

# Cost–Benefit Analysis of in vivo Reflectance Confocal Microscopy for Melanoma Diagnosis in a Real-World Clinical Setting

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**Background:** In a recent prospective, multicenter, two-arm randomized controlled trial (RCT), we demonstrated that adjunctive reflectance confocal microscopy (RCM) in routine clinical practice provides clinical benefits, including safe melanoma detection and a 43.3% reduction in the number needed to excise (NNE).

**Methods:** A cost–benefit analysis was conducted based on NNEs for standard care (5.3) and adjunctive RCM (3.0). Cost data were supplied by one center, applying a micro-costing approach from the hospital’s perspective. Costs were calculated for dermatology exams, excisions, medications, histopathology, and follow-up. The outcomes were extrapolated to provincial and national settings to assess the economic benefits of RCM.

**Results:** The cost per patient for standard care was €143.63, compared to €114.74 for adjunctive RCM. The cost per melanoma excised with standard care (NNE 5.3) was €904.87, almost twice the cost for RCM (€458.96). Annual regional and national costs for standard care were €864,150.85 and €11,491,849.00, respectively, while RCM reduced these to €438,306.80 and €5,828,792.00. Estimated annual savings with adjunctive RCM were €425,844.05 regionally and €5,663,057.00 nationally. The cost–benefit ratio for RCM was 3.89, meaning that for every €1 spent on RCM, there is a benefit of €3.89.

**Conclusion:** In real-world clinical practice, adjunctive RCM offers significant economic advantages at local, regional, and national levels while maintaining patient safety and reducing unnecessary surgