with stage I and II melanoma, a less frequent monitoring schedule only resulted in a minimal delay in diagnosis of recurrence or a new primary tumour [43].

Due to the lack of evidence, the members of the Working Group used a consensus approach to make a recommendation for clinical follow-up of melanoma survivors. Full details of the consensus process are outlined in Section 3 of this guideline document. When creating the recommendation, the Working Group members considered clinical practice guidelines from other organizations and their own clinical experience, taking into account the stage of the originally diagnosed melanoma, and the presence of ulceration, lymph node status and mitotic rate. Although the Melanoma Disease Site Group cannot recommend an evidence-based surveillance schedule, the group members suggest that routine clinical follow-up should occur in a shared care model with an oncologist and a dermatologist, and that clinical visits should always include a medical history and physical examination. Patients who received treatment with curative-intent for an in situ melanoma should undergo a full skin examination by their dermatologist annually. Similarly, patients diagnosed with a stage IA melanoma should have scheduled visits with their dermatologist every six to 12 months, or as clinically indicated. For patients who were diagnosed with stage IIIA melanoma as well as with high risk IIIB and IIC disease based on pathologic features (ulceration and high mitotic rate), follow-up schedules should include a clinical visit with an oncologist every six months in years 1 through 3, followed by annually until year 5. These patients should also receive follow-up visits with a dermatologist every six to 12 months, or as clinically indicated. Patients who were diagnosed with stage IIIB to IIIC and resected stage IV melanoma should receive a scheduled clinic visit with an oncologist every three months to six months in years 1 through 3, followed by every six months in years 4 and 5, or as clinically indicated. These patients, who are at a high risk for second melanomas, should also be followed by a dermatologist every six to 12 months or as clinically indicated. The recommendations are grouped by stage; however, in patients with a high mitotic rate, ulceration, or positive lymph node involvement, the frequency of clinical follow-up visits may be increased at the healthcare provider’s discretion. It is important to note here that oncologists and dermatologists have distinct skill sets and training, leading to the recommendation for follow-up with both specialists. Lifelong follow-up with the dermatologist may also be recommended at the discretion of the physician.

A systematic review that compared stage-specific surveillance schedules from several countries indicated that schedules vary considerably [44]. The Melanoma Follow-up Working
Group similarly found great variability in the recommendations provided by identified clinical practice guidelines. Appendix 5 summarizes recommendations proposed by the American Academy of Dermatology (AAD) [45], British Association of Dermatologists (BAD) [6], European Society of Medical Oncology (ESMO) [46], German Cancer Society and German Dermatologic Society [8], Australian Cancer Network [9], National Comprehensive Cancer Network (NCCN) [10], and the Swiss Melanoma Guidelines [11]. Of the identified clinical practice guidelines, only the BAD guideline [6] similarly recommends a multidisciplinary follow-up team, which has been noted above, is a very important component of follow-up in the opinion of the members of the Melanoma Disease Site Group. Also similar to the current proposed schedule, the BAD [6], German [8], Australian [9], NCCN [10], and Swiss [11] guidelines all base the follow-up schedule on the melanoma stage. At first glance it appears that the current proposed schedule is less intensive than all the other clinical practice guidelines; however, if oncologist and dermatologist follow-up visits are combined, then the proposed follow-up schedule is in-line with BAD [6], Australian [9], and NCCN [10] guidelines.

Diagnostic Imaging Modalities

Very limited evidence was identified for appropriate diagnostic imaging in a melanoma survivor population. The studies that were identified focused on CT, PET, PET/CT, ultrasound and chest x-ray. Unfortunately, of the studies identified, many reported on diagnostic accuracy, but very few reported on an actual survival benefit associated with any imaging modality compared with another modality or with physical examination alone. An identified meta-analysis compared the diagnostic odds ratio for ultrasound, CT, PET, and PET/CT when used for surveillance of regional lymph nodes and distant metastatic sites and found that ultrasound had the highest diagnostic odds ratio for lymph node involvement while PET/CT performed best for surveillance of distant metastases [12]. Another systematic review demonstrated high sensitivity and specificity of PET for detection of relapse following curative treatment of melanoma patients [13]. Three additional prospective cohort studies found a benefit for ultrasound in detection of lymph node metastases [14-16]. When compared with clinical examination, one study found that ultrasound had a higher sensitivity than clinical examination, but this difference was not statistically investigated [15]. The second cohort study found that clinical examination plus ultrasound was significantly (p<0.0001) superior to clinical examination alone for detection of lymph node metastases, based on an increase in both sensitivity and specificity [14]. Although ultrasound appears to provide some detection benefit, screening of the lymph node basin with ultrasound is not in routine practice in Canada. Additionally, although PET/CT may appear to have some benefit in the early detection of metastases, in Canada PET/CT is currently not recommended for routine screening purposes due to the lack of clinical evidence. A recent meta-analysis, which was not included in this systematic review as it investigated PET in a staging setting, examined the ability of PET to detect systemic metastases in patients with stage III melanoma, demonstrated a high sensitivity (89.42%; 95%CI, 65.07-97.46) and specificity (88.78%; 95%CI, 77.04-94.91) for PET in detecting metastases and resulted in a change in the management of 22% of patients [47]. This data along with the rapidly changing availability of new systemic treatment modalities capable of prolonging survival rates in metastatic melanoma, leads us to suggest that PET/CT may play an increasingly important role in future in melanoma surveillance. Further trials are necessary before firm recommendations can be made.

