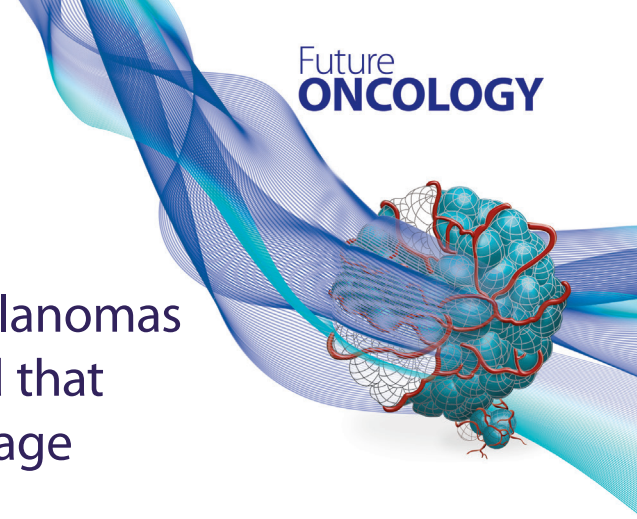
Plain Language Summary of Publication

Future ONCOLOGY



Development and validation of risk calculators for people with "thin" melanomas on their skin to predict the likelihood that their cancer will return: a plain language summary of publication

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Summary

What is this summary about?
This is a summary of an article describing the development of risk calculators for use in people who develop a type of melanoma on their skin called "thin" melanoma to predict the likelihood that their cancer will return. The article was originally published in the *Journal of Clinical Oncology* in 2021.

How to say...

- **Melanoma:** meh-luh-NOW-muh
- **Recurrance:** ruh-KUH-ruhns
- **Nomogram:** NO-muh-gram

How were the calculators developed?
Calculations were performed to predict the chance of people with thin melanomas surviving without their melanoma recurring. Three graphical prediction calculators (called nomograms) were developed, along with easy-to-use online calculators using the same underlying calculation methods. The model was developed using data for 25,930 Dutch people diagnosed with thin melanomas (called the "development set"). To test its ability to predict melanoma recurrence, it was then compared with data for 2,968 Australian people with melanoma (the "validation set"). The calculators developed in the Dutch patients were found to accurately predict the risk of melanoma recurring for people with melanoma in the Australian "validation" group.

What do the results mean?
The calculators provide estimates of the risk of the melanoma returning for people with thin melanomas. The easy-to-use online calculators are freely available on a smartphone, tablet or computer, and will assist in providing accurate estimates of recurrence risks for individuals with thin melanomas, allowing more intensive follow-up of those whose predicted risk of their melanoma returning is high.

Where can I find the original article on which this summary is based?

You can read the original article published in *Journal of Clinical Oncology* for free at:
https://ascopubs.org/doi/full/10.1200/JCO.20.02446

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Who is this article for?

This article may be helpful for people with melanoma, their families and treating clinicians to explain how the online calculators were developed and to help identify the risk of a thin melanoma returning. The calculators can estimate the risk level for each person with a thin melanoma. This knowledge can help them discuss that risk with their doctor and guide their management and follow-up.

What is melanoma?

Melanoma is a type of skin cancer that usually develops when the pigment-producing cells in the skin (called melanocytes) grow out of control and become cancer. Melanoma is less common than other types of skin cancer but is more dangerous because of its ability to spread rapidly to other parts of the body if left untreated.

What are melanocytes?

Melanocytes are cells found in the upper layer of the skin (the epidermis). They produce a pigment known as melanin, which gives skin its color.

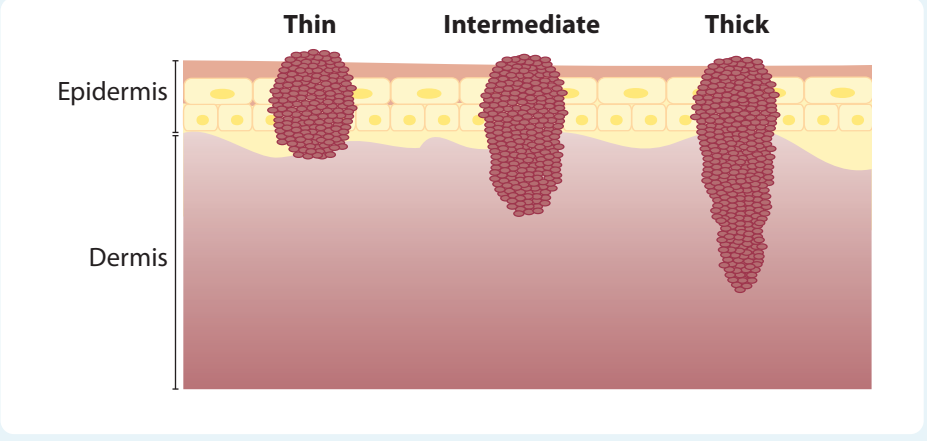
Why is the thickness of a melanoma important?

Melanomas are categorized according to how much risk they pose to someone's life using an international staging system published by the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC). In this system, how melanomas are classified depends on how deeply they have grown beneath the skin surface.

The melanoma thickness is often referred to as Breslow thickness, after Alexander Breslow, the pathologist who first described the association between melanoma thickness and the chance of survival.

The thickness of a melanoma is measured by a pathologist. Using a sample of skin the pathologist uses a microscope to measure how deeply the cancer cells have extended beneath the skin surface

According to how deeply a melanoma has grown and invaded below the skin surface, it can be categorized as:
- "thin" (where cells extend downwards to less than 1 mm below the skin surface)
- "intermediate" (where cells extend 1–4mm below the skin surface)
- "thick" (where cells have extended more than 4mm below the skin surface)



The risk of a melanoma returning after treatment (called 'recurring') and spreading to other parts of the body (called metastasizing) is strongly related to its thickness and how deeply the melanoma has extended.

Probability of dying within 10 years of primary melanoma diagnosis date:

2%
2 out of every 100 people with **thin** melanomas

17%
17 out of every 100 people with **intermediate thickness** melanomas

40%
40 out of every 100 people with **thick** melanomas

The majority of people (about 70%) who go to see a doctor with a new (primary) melanoma on their skin have "thin" melanomas.

In people with thin melanomas, the risk for the melanoma coming back (recurring) after treatment is usually low.

However, thin melanomas do recur in some people, sometimes many years after the original cancer has been removed. Although people with thin melanoma are much less likely to die than people with thick melanoma, more deaths occur from thin than from thick melanomas. This apparent contradiction arises because proportionally, of all people diagnosed with melanoma, many more are diagnosed with thin melanomas.

Why was this study carried out?

Until now, there have been few attempts to identify the small percentage of individuals with thin melanomas who are at particularly high risk of their cancer coming back and of dying of melanoma.

When trying to estimate recurrence risks for people with melanoma, doctors now mainly use the international staging systems published by the AJCC and the UICC. These systems predict survival but consider only the thickness of the primary tumor, whether there was disruption of the skin (an open sore, also called an ulcer), and whether there was any evidence of spread away from the site of the initial melanoma. For more serious melanomas (thicker than 1mm, and some thin ones which have caused disruption of the skin), a surgical procedure known as 'sentinel lymph node biopsy' is often used to remove the lymph node that is most likely to be the one to which any melanoma cells have spread. The sentinel node is then carefully examined under a microscope by a pathologist and is 'positive' if it contains melanoma cells.

The goals of this study were:

1. To use additional, readily-available clinical and pathologic information to develop graphical prediction calculators (also called nomograms) to indicate the chance of surviving without recurrence for people with thin melanomas. To do this, the chance of melanoma recurring was calculated for three different scenarios:
   - local recurrence, where the melanoma recurs within 5cm of the original melanoma site on the skin
   - regional recurrence, where the melanoma has spread to nearby lymph nodes
   - recurrence in distant organs such as the lungs, liver or brain, where the melanoma has spread to these organs

For example, the calculators indicate that a 39-year-old man with a thin melanoma that originally developed on his cheek will have:
- a 2% chance of local recurrence
- a 3% chance of regional recurrence
- an 8% chance of recurrence in distant organs

2. An additional objective of the study was to use the validated calculators to produce simple, free online calculators that provide a person who has a thin melanoma with a reliable estimate of their chance of a melanoma not returning after treatment (also known as "recurrence-free survival").

Who took part in the study?

