Evaluation proposal for the Danish Health Technology Council regarding the Merlin Assay for newly diagnosed SLNB-eligible primary malignant melanoma patients

Instructions for the applicant

This template is used for submitting evaluation proposals to the Danish Health Technology Council in connection with the request of an assessment of new or existing health technology. Evaluation proposals are completed by the applicant and aim to provide the Danish Health Technology Council with a background for launching evaluations. Applicants are recommended to engage in a dialogue with the Danish Health Technology Council's secretariat to receive guidance for proper completion.

The template covers the following main topics:

- Information about the applicant
- Information about the health technology
- Information about the evidence base for the health technology

The Danish Health Technology Council defines health technologies broadly as any use of medical devices, procedures, or processes applied in the treatment or diagnosis of patients. Evaluations of health technologies by the Danish Health Technology Council are always conducted with the consideration of four perspectives: Clinical Effectiveness and Safety, the Patient Perspective, Organizational Implications, and Health Economics.

Evaluation proposals that are considered by the Danish Health Technology Council will be published on the Danish Health Technology Council's website. If there is confidential information in the evaluation proposal, it must be clearly marked using yellow text highlighting ("example").

The evaluation proposal should be kept as concise as possible and be in either Danish or English. At the end of the document, there is an example of a completed evaluation proposal that applicants can use for inspiration.

If questions arise during the preparation of the evaluation proposal, applicants may contact the Danish Health Technology Council's secretariat for elaboration or clarifications.

In addition to the evaluation proposal, companies, regions, and hospital administrations can complete and include a cost outline that provides an overview of the total costs associated with the use of the health technology. The Danish Health Technology Council's secretariat provides a cost outline template that can be accessed on the Danish Health Technology Council's website.

The completed evaluation proposal is the applicant's product.

Information about the applicant

Name of the applicant (company name or the name of the hospital/region)*:

SkylineDx B.V.

* If you are a public applicant, the Danish Health Technology Council refers to the requirement that the evaluation proposal in its entirety must be approved by the hospital or regional management.

Contact person (name, position):

Arjan van Manen, Chief Strategy Officer & Jelle Spoorendonk, Market access and HEOR lead

Date of submission of the evaluation proposal:

31 January 2024

Information about the health technology

Briefly describe the health technology to be evaluated:

The Merlin Assay is a non-invasive gene expression profiling (GEP) test co-developed with the Mayo Clinic in the United States. It analyses the melanoma tumour tissue and determines the patient's risk of having metastases in the sentinel lymph nodes. The test is based on a CP-GEP algorithm that combines clinical and pathological parameters and gene expression of 8 genes to assess the individual risk based on a low- and high-risk rest result. The test does not require additional tumour material beyond the biopsy of the primary melanoma. The diagnostic test can be performed in local Danish laboratories.

Provide a rationale for why it is relevant to conduct an evaluation of the health technology:

In current clinical (Danish) practice and according to Danish guidelines, for staging purposes of melanoma, specialists need to assess whether there is a risk of higher than 5% of having nodal involvement, physicians will deem patients sentinel lymph node biopsy (SLNB)-eligible.[1] This sentinel lymph node surgery allows specialists to stage the melanoma patient further clinically. The clinical stage will inform subsequent treatment pathways of a patient and whether this patient requires adjuvant therapy or can be put under observation. To assess nodal involvement, a SLNB is carried out, in which the patient in some cases goes under full anesthesia, whereas the lymph node(s) to which the cancer cells are most likely to spread are taken out for further assessment and to determine whether cancer cells are present. In about 80-85% of these SLNBs, lymph nodes are negative and cancer has likely not spread. This means that 4 of the 5 patients would undergo a surgery that they may not need.[2,3] In addition, SLNB is associated with complications in about ~17% of the patients. Peer-reviewed evidence published on the Merlin Assay concludes that patients with a low-risk test result can forgo the SLNB, whereas patients with a high-risk test result would still undergo a SLNB. [redacted]