The members of the Working Group are concerned about the lack of evidence in this area, especially the lack of evidence investigating the survival rate benefit for recurrence and metastatic disease when detected by diagnostic imaging modalities compared with physical examination alone. Only one identified study compared survival based on how the recurrence
was detected and found that the post-recurrence survival rate was higher for patients who self-detected their recurrence compared with recurrences detected by diagnostic imaging modalities (p<0.001), but this was in a retrospective review that compared 109 patient detected recurrences with 41 that were detected by routine imaging with chest x-ray, CT or PET [3]. With treatments for recurrence and metastatic disease evolving, the detection of recurrent disease at an earlier stage with diagnostic imaging modalities may be of increasing benefit. In fact, the latest data from the Multicenter Selective Lymphadenectomy Trial (MSLT-I) indicates that early treatment following a positive SLNB, when burden of disease is low, is associated with an improved survival rate [18]; however, with the available current treatment options, and without survival data from diagnostic imaging studies, the benefit is not yet clear. Additionally, it is known that CT scans can lead to accumulated radiation doses in patients and potentially radiation-induced malignancies. For patients receiving routine chest CT scans at age 20, a retrospective study which analyzed radiation dose delivered by CT and the correlation with developing of new cancer, estimated that one in 390 women and one in 1040 men would develop a radiation-induced cancer, while for 40 year old patients, the estimates were one in 720 women and one in 1566 men [20]. When assessing patients receiving routine abdomen and pelvis CT scans, for patients at age 20, an estimated one in 500 women and one in 660 men will develop a radiation-induced cancer, and one in 930 women and one in 1002 men if receiving CT scans at 40 years of age [20]. Thus members of the Working Group are concerned about the overuse of diagnostic tests that do not affect patient management. In order to create a recommendation, the Working Group members once again relied on a consensus process (Section 3) and weighed the ability of the test to inform the next stage of treatment and the availability of treatment options against the overuse of the test and its effect on the health of the patient. The appropriateness for each diagnostic imaging modality is summarized in Table 4. The BAD [6], ESMO [46], the NCCN [10], and the German [8] guidelines make similar recommendations for CT+/PET surveillance for high-risk patients. Similarly, ultrasound surveillance of the lymph node basin where appropriate is recommended by the German [8], Australian [9], and Swiss [11] guidelines (Appendix 5).

### Table 4-4. Diagnostic imaging modalities for melanoma follow-up care

<table>
<thead>
<tr>
<th>Diagnostic Test</th>
<th>Notes</th>
</tr>
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<tbody>
<tr>
<td>CT scan</td>
<td>• CT scan of the chest, abdomen and pelvis every 12 months (or as clinically indicated) may be appropriate in patients at high risk for recurrence or death.</td>
</tr>
<tr>
<td>Chest x-ray</td>
<td>• Only appropriate when CT scan cannot be performed.</td>
</tr>
<tr>
<td>CT/MRI of brain</td>
<td>• Appropriate at baseline and as clinically indicated.</td>
</tr>
<tr>
<td>Bone scan</td>
<td>• Not routinely recommended unless clinically indicated.</td>
</tr>
<tr>
<td>PET scan</td>
<td>• Could be considered, as per the <a href="#">PEBC PET Imaging in Melanoma Recommendation Report</a>.</td>
</tr>
</tbody>
</table>
| Ultrasound      | • May be appropriate for surveillance within the lymph node basin or as clinically indicated.  
  • Useful when CT scan cannot be performed. |

Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography.

### Laboratory Tests

According to the American Joint Committee on Cancer (AJCC) melanoma staging and classification system, patients with stage IV melanoma should have their serum LDH levels measured to delineate the M1 stage into its subcategories [23]. The role of LDH in the
surveillance of patients with melanoma after curative intent treatment therefore was of great interest to the members of the Working Group. A literature search was also performed to evaluate laboratory tests during follow-up care and was designed to identify studies assessing serum levels S100B, total blood counts, liver function, and electrolytes. The only studies identified however focused on S100B and LDH. Since S100B testing is not routinely available in Canada, only the studies that assessed LDH levels were considered to inform the recommendation on laboratory testing for melanoma survivors. A longitudinal study that enrolled high-risk melanoma patients on adjuvant treatment found that for detection accuracy LDH has a low overall sensitivity of 17%, but a high specificity of 98% [21]. A second cohort study that compared LDH levels in patients with positive versus negative sentinel lymph node involvement found that LDH has no prognostic impact on overall survival rate, disease-free survival rate, or distant metastasis-free survival rate and no correlation with sentinel node status [22]. The Melanoma Disease Site Group members are aware that the use of routine blood work, including complete blood count (CBC) and blood chemistry, as well as circulating LDH is common practice for melanoma surveillance in Ontario; however, due to the lack of evidence to support this practice, the Melanoma Disease Site Group is unable to recommend routine blood work or circulating LDH for high-risk patients.

Photo Surveillance and Specialized Dermatological Imaging Devices/Examinations

The members of the Working Group were interested in determining if there is a role for photo-surveillance and specialized dermatological imaging devices/examination in a melanoma survivor population for detection of new primary melanomas. Unfortunately, it was known that there would be no studies conducted for the population of interest, so the literature search for this intervention was expanded to include melanoma-naive individuals as well as patients with melanoma. The literature search identified one meta-analysis and two cohort studies that were published after the meta-analysis. The meta-analysis calculated that 348 (range, 31-1008) lesions needed to be monitored by dermoscopy to detect one melanoma [27]. In one cohort study, 87% of enrolled patients had been previously diagnosed with an invasive melanoma, but these patients were not analyzed separately from the melanoma-naive patients [26]. For all patients, the study found that 38% of new melanomas were detected with the aid of photo surveillance, and 39% were detected with the aid of sequential digital dermoscopy imaging [26]. The second cohort study followed patients who were undergoing surveillance with dermoscopy and found that of 38 lesions excised based on dermatoscopic findings, seven were melanomas in situ, four were thin invasive melanomas and 27 were melanocytic nevi [28]. The identified literature indicates that dermoscopy may be a beneficial tool for assessing pigmented lesions; however, dermatologists in the Working Group caution that use of dermatoscopes requires specific training. Although the value of photo-surveillance was only assessed by one identified study, for patients with multiple nevi, the use of whole body photographs as a baseline for skin examination and surveillance is a common practice among dermatologists.

Patient Education

Since it has been well established that a substantial portion of recurrences are self-detected by melanoma survivors, the current review examined the prevalence of skin self-examination and sun protection techniques among melanoma survivors. One identified survey study reported that only 17% of survivors were conducting deliberate and systematic skin self-examinations and 23% were adherent to sun protection practices [24]. A second survey study found that 84% of survivors reported conducting a skin self-examination in the preceding year, but only 13.7% performed a thorough examination [25]. This survey also reported that 80.3% of the survivors indicated that their physician recommended skin-self examination, but only
46.1% demonstrated how to perform a skin self-examination. The data in these studies need to be considered with caution as all survey studies carry a high risk of recall bias; however, they do indicate that patient education is important in ensuring melanoma survivors practise skin self-examination and sun safety practices. With no regulated literature available to provide to patients, healthcare professionals should provide patient education regarding skin self-examination and sun safety. Patient education should focus on self-examination for local recurrence, in-transit metastatic disease, and loco-regional adenopathy. The importance of promoting self-examination is underscored by the finding that two-thirds of patients currently detect their own recurrences and that early detection of curable disease will necessarily alter patient outcome.

**Signs and Symptoms of Recurrence, Metastatic Disease, or New Primary Melanoma**

Unfortunately, the literature search designed to identify the signs and symptoms of melanoma recurrence, metastatic disease and new primary melanomas did not return any systematic reviews or studies. The signs and symptoms of melanoma recurrence are myriad given the numerous organ systems that may become involved with metastatic disease. Physicians in clinical practice are well versed in conducting a functional enquiry to elicit symptoms of recurrence/metastatic disease. Also, the mole examination criteria of “ABCDE” (asymmetry, border, colour, diameter, evolution) is well established in clinical practice. For this reason, and due to the lack of data in the literature, the members of the Working Group, upon approval by the Melanoma Disease Site Group, deemed it inappropriate to provide a list of potential signs and symptoms in their expert opinion.

**CONCLUSIONS**

Patients with melanoma in follow-up care should receive scheduled visits with both their treating oncologist and their dermatologist to ensure detection of recurrences and new primary melanomas. Published evidence to inform this guideline was very limited. Without high-quality studies that evaluate follow-up surveillance schedules, the authors of this guideline are left to rely on clinical experience, taking into consideration primary disease stage and risk factors for recurrence. The lack of high-quality evidence is also apparent when seeking to recommend appropriate diagnostic imaging modalities for both recurrence and new primary melanomas. Studies that assess the overall survival rate benefit of individual imaging modalities are needed in addition to studies that assess only the diagnostic accuracy of the available modalities. As more effective treatments become available for the management of metastatic and recurrent melanoma, the need for evaluation of the benefit of tests allowing for early detection of recurrence is underscored. Finally, since many patients with melanoma detect their own recurrence after curative-intent treatment, it is imperative that patients receive education on prevention and detection from their oncologist and dermatologist.
Follow-up of Patients with Cutaneous Melanoma who were Treated with Curative Intent

Section 5: Internal and External Review

INTERNAL REVIEW
The guideline was evaluated by the Guideline Development Group (GDG) Expert Panel and the Program in Evidence-based Care (PEBC) Report Approval Panel (RAP) (Appendix 1). The results of these evaluations and the Working Group’s responses are described below.

Expert Panel Review and Approval
Of the 11 members of the GDG Expert Panel, nine members cast votes and two abstained, for a total of 81.2% response in April 2015. Of those that cast votes, nine approved the document (100%). The main comments from the Expert Panel and the Working Group’s responses are summarized in Table 1.

Table 5-1. Summary of the Working Group’s responses to comments from the Expert Panel.

<table>
<thead>
<tr>
<th>Comments</th>
<th>Responses</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. What is the recommendation for stage IIIB-C and resected stage IV after 5 years of diagnosis?</td>
<td>We have added a Qualifying Statement to Recommendation 1 that states low-risk patients can be discharged to dermatologic care after five years.</td>
</tr>
<tr>
<td>2. We do indicate that follow up with dermatology should be every 6-12 months or as clinically indicated, but we do not have a time line for this follow-up. Is this life-long or 5 years or at discretion of dermatologist?</td>
<td>The length of follow-up is at the discretion of the dermatologist. A Qualifying Statement that states this has been added to Recommendation 1.</td>
</tr>
<tr>
<td>3. I think there is no evidence to support the inclusion of Stage IIB/C patients into recommendation 2 regarding CT scans every 12 months.</td>
<td>We have changed the recommendation to indicate only high-risk patients should be followed with CT scans every 12 months. Only stage IIB/C patients with high-risk pathologic features are included.</td>
</tr>
<tr>
<td>4. Key evidence for Recommendation 4 discusses how many patients actually do skin surveillance and really does not discuss the benefit of doing it.</td>
<td>No literature was found. We added this fact to the Key Evidence of Recommendation 4.</td>
</tr>
<tr>
<td>5. As newer therapies become available to treat metastatic melanoma, early detection of the disease will be the key. Many of the studies available were done in the era when melanoma treatment was limited. How do we take this into consideration?</td>
<td>Discussion of this topic has been added to the Discussions within Section 4.</td>
</tr>
</tbody>
</table>

Abbreviations: CT, computed tomography.

RAP Review and Approval
Three RAP members, including the PEBC Director, reviewed this document in March 2015. The RAP did not approve the document. After revision by the GDG Working Group, the RAP reviewed the document again in July 2015 and approved the document. The main comments from the RAP and the Working Group’s responses are summarized in Table 2.
Table 5-2. Summary of the Working Group’s responses to comments from the RAP.