The study had two parts: a development phase and a testing (validation) phase.

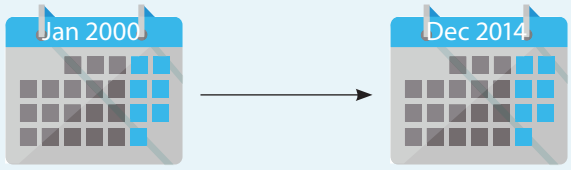
1 Development phase

Information was obtained from the Dutch pathology registry (PALGA), which collects information from all pathology laboratories in the Netherlands for people diagnosed with a new melanoma of their skin.

2 Testing (validation) phase

Information was obtained from the database of Melanoma Institute Australia for people initially treated at that specialized melanoma treatment center.

The study involved patients treated between January 2000 and December 2014.



All people who took part in the study presented with thin melanomas, that is melanomas that were less than 1.0 mm in Breslow thickness.

People who were excluded from the study included:

- Those who had clinical evidence of spread to lymph nodes or to distant body sites at the time of initial presentation
- Those who were less than 18 years of age
- Those who had more than one primary melanoma

How were the calculators developed?

Several items of information about factors that are known to influence prognosis were used to develop the risk calculators. The information included:

- patient age
- patient sex
- location of the melanoma on the body, such as head and neck, arms, legs or trunk
- Breslow thickness of the melanoma
- presence of an open sores (ulcer)
- frequency of cells observed to be replicating (mitoses)
- melanoma subtype (based on its appearance under the microscope),
- results of sentinel lymph node biopsy, if performed (to check whether any melanoma cells were present in lymph nodes).

Prediction calculators were developed based on information for participants in the development phase (the Dutch group) and then tested in the validation phase (the Australian group).

What were the overall results?

- 25,930 people were included in the development phase (the Dutch group); they were followed up for 6.7 years after their melanoma diagnosis; and
- 2,968 people were included in the validation phase (the Australian group); they were followed up for 12 years after their melanoma diagnosis

In the Dutch group, 807 (3.1%) of all the people with thin melanomas experienced a recurrence. Of these, 209 (0.8%) were local recurrences, 503 (1.9%) were regional recurrences and 203 (0.8%) were distant recurrences. In the Australian group, 124 (4.2%) people altogether experienced a recurrence, of which 23 (0.8%) were local recurrences, 61 (2.1%) were regional recurrences and 75 (2.5%) were distant recurrences. The greater recurrence* risks for the Australian patients were likely due to the longer follow-up time.

The predictions for the risk of recurrence for both the development and the validation groups were better than predictions provided by on AJCC/UICC staging, which is based on only three of the factors that we included (Breslow thickness, ulceration status and sentinel node biopsy result). The predictive accuracy for the various forms of recurrence-free survival improved by 9–12% for the development group, and by 11–15% for the validation group, relative to AJCC/UICC staging.

*Some patients had multiple recurrences (e.g. a skin recurrence and a lung recurrence). The calculators were developed per type of recurrence – thus, such a patient is included once for the "local" recurrence calculator and once for the "distant" recurrence calculator

What do the study results mean?

The prognosis for people with thin melanomas is generally very good or excellent, but a small number of them develop recurrent disease. The calculators that we have developed can accurately identify people with thin melanomas who are at higher risk of developing recurrence of their skin cancer. We found in our study that the prediction of surviving without recurrence was substantially more accurate using our calculators than prediction based only on the original AJCC criteria. That is, prediction accuracy was improved using calculators that included both the original AJCC/UICC criteria (Breslow thickness, ulceration status and sentinel node status) and other readily-available clinical and pathological parameters, as previously described (See "How was the calculator developed"). The easy-to-use online calculators can be accessed readily on a smartphone, tablet or computer, and are freely available online at: www.melanomarisk.org.au

Where can the reader find more information about this study?

The original article discussed in this summary was entitled 'Development and validation of nomograms to predict local, regional and distant recurrence in patients with thin (T1) melanomas'. It was published in the *Journal of Clinical Oncology* in April 2021. You can read the original article at: https://ascopubs.org/doi/abs/10.1200/JCO.20.02446.

The online calculators can be accessed at: https://www.melanomarisk.org.au.

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