

Title	Second-line non-invasive skin imaging techniques, including <i>in vivo</i> reflectance confocal microscopy (RCM), for the diagnosis and preoperative mapping of melanoma.
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Reference	ISBN number: : 978-2-11-179600-3, link to full report: Haute Autorité de Santé - Imageries de seconde ligne dont la microscopie confocale in vivo pour le diagnostic et la cartographie préopératoire d'un mélanome

Aim

This evaluation was conducted by the French National Authority for Health (HAS) to assess the relevance of reimbursing second-line non-invasive skin imaging techniques, including *in vivo* confocal microscopy, by the French National Health Insurance. The aim of this report was to determine the clinical utility of integrating these technologies into the diagnostic strategy compared to the current standard approach for diagnosing pigmented lesions (naevi) and for preoperative mapping of complex facial melanomas, particularly lentigo maligna. Systematic lesion excision, or at least a precautionary biopsy, remains the standard approach to obtain a histological diagnosis.

The assessment primarily focused on determining the clinical utility of the new strategy based on an evaluation of the benefit–risk balance, and other considerations, such as procedure feasibility, stakeholder acceptability, improvements in equity and access to care, required resources, and implementation measures).

These second-line imaging techniques are intended to provide additional diagnostic information in the management of equivocal pigmented lesions suspected to be melanoma. This helps to avoid unnecessary excisions or biopsies of benign lesions— which carry their own constraints and complications. In this report, three different techniques were identified: Reflectance Confocal Microscopy (RCM); Optical Coherence Tomography (OCT); Line-field Confocal Optical Coherence Tomography (LC OCT).

With regards to the diagnostic approach, second-line imaging may be indicated for pigmented lesions suspected of being melanoma, where the appearance remains equivocal on dermoscopy (intended use #1). Other intended uses include facial lentigo maligna in particular: including identifying and targeting the area most likely to be malignant, for a reliable biopsy (intended use #2) and preoperative mapping of safety margins to enable single-step oncological re-excision of cancer (intended use #3)

Conclusions and results

For the first intended use, based on the results of a systematic review and critical appraisal of the highest level of evidence available in the literature (randomized or non-randomized interventional studies), including a large randomized study comparing the strategy incorporating RCM with the standard approach (3,200 lesions) the HAS was unable to issue a favourable opinion on the benefit–risk balance of the RCM strategy. This is due to the current mismatch between the available data and the clinical need to be addressed (low clinical applicability, low certainty based on the available evidence), and specifically:

- the absence of specific data or subgroup analyses for facial lentigo maligna, which constitutes an identified target subpopulation with an insufficiently addressed medical need. According to a French practice survey on RCM, facial lesions accounted for 58% of diagnostic assessments and 91% of preoperative mapping procedures,
- the impossibility of extrapolating the available data: most results concerning the RCM-incorporating strategy relate to non-complex, flat-surface lesions. This means that the observed benefits in terms of reduced excisions and estimated missed diagnoses cannot be applied to the target subpopulation. The missed diagnoses were statistically and clinically significant, ranging from 5% to 10% depending on whether a follow-up examination was conducted at least six months after the initial examination. However, this was limited to melanoma *in situ*. This estimated loss originated from university hospital teams that were experienced nonetheless,
- According to a French practice survey, post-examination follow-up was only observed in 50% of diagnostic assessments for suspected tumours. Where applicable, follow-up lasted no longer than six months in 55% of cases. Thus, the substantial 45% reduction in excisions reported in the randomized study (95% CI [42.5-47.5]) came at the cost of an estimated 5.5% (95% CI [3.4-8.7]) of missed melanoma diagnoses, even with six months or more of follow-up. Without any follow-up, this figure could potentially reach 10.5% (95% CI [7.5-14.6]). This loss, primarily observed for melanoma *in situ*, exceeded the 2% safety threshold specified in the study protocol,

- the virtual absence of interventional data generated with the handheld-probe RCM device Vivascope® 3000, even though the device is both the most widely used device in France (according to a French practice survey) and the only one suitable for examining the most complex facial lesions. Most of the available interventional studies were conducted with the Vivascope® 1500, which is suited for flat, uncomplicated lesions,
- the lack of informative complementary data from the five non-randomized interventional studies (2,300 lesions in total),
- the absence of data regarding changes in the number of clinical visits related to the newly required follow-up procedures compared to the standard approach when a lesion suspected of melanoma is not biopsied or excised based solely on the RCM result.

Additionally, it should be noted that the estimated 57% (95% CI [41-71]) of missed diagnoses for the few (pigmented) carcinomas included in the randomized study occurred despite six months or more of follow-up, which is a preliminary finding that requires confirmation by studies specifically focused on carcinoma diagnosis.

Furthermore, as no interventional studies were identified in the systematic review, the HAS was unable to address the questions related to the second and third intended uses for RCM (#2 and #3), nor those concerning the two other second-line skin imaging modalities: OCT and LC OCT.

Recommendations

The French National Authority for Health (Haute Autorité de santé, HAS) has issued an unfavourable opinion on covering second-line non-invasive skin imaging procedures using RCM, OCT and LC OCT for the three identified intended uses in melanoma based on available evidence.

Methods

A systematic review of existing systematic reviews and interventional studies (randomized or non-randomized) published in the Medline and Embase databases up to 26 May 2025 was conducted. An interventional study was defined as one in which the test result is directly linked to the medical decision and to a clinically relevant patient outcome. Eligible interventional studies were assessed using internationally validated tools (Cochrane RoB 2 and RoBINS-I). Involving healthcare professionals (expert reviewers and professional stakeholders) and patient and consumer organizations, ensured the scientific rigor of the report, and the data to be contextualized more effectively within the French healthcare setting. This enables additional non-clinical considerations to be collected to further inform public health decision-making, in line with the GRADE Evidence to Decision (EtD) framework.

Further research/reviews required

The work highlights the importance of obtaining additional comparative data targeting the subpopulation with the most complex facial cases. This is particularly pertinent for individuals examined with the Vivascope® 3000, since a highly highly specialized, technically demanding, and time-consuming dermatological examination can be used as a second-line imaging technique.

These specific data will be essential to evaluate the clinical utility and constraints of the new strategy incorporating RCM such as its benefit–risk balance, and its effect on the number of follow-up consultations required) in comparison with the standard approach. The data will also be necessary for making recommendations about follow-up procedures after the examination, to ensure the long-term safety of patients whose lesions would not be excised or biopsied based solely on the results of this examination.

These data also appear to be necessary for the intended three uses of other two identified imaging techniques (OCT and LC OCT) in this subpopulation.

Finally, the work highlights the importance of creating a comprehensive, integrated of accredited academic training including theory and practice—supplemented by a post-university recognition mechanism. It is also crucial to develop French validated technical guidelines. It will ensure that, should these procedures be implemented on a larger national scale, they can be executed optimally and reproducibly.

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