<table>
<thead>
<tr>
<th>Comments</th>
<th>Responses</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. I am assuming the frequency of follow-up visits is based on the timing of most recurrences but this is never stated.</td>
<td>We have added timing of recurrence data to the Key Evidence for Recommendation 1.</td>
</tr>
<tr>
<td>2. From a policy perspective, it unclear the specific purpose/goal of the dermatology and the oncologist. What is the unique role of each discipline?</td>
<td>We have added a Qualifying Statement to Recommendation 1 which outlines the goal of follow-up with both an oncologist and a dermatologist.</td>
</tr>
<tr>
<td>3. Two of the research questions, Ib and Iic, are specifically addressed and stated that there is no literature. Yet Recommendation 4 makes no mention of this and is not specifically incorporated into Recommendation 4. Recommendation 4 reads as though there is data to support specific signs and symptoms.</td>
<td>We have added to the Key Evidence of Recommendation 4 that no studies were identified.</td>
</tr>
<tr>
<td>4. In recommendation 5, dermoscopy ‘may be used’ but they make no mention if it is useful or not, required, better than the rest, etc.</td>
<td>We have altered the Interpretation of Evidence to indicate that dermoscopy may be beneficial for following pigmented lesions.</td>
</tr>
</tbody>
</table>

EXTERNAL REVIEW
External Review by Ontario Clinicians and Other Experts

Targeted Peer Review
Six targeted peer reviewers from Ontario, Alberta, and British Columbia, who are considered to be clinical and/or methodological experts on the topic, were identified by the Melanoma Follow-Up GDG. Three agreed to be the reviewers (Appendix 1) and review responses were received from all three. Results of the feedback survey are summarized in Table 5-3. The comments from targeted peer reviewers and the Working Group’s responses are summarized in Table 5-4.

Table 5-3. Responses to nine items on the targeted peer reviewer questionnaire.

<table>
<thead>
<tr>
<th>Question</th>
<th>Lowest Quality (1)</th>
<th>(2)</th>
<th>(3)</th>
<th>(4)</th>
<th>Highest Quality (5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Rate the guideline development methods.</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Rate the guideline presentation.</td>
<td></td>
<td>3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Rate the guideline recommendations.</td>
<td>1</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Rate the completeness of reporting.</td>
<td></td>
<td>2</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Does this document provide sufficient information to inform your decisions? If not, what areas are missing?</td>
<td></td>
<td></td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Rate the overall quality of the guideline report.</td>
<td></td>
<td></td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. Does this document provide sufficient information to inform your decisions? If not, what areas are missing?</td>
<td>Strongly Disagree (1)</td>
<td>(2)</td>
<td>Neutral (3)</td>
<td>(4)</td>
<td>Strongly Agree (5)</td>
</tr>
</tbody>
</table>
7. I would make use of this guideline in my professional decisions. | 2 | 1 |
8. I would recommend this guideline for use in practice. | 1 | 2 |

9. What are the barriers or enablers to the implementation of this guideline report?

Barriers:
1) The frequency of follow-up visits and the partnering of oncologists and dermatologists may lead to staffing and space limitations in the centres.
2) Making the guidelines universally available and somehow ensuring they are read proactively is the biggest barrier to implementation.

| Table 5-4. Responses to comments from targeted peer reviewers. |
| Comments | Responses |
| 1. I found the layout of the recommendations too dense (too bunched up) and this makes it hard to read. Bullet formation may be better suited at least for the specific recommendations. | The Working Group agreed that the recommendations would be more readable as bulleted points. The Recommendations in Section 1 and 2 have been reformatted to reflect this decision. |
| 2. With respect to the recommendation regarding the use of diagnostic and functional imaging in surveillance, there is no mention of potential detrimental effects, such as cumulative radiation exposure and patient anxiety. | Recommendation 2 is only targeted for patients with a high risk of recurrence, for whom detection of recurrent disease may outweigh the potential risk of accumulated radiation exposure. The first Qualifying Statement for Recommendation 2 has been altered to direct healthcare providers to consider the risk of potential accumulated radiation exposure when considering the health of the patient and the available treatment options. |
| 3. Regarding Recommendation 2 I think most physicians are still happy with a basic CXR and US of the abdomen for routine staging imaging when it is necessary. The guideline makes it sound that CT scan and nothing but is appropriate. The cost of this imaging modality and the radiation exposure of this test needs to be considered as well. Furthermore, we prefer a PET CT scan. | The Working Group disagrees with this comment given the limited data that does show the superiority of CT to both ultrasound and chest x-ray. Additionally there was no identified evidence to back a recommendation for PET in a surveillance setting. |
| 4. The reason for not likely using the guidelines is because I am a dermatologist who plays an active role in the treatment and follow-up of melanoma patients. The guidelines here have relegated me to a peripheral player. I am certain other dermatologists who are active in the management of melanoma like me would feel the same way. | The Recommendations were drafted with the goal of making dermatologists and oncologists partners. When originally drafted, each Recommendation either directly mentioned a role for dermatologists, or deliberately used “healthcare provider” to include both dermatologists and oncologists. As such, the Working Group was surprised by this comment. The second Qualifying Statement for Recommendation 1 has been altered to indicate that dermatologist follow-up may also occur when patients note a new pigmented lesion, as the role of the dermatologist was not obvious in the Qualifying Statement previously. |
Professional Consultation

Feedback was obtained through a brief online survey of healthcare professionals and other stakeholders who are the intended users of the guideline. All individuals in the PEBC database who had indicated interest in survivorship and melanoma, systemic treatment and melanoma, radiation and melanoma, surgery and melanoma, primary care and melanoma, imaging and melanoma, nursing and melanoma, or post-treatment follow-up and melanoma, were contacted by email to inform them of the survey. Sixty-six professionals who practise in Ontario and one professional who practises in Saskatchewan were contacted. Fourteen (20.9%) responses were received. Three stated that they did not have interest in this area or were unavailable to review this guideline at the time. The results of the feedback survey from 11 people are summarized in Table 5-5. The main comments from the consultation and the Working Group’s responses are summarized in Table 5-6.

Table 5-5. Responses to four items on the professional consultation survey.