1. Danish guideline SLNB accessed at: https://www.dmcg.dk/siteassets/forside/kliniske-retningslinjer/godkendte-kr/dmg/dmg_sentinel-node-biopsi_v1.0_admgodk221121.pdf
2. Morton DL, Thompson JF, Cochran AJ, et al. Final Trial Report of Sentinel-Node Biopsy versus Nodal Observation in Melanoma. N Engl J Med. 2014;370(7):599-609.
3. Dansk Melanom Database (DMD) Årsrapport 2022 accessed at: https://www.sundhed.dk/content/cms/30/57130_dansk-melanom-database_dmd_aarsrapport-2022.pdf
4. [redacted]

What is the classification of the health technology?

☐Medical device, which is CE marked*

- ☐ Class I
- ☐ Class IIA
- ☐ Class IIB
- ☐ Class III

☒Diagnostic technology, which is CE marked**

- ☐ Class A
- ☐ Class B
- ☒ Class C
- ☐ Class D

☐Procedure (workflow related to diagnostics, treatment, rehabilitation, and/or with a preventive purpose)

If the procedure involves the use of one dominant health technology, describe it, and provide its CE marking and classification

* The Danish Health Technology Council only evaluates medical devices that are CE marked or otherwise meets the legal requirements for medical devices.

** Diagnostic technology utilizing medical equipment for *in vitro* diagnostics.

☒ the applicant hereby declares under penalty of perjury that the above information is accurate and complies with the relevant legislation concerning CE marking.

Briefly describe the current status of the use of the health technology in Denmark and abroad.

The technology has been well established and researched in multiple countries and settings in the US and Europe and has received CE-marking as of 2022. [redacted]

Proposed PICO specification (Population, Intervention, Comparator, Outcome) for framing the evaluation question:

Population – The patient group in/for which the health technology is utilized and which the	Patients with newly diagnosed primary malignant melanoma that are SLNB eligible pT1-pT3 primary cutaneous melanoma

evaluation focuses on, including the annual number of patients in Denmark:	
Intervention – The specific health technology to be evaluated:	Merlin Assay (CP-GEP)
Comparator – The health technology or treatment that is natural to compare with and currently used as the best and most widely adopted alternative to the intervention in Denmark (I):	Sentinel lymph node biopsy (this procedure is being used to assess whether there is nodal metastasis. Patients that receive a low risk test result with Merlin Assay can forgo SLNB, whereas patients that receive a high risk test result would undergo SLNB)
Outcome – The clinical effectiveness measures that would be relevant to assess the health technology compared to the comparator are:	Specificity, Sensitivity, negative predictive value, SLNB reduction rate, relapse-free survival, distant metastatic-free survival, melanoma-specific survival

* PICO is a tool utilized by the Danish Health Technology Council to formulate precise issues and is crucial in the planning and execution of an evaluation by the Danish Health Technology Council. PICO is further detailed in the Danish Health Technology Council's methods guide, available on the Danish Health Technology Council's website.

Provide a brief description of the proposed comparator and whether the suggested health technology (intervention) is suggested to replace or to be an add on to the current alternative:

The suggested health technology is assumed to replace a part of the patients of the existing current alternative SLNB; namely patients that receive a low-risk test result with the Merlin Assay can forgo the SLNB procedure, whereas patients that receive a high-risk test result would still undergo SLNB for further diagnosis and staging.

Is the health technology mentioned in professional clinical guidelines from institutions like the Danish Health Authority or medical scientific societies? Specify which ones:

No

Has the health technology been evaluated by other HTA institutions (e.g. NICE, Nye Metoder)? Specify which ones:

Merlin has been evaluated by Medicare and received positive recommendation in the US (reimbursed for all patients).