<table>
<thead>
<tr>
<th>General Questions: Overall Guideline Assessment</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Rate the overall quality of the guideline report.</td>
<td>Lowest Quality (1)</td>
</tr>
<tr>
<td></td>
<td>1 (9.1%)</td>
</tr>
<tr>
<td>2. I would make use of this guideline in my professional decisions.</td>
<td>Strongly Disagree (1)</td>
</tr>
<tr>
<td></td>
<td>1 (9.1%)</td>
</tr>
<tr>
<td>3. I would recommend this guideline for use in practice.</td>
<td></td>
</tr>
<tr>
<td>4. What are the barriers or enablers to the implementation of this guideline report?</td>
<td>Barriers:</td>
</tr>
</tbody>
</table>

Table 5-6. Modifications/Actions taken/Responses regarding main written comments from professional consultants.

<table>
<thead>
<tr>
<th>Comments</th>
<th>Responses</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Clarification of whether oncology visits and dermatology visits should be staggered would be helpful. Visits every 6 months are recommended for most stages. If visits are staggered, patients are in effect being examined every three months by an expert. Is this the intent? Patients at times complain if they are seeing two physicians for the same purpose at the same time especially if they are well and further along in their recovery</td>
<td>Both Recommendation 1 and the Qualifying Statement for Recommendation 1 have been altered to make it clear that visits should be alternating.</td>
</tr>
</tbody>
</table>
CONCLUSION

The final guideline recommendations contained in Section 2 and summarized in Section 1 reflect the integration of feedback obtained through the external review processes with the document as drafted by the GDG Working Group and approved by the GDG Expert Panel and the PEBC RAP.
References


19. Author. Title. Presented at: Conference Name; Year of Conference; Date; Conference Location.


Appendix 1: Members of the Melanoma Follow-up Guideline Development Group

### Working Group Members

<table>
<thead>
<tr>
<th>Name and Expertise</th>
<th>Affiliation</th>
<th>Conflict of Interest</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sudha Rajagopal, Medical Oncologist</td>
<td>Credit Valley Hospital Peel Regional Cancer Centre Mississauga, ON</td>
<td>No conflict declared</td>
</tr>
<tr>
<td>Tara Baetz, Medical Oncologist</td>
<td>Cancer Centre of Southeastern Ontario Kingston General Hospital Kingston, ON</td>
<td>No conflict declared</td>
</tr>
<tr>
<td>Alexandra Easson, Surgical Oncologist</td>
<td>Princess Margaret Hospital Toronto, ON</td>
<td>No conflict declared</td>
</tr>
<tr>
<td>Jadranka Jambrosic, Dermatologist</td>
<td>Toronto, ON</td>
<td>No conflict declared</td>
</tr>
<tr>
<td>Gregory Knight, Medical Oncologist</td>
<td>Grand River Regional Cancer Centre Kitchener, ON</td>
<td>Financial support for conferences from two pharmaceutical companies</td>
</tr>
<tr>
<td>Elaine McWhirter, Medical Oncologist</td>
<td>Juravinski Cancer Centre Hamilton, ON</td>
<td>No conflict declared</td>
</tr>
<tr>
<td>Cheryl Rosen, Dermatologist</td>
<td>Toronto Western Hospital Toronto, ON</td>
<td>No conflict declared</td>
</tr>
<tr>
<td>Alexander Sun, Radiation Oncologist</td>
<td>Princess Margaret Hospital Toronto, ON</td>
<td>No conflict declared</td>
</tr>
<tr>
<td>Wadid Abadir, Dermatologist</td>
<td>Toronto, ON</td>
<td>No conflict declared</td>
</tr>
<tr>
<td>Frances Wright, Surgical Oncologist</td>
<td>Sunnybrook Cancer Centre Toronto, ON</td>
<td>No conflict declared</td>
</tr>
<tr>
<td>Teresa Petrella, Medical Oncologist</td>
<td>Odette Cancer Centre Toronto, ON</td>
<td>No conflict declared</td>
</tr>
<tr>
<td>Lesley Souter, PEBC Methodologist</td>
<td>Juravinski Hospital Hamilton, ON</td>
<td>No conflict declared</td>
</tr>
</tbody>
</table>

### Report Approval Panel Members

<table>
<thead>
<tr>
<th>Name and Expertise</th>
<th>Affiliation</th>
<th>Conflict of Interest</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melissa Brouwers, PhD Director, Program in Evidence-based Care</td>
<td>Cancer Care Ontario Toronto, ON</td>
<td>No conflict declared</td>
</tr>
<tr>
<td>Laurie Elit Gynecology Oncologist</td>
<td>Juravinski Cancer Centre Hamilton, ON</td>
<td>No conflict declared</td>
</tr>
<tr>
<td>Donna Maziak Surgical Oncologist</td>
<td>Ottawa Hospital Ottawa, ON</td>
<td>No conflict declared</td>
</tr>
</tbody>
</table>

### Expert Panel Members

<table>
<thead>
<tr>
<th>Name</th>
<th>Affiliation</th>
<th>Conflict of Interest</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pablo Cano</td>
<td>Northeastern Ontario Regional Cancer Centre Sudbury, ON</td>
<td>No conflict declared</td>
</tr>
<tr>
<td>Annette Cyr</td>
<td>Melanoma Network of Canada Toronto, ON</td>
<td>No conflict declared</td>
</tr>
<tr>
<td>Danny Ghazarian</td>
<td>Toronto General Hospital Toronto, ON</td>
<td>No conflict declared</td>
</tr>
<tr>
<td>Caroline Hamm</td>
<td>Windsor Regional Cancer Centre Toronto, ON</td>
<td>No conflict declared</td>
</tr>
<tr>
<td>Timothy Hanna</td>
<td>Cancer Research Institute at Queen's University</td>
<td>No conflict declared</td>
</tr>
</tbody>
</table>
### Guideline 8-7

<table>
<thead>
<tr>
<th>Name</th>
<th>Affiliation</th>
<th>Conflict of Interest</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthony Joshua</td>
<td>Princess Margaret Hospital Toronto, ON</td>
<td>No conflict declared</td>
</tr>
<tr>
<td>Adam Mamelak</td>
<td>Sanova Dermatology Austin, Texas</td>
<td>No conflict declared</td>
</tr>
<tr>
<td>David McCready</td>
<td>Princess Margaret Hospital Toronto, ON</td>
<td>No conflict declared</td>
</tr>
<tr>
<td>Christian Murray</td>
<td>Skin Surgery Centre, University of Toronto Toronto, ON</td>
<td>No conflict declared</td>
</tr>
<tr>
<td>Xinni Song</td>
<td>The Ottawa Hospital Cancer Centre Ottawa, ON</td>
<td>Local principal investigator for COBRIM/Combi-AD BMS Check Mate</td>
</tr>
<tr>
<td>John Toye</td>
<td>Plastic Surgery Practice Orillia, ON</td>
<td>No conflict declared</td>
</tr>
</tbody>
</table>

### Targeted Peer Reviewers

<table>
<thead>
<tr>
<th>Name</th>
<th>Affiliation</th>
<th>Conflict of Interest</th>
</tr>
</thead>
<tbody>
<tr>
<td>Greg McKinnon</td>
<td>Tom Baker Cancer Centre Calgary, AB</td>
<td>No conflict declared</td>
</tr>
<tr>
<td>Christopher Lee</td>
<td>BC Cancer Agency Surrey, BC</td>
<td>No conflict declared</td>
</tr>
<tr>
<td>Tom Salopek</td>
<td>Cross Cancer Institute Edmonton, AB</td>
<td>No conflict declared</td>
</tr>
</tbody>
</table>
Appendix 2: Literature Search Strategy

**MEDLINE**
1. exp melanoma/
2. melanoma.mp or melanoma/
3. (malignan$ adj5 melanoma$).tw
4. Or/1-3
5. care.mp.
6. continuity.mp.
7. follow up.mp.
8. shared care.mp.
9. (after care or aftercare).mp.
10. surveillance.mp.
11. survivo$mp.
12. or/5-11
13. recurrence/
14. neoplasm recurrence, local/
15. recurren$mp.
16. second$ primary tumor$.mp.
17. second$ primary tumour$.mp.
18. Or/13-17
19. 12 or 18
20. exp "sensitivity and specificity"/
21. (sensitivity or specificity).tw.
22. exp Diagnostic Errors/
23. predictive value$.tw.
24. predictive value$ of test$.tw.
25. (false adj (negative or positive)).tw.
26. accuracy.tw.
27. reference value$.tw.
28. likelihood ratio$.tw.
29. ((pre-test or pretest) adj probability).tw.
30. post-test probability.tw.
31. Diagnosis, differential/
32. Diagnostic tests, routine/
33. reproducibil$.tw.
34. Or/20-33
35. CT.mp
36. Tomography, x-ray computed/
37. (CT adj scan$).mp.
38. (chest adj x-ray$).mp
39. PET.mp
40. (PET adj scan$).mp
41. (PET adj CT).mp
42. mri.mp.
43. magnetic resonance imaging/
44. (circuit$ adj LDH).mp
45. (circuit$ adj $100).mp
46. (LDH or S100 or CBC or FBC or full blood count).mp.
47. Electrolyte$.mp
48. (liver adj function$).mp
49. exp blood cell count/
50. (photo$ adj2 surveillance).mp
51. Dermoscopy.mp
52. Melafind.mp
53. Verisante aura.mp
54. Or/35-53
55. 34 or 54
56. well-being.mp.
57. well being.mp.
58. quality of life/
59. quality of life.mp.
60. qol.mp.
61. (psychosocial adj distress).mp.
62. psychosocial.mp.
63. (psychosocial adj care).mp.
64. (social adj relation$).mp.
65. (relation$ adj (spouse$ or famili$ or partner$)).mp.
66. “signs and symptoms”/
67. Clinical feature$.mp
68. (recurrence adj symptom$).mp
69. or/56-68
70. 55 or 69
71. 4 and 19 and 70
72. (comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or case report or historical article).pt.
73. 71 not 72
74. limit 73 to English
75. Animal/
76. Human/
77. 75 not 76
78. 74 not 77
79. limit 78 to yr="2000-2013"