Provide the names of manufacturers/suppliers of the health technology, if relevant:

[redacted]

Information about the evidence base for the health technology:

Indicate whether the health technology (compared to the current alternative) aims to improve treatment/diagnosis of the patient group as perceived from one or more of the following perspectives (indication of the primary impact of using of the health technology):

☒ Clinical effectiveness and safety ☐ Patient preferences and experiences

☒ Organizational aspects, such as changes to workflows ☒ Costs associated with treatment/diagnostics

*For the evaluation of health technologies, the Danish Health Technology Council employs four perspectives: Clinical Effectiveness and Safety, the Patient Perspective, Organizational Implications, and Health Economics. For further elaboration on these perspectives, refer to the Danish Health Technology Council Council's methods guide for the evaluation of health technologies, available on the Danish Health Technology Council Council's website.

State the expected impact of the health technology within the indicated perspectives above:

Clinical effectiveness and safety:

- The Merlin Assay supports physicians in determining whether SLNB eligible patients would require an invasive SLNB procedure based on a high or low risk score for nodal metastases. By using the Merlin assay and being assigned a low-risk score, patients can safely forgo SNLB, which could potentially lead to less patients requiring invasive SNLB surgery in current standard practice. [redacted]

Organizational aspects:

- The Merlin Assay is a less time-consuming test which requires less resource use and different disciplines within the hospital compared to a SLNB for a patient that would be deselected. This would reduce the number of procedures (e.g., medical evaluation and imaging prior to SNLB, SNLB surgery, pathology, and surgical follow-up) required compared to current standard practice.

Costs associated with treatment/diagnostics:

- In a cost-effectiveness study published in 2022 analyzing the break-even point between a scenario with and a scenario without Merlin, authors concluded that Merlin testing for thin melanomas could be potentially cost saving depending on the cost of the molecular assay and SLNB reimbursement rates.
- The SNLB procedure itself is associated with complications due to the procedure, such as seroma, lymphedema, infection/cellulitis, hematoma and wound dehiscence. These complications and the associated costs and resource use could be reduced if these procedures are only being conducted in those patients that have the highest risk of nodal metastases.

Provide references* for documentation of the health technology's effects (if possible, include up to 2 key references per perspective):

Clinical effectiveness and safety	1. Bellomo D, Arias-Mejias SM, Ramana C, etal. Model Combining Tumor Molecular and Clinicopathologic Risk Factors Predicts Sentinel Lymph Node Metastasis in Primary Cutaneous Melanoma. JCO Precis Oncol. 2020;4:319-334. 2. Arias-Mejias SM, Quattrocchi E, Tempel D, et al. Primary cutaneous melanoma risk stratification using a clinicopathologic and gene expression model: a pilot study. Int J Dermatol. 2020 Nov;59(11):e431-e433. 3. Mulder E.E.A.P., Dwarkasing J.T., Tempel D. Et al. Validation of a clinicopathological and gene expression profile model for sentinel lymph node metastasis in primary cutaneous melanoma, British Journal of Dermatology, Vol. 184; 1: 944–951, 4. Yousaf, A., Tjien-Fooh, F.J., Rentroia-Pacheco, B., et al. (2021), Validation of CP-GEP (Merlin Assay) for predicting sentinel lymph node metastasis in primary cutaneous melanoma patients: A U.S. cohort study. Int J Dermatol, 60: 851-856. 5. Johansson I, Tempel D, Dwarkasing JT, Rentroia-Pacheco B, Mattsson J, Ny L, Olofsson Bagge R. Validation of a clinicopathological and gene expression profile model to identify patients with cutaneous melanoma where sentinel lymph node biopsy is unnecessary. Eur J Surg Oncol. 2022 Feb;48(2):320-325 6. Eggermont AMM, Bellomo D, Arias-Mejias SM, Quattrocchi E, Sominidi-Damodaran S, Bridges AG, Lehman JS, Hieken TJ, Jakub JW, Murphree DH, Pittelkow MR, Sluzevich JC, Cappel MA, Bagaria SP, Perniciaro C, Tjien-Fooh FJ, Rentroia-Pacheco B, Wever R, van Vliet MH, Dwarkasing J, Meves A. Identification of stage I/IIA melanoma patients at high risk for disease relapse using a clinicopathologic and gene expression model. Eur J Cancer. 2020 Nov;140:11-18. 7. Mulder EEAP, Dwarkasing JT, Tempel D, van der Spek A, Bosman L, Verver D, Mooyaart AL, van der Veldt AAM, Verhoef C, Nijsten TEC, Grunhagen DJ, Hollestein LM. Validation of a clinicopathological and gene expression profile model for sentinel lymph node metastasis in primary cutaneous melanoma. Br J Dermatol. 2021 May;184(5):944-951. 8. Amaral T, Sinnberg T, Chatziioannou E, Niessner H, Leiter U, Keim U, Forschner A, Dwarkasing J, Tjien-Fooh F, Wever R, Flatz L, Eggermont A, Forchhammer S. Identification of stage I/II melanoma patients at high risk for recurrence using a model combining clinicopathologic factors with gene expression profiling (CP-GEP). Eur J Cancer. 2023 Mar;182:155-162. 9. Stassen RC, Mulder EEAP, Mooyaart AL, Francken AB, van der Hage J, Aarts MJB, van der Veldt AAM, Verhoef C, Grünhagen DJ. Clinical evaluation of the clinicopathologic and gene expression profile (CP-GEP) in patients with melanoma eligible for sentinel lymph node biopsy: A multicenter prospective Dutch study. Eur J Surg Oncol. 2023 Dec;49(12):107249. ~~10.~~ [redacted]
The Patient perspective	1. Meves A, Eggermont AMM. Deselecting Melanoma Patients for Sentinel Lymph Node Biopsy During COVID-19: Clinical Utility of Tumor Molecular Profiling. Mayo Clin Proc Innov Qual Outcomes. 2020 Oct;4(5):586-587.