**EMBASE**
1. exp melanoma/
2. melanoma.mp
3. (malignan$ adj5 melanoma$).tw
4. Or/1-3
5. care.mp.
6. continuity.mp.
7. (follow-up or follow up).mp.
8. (false adj (negative or positive)).tw.
9. shared care.mp.
10. after care/
11. long term care/
12. (after care or aftercare).mp.
13. surveillance$.mp.
14. survivor$.mp.
15. or/5-14
16. exp recurrent cancer/ or exp recurrent disease/
17. recurren$.mp.
18. neoplasm recurrence, local/
19. Second$ primary tumor$.mp
20. Second$ primary tumour$.mp
21. Second primary cancer$.mp
22. Or/16-21
23. 15 or 22
24. "sensitivity and specificity"/
25. sensitivity.tw.
26. specificity.tw.
27. exp "prediction and forecasting"/
28. predictive value$.tw.
29. predictive value$ of test$.tw.
30. exp diagnostic error/
31. (false adj (positive or negative)).tw.
32. diagnostic accuracy/
33. accuracy.tw.
34. reference value/
35. reference value$.tw.
36. likelihood ratio$.tw.
37. ((pre-test or pretest) adj probability).tw.
38. post-test probability.tw.
39. differential diagnosis/
40. reproducibilit$.mp.
41. Or/24-40
42. CT.mp
43. Tomography, x-ray computed/
44. (CT adj scan$).mp
45. (chest adj x-ray$).mp
46. PET.mp
47. (PET adj scan$).mp
48. (PET adj CT).mp
49. mri.mp.
50. magnetic resonance imaging/
51. (circulat$ adj LDH).mp
52. (circulat$ adj $100).mp
53. (CBC or FBC or full blood count).mp.
54. Electrolyte$.mp
55. (liver adj function$).mp
56. exp blood cell count/
57. (photo$ adj2 surveillance).mp
58. Dermoscopy.mp
59. Melafind.mp
60. Verisante aura.mp
61. Or/42-60
62. 41 and 61
63. well-being.mp.
64. well being.mp.
65. quality of life/
66. quality of life.mp.
67. qol.mp.
68. (psychosocial adj distress).mp.
69. psychosocial.mp.
70. (psychosocial adj care).mp.
71. (social adj relation$).mp.
72. (relation$ adj (spouse$ or famil$ or partner$)).mp.
73. "signs and symptoms"/
74. Clinical feature$.mp
75. (recurr$ adj2 symptom$).mp
76. or/63-75
77. 62 or 76
78. 4 and 23 and 77
79. (editorial or note or letter erratum or short survey).pt. or abstract report/ or letter/ or case study/
80. 78 not 79
81. Limit 80 to English
82. Animal/
83. Human/
84. 82 not 83
85. 81 not 84
86. Limit 85 to yr="2000-2013"
**Appendix 3: AMSTAR Quality Assessment of Included Systematic Reviews**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Was an ‘a priori’ design provided?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Was there duplicate study selection and data extraction?</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Was a comprehensive literature search performed?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Was the status of the publication used as an inclusion criterion?</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Was a list of studies (included and excluded) provided?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Were the characteristics of the included studies provided?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Was the scientific quality of the included studies assessed and documented?</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Was the scientific quality of the included studies used appropriately in</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>formulating conclusions?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Were the methods used to combine the findings appropriate?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Was the likelihood of publication bias assessed?</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Was the conflict of interest stated</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>
## Appendix 4: Quality Assessment of Included Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design</th>
<th>Sample Size</th>
<th>Intervention and Comparison</th>
<th>Outcome(s)</th>
<th>Country</th>
<th>Funding Body</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beyeler et al, 2006 [41]</td>
<td>Retrospective cohort</td>
<td>n = 127</td>
<td>S100B vs. scheduled imaging modality</td>
<td>Recurrence detection rate</td>
<td>Switzerland</td>
<td>Not specified</td>
</tr>
<tr>
<td>Blum et al, 2000 [15]</td>
<td>Comparative cohort</td>
<td>n = 1,288</td>
<td>Ultrasound vs clinical exam</td>
<td>Diagnostic accuracy</td>
<td>Germany</td>
<td>Not specified</td>
</tr>
<tr>
<td>DeRose et al, 2011 [38]</td>
<td>Retrospective</td>
<td>n = 52</td>
<td>Head CT/MRI and torso CT</td>
<td>Recurrence detection rate</td>
<td>USA</td>
<td>Not specified</td>
</tr>
<tr>
<td>Egberts et al, 2009 [21]</td>
<td>Before-and-after comparison</td>
<td>n = 97</td>
<td>LDH and S100B</td>
<td>Diagnostic accuracy</td>
<td>Germany</td>
<td>Not specified</td>
</tr>
<tr>
<td>Egberts et al, 2010 [22]</td>
<td>Comparative cohort</td>
<td>n = 259</td>
<td>LDH and S100B</td>
<td>Survival rate</td>
<td>Germany</td>
<td>Not specified</td>
</tr>
<tr>
<td>Etchebehere et al, 2010 [39]</td>
<td>Retrospective</td>
<td>n = 78</td>
<td>Restaging with FDG PET/CT</td>
<td>Diagnostic accuracy, treatment planning</td>
<td>Brazil</td>
<td>Not specified</td>
</tr>
<tr>
<td>Fikrle et al, 2013 [28]</td>
<td>Before-and-after comparison</td>
<td>n = 121</td>
<td>Dermatoscope</td>
<td>Detection rate</td>
<td>Czech Republic</td>
<td>Not specified</td>
</tr>
<tr>
<td>Kruger et al, 2011 [14]</td>
<td>Comparative cohort</td>
<td>n = 433</td>
<td>Clinical exam compared with clinical exam plus ultrasound</td>
<td>Recurrence detection rate, diagnostic accuracy</td>
<td>Germany</td>
<td>Not specified</td>
</tr>
<tr>
<td>Manne and Lessin, 2006 [25]</td>
<td>Survey</td>
<td>n = 229</td>
<td>Skin self-examination</td>
<td>Rate of performing skin self-examination and sun protection</td>
<td>USA</td>
<td>Grants from Greater Harrisburg Foundation and National Cancer Institute</td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>n</td>
<td>Practices</td>
<td>Detection Rate</td>
<td>Country</td>
<td>Funding Sources</td>
</tr>
<tr>
<td>------------------------------</td>
<td>-------------------------</td>
<td>------</td>
<td>---------------------------------------------------------------------------</td>
<td>----------------</td>
<td>---------</td>
<td>--------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Solivetti et al, 2014 [16]</td>
<td>Retrospective cohort</td>
<td>480</td>
<td>Ultrasound</td>
<td>Diagnostic accuracy</td>
<td>Italy</td>
<td>Not specified</td>
</tr>
<tr>
<td>Tarhini et al, 2009 [40]</td>
<td>Before-and-after comparison</td>
<td>670</td>
<td>S100B</td>
<td>Survival rate</td>
<td>USA</td>
<td>Supported by DiaSorin</td>
</tr>
</tbody>
</table>

Abbreviations: CT, computed tomography; FDG, fluorodeoxyglucose; LDH, lactate dehydrogenase; MRI, magnetic resonance imaging; PET, positron emission tomography; S100B, S100 calcium-binding protein B.
## Appendix 5: Summary of Published Melanoma Follow-up Clinical Practice Guideline Recommendations

<table>
<thead>
<tr>
<th>Healthcare Provider</th>
<th>Basis of Guideline</th>
<th>Stage/Breslow Thickness</th>
<th>History and Physical Exam*</th>
<th>Imaging and Laboratory Evaluations</th>
<th>Other Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>American Academy of Dermatology (AAD) [45]</td>
<td>General recommendations for all patients with melanoma</td>
<td>N/A</td>
<td>• At least annually, possibly every 3-12 months</td>
<td>• Not recommended in asymptomatic patients</td>
<td>• Lifelong clinical exams • Follow-up should be based on individual risk factors</td>
</tr>
<tr>
<td>British Association of Dermatologists (BAD) [6]</td>
<td>Specialist skin cancer multidisciplinary team</td>
<td>In situ Stage IA</td>
<td>• 2-4 times for 12 months</td>
<td>• No specific recommendations</td>
<td>• Skin self-exam recommended</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Stage IB - IIIB (resected)</td>
<td>• Every 3 months for 3 years, then every 6 months for 2 years</td>
<td>• No specific recommendations</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Stage IIIB - IV (unresected)</td>
<td>• Every 3 months years 1-3, then every 6 months years 4-5, and then annually for the next 5 years</td>
<td>• Consider CT</td>
<td></td>
</tr>
<tr>
<td>European Society for Medical Oncology (ESMO) [46]</td>
<td>Not discussed</td>
<td>Low risk / thin melanomas</td>
<td>• No specific recommendations</td>
<td>• Not recommended</td>
<td>• Emphasis on patient education and lifelong regular self-exams</td>
</tr>
<tr>
<td></td>
<td></td>
<td>High risk</td>
<td>• No specific recommendations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>German Cancer Society and German Dermatologic</td>
<td>Stage and Breslow thickness specific</td>
<td>Stage I &lt;1mm</td>
<td>• Every 6 months years 1-5, then every 6-12 months for years 6-10</td>
<td>• No imaging or blood work</td>
<td>• Limit clinical visits to 10 years • Use of lymph node</td>
</tr>
<tr>
<td>Healthcare Provider</td>
<td>Basis of Guideline</td>
<td>Stage/Breslow Thickness</td>
<td>History and Physical Exam*</td>
<td>Imaging and Laboratory Evaluations</td>
<td>Other Comments</td>
</tr>
<tr>
<td>---------------------</td>
<td>--------------------</td>
<td>-------------------------</td>
<td>---------------------------</td>
<td>-----------------------------------</td>
<td>----------------</td>
</tr>
<tr>
<td>Society [8]</td>
<td></td>
<td>Stage I, II  &gt;1mm</td>
<td>• Every 3 months years 1-5, then every 6 months years 6-10</td>
<td>• Lymph node sonography every 6 months years 1-5</td>
<td>sonography and S100B levels emphasized</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Stage III</td>
<td>• Every 3 months years 1-5, then every 6 months years 6-10</td>
<td>• S100B level every 3-6 months years 1-5</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Stage IV</td>
<td>• Not discussed</td>
<td>• S100B level every 3-6 months years 1-5</td>
<td></td>
</tr>
<tr>
<td>Australian Cancer Network [9]</td>
<td>Preferred health professional and/or patients themselves</td>
<td>Stage specific</td>
<td>Stage I</td>
<td>• Every 6 months for 5 years</td>
<td>Ultrasound may be used in conjunction with clinical examination only in patients with more advanced primary disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Stage II, III</td>
<td>• Every 3-4 months for 5 years, then annually thereafter</td>
<td></td>
<td>Individual patient’s needs must be considered before appropriate follow-up is offered</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Stage IV</td>
<td>• Not discussed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>National Comprehensive</td>
<td>Not discussed</td>
<td>Stage specific</td>
<td>Stage 0</td>
<td>• Annually for life</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lifelong clinical</td>
</tr>
</tbody>
</table>
### Guideline 8-7

<table>
<thead>
<tr>
<th>Healthcare Provider</th>
<th>Basis of Guideline</th>
<th>Stage/Breslow Thickness</th>
<th>RECOMMENDATIONS</th>
<th>Imaging and Laboratory Evaluations</th>
<th>Other Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer Network (NCCN) [10]</td>
<td></td>
<td>Stage IA - IIA</td>
<td>• Every 3-12 months for 5 years, then annually as clinically indicated</td>
<td>• Not recommended</td>
<td>exams</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Stage II B - IV</td>
<td>• Every 3-6 months for first 2 years, then every 3-12 months for 3 years and then annually as clinically indicated</td>
<td>• Consider CXR, CT+/-PET every 3-12 months and annual MRI of brain. No imaging necessary in asymptomatic patients after 5 years</td>
<td></td>
</tr>
<tr>
<td>Swiss Melanoma Guidelines [11]</td>
<td>Not discussed</td>
<td>Stage I (≤T1N0)</td>
<td>• Every 6 months years 1-3, then annually years 6-10</td>
<td>• None</td>
<td>Lifelong clinical surveillance is recommended</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Stage I (T2N0) - IIB</td>
<td>• Every 3 months years 1-3, then every 6 months years 4-5, and then every 6-12 months years 6-10</td>
<td>• Lymph node sonography and S100 every 6-12 months years 1-5</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Stage IIC - III</td>
<td>• Every 3 months years 1-5, then every 6 months years 6-10</td>
<td>• Lymph node sonography and S100 every 6 months years 1-5</td>
<td>CT, MRI, PET, or PET/CT every 6-12 months years 1-5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Stage IV</td>
<td>• Individual</td>
<td>• Individual</td>
<td></td>
</tr>
</tbody>
</table>

Note: History and physical exam includes review of systems, full skin examination, and lymph node examination.

Abbreviations: CT, computed tomography; CXR, chest x-ray; MRI, magnetic resonance imaging; PET, positron emission tomography; S100B, S100 calcium-binding protein B.