	2. Hieken TJ, Sadurní MB, Quattrocchi E, et al. Using the Merlin assay for reducing sentinel lymph node biopsy complications in melanoma: a retrospective cohort study. Int J Dermatol. 2022 Jul;61(7):848-854.
Organizational Implications	1. Meves A, Eggermont AMM. Deselecting Melanoma Patients for Sentinel Lymph Node Biopsy During COVID-19: Clinical Utility of Tumor Molecular Profiling. Mayo Clin Proc Innov Qual Outcomes. 2020 Oct;4(5):586-587.
Health Economics	1. Thao V, Dholakia R, Moriarty JP, et al. Cost evaluation of the Merlin assay for predicting melanoma sentinel lymph node biopsy metastasis. Int J Dermatol. 2023 Jan;62(1):56-61.

* Reference to published, ongoing, or unpublished data.

Indicate whether the health technology is expected to incur additional costs, cost reductions, or be cost-neutral compared to the current alternative. Briefly describe how the costs are expected to be distributed across sectors (hospital, general practice, municipalities, patients, etc.), and what is considered to drive the potential addition or reduction in costs. The Danish Health Technology Council encourages applicants to complete and include the Danish Health Technology Council's cost outline, accessible on the Danish Health Technology Council's website.

☐ Additional costs ☒ Cost reductions ☒ Cost-neutral

Ideally, the implementation of Merlin would not induce additional budget impact. Cost reductions, or cost neutrality heavily depends on the price of the molecular assay and the reimbursement rates for SLNB. However, costs and DRG codes associated with SLNB are often separated from the costs associated with the pathological work-up and the identification of tumour cells in the biopsy itself. Both are not necessary when patients are deselected for SLNB through Merlin. In addition, there is uncertainty whether costs would differ if multiple nodes would need to be assessed compared to assessing only one node. [redacted]

Free-text field (optional additional information, max 300 words):

Denmark is in the highest ranking worldwide for the incidence of cutaneous melanoma. At the same time, the efforts to capture information on this disease are unique in the world. The Danish melanoma registry provides a wealth on data to help understand the disease and patients confronted with this life-threating disease. [redacted]

Hence, SkylineDx seeks this opportunity to work with different stakeholders in Denmark to facilitate clinical implementation for this test. The ambition is to reserve surgeries for those patients that would benefit from it most and refrain from it when it is not needed. To provide access to patients and have their tumor biology better understood, would have a positive impact on the patient treatment pathway. This requires a structure for implementation and coverage for the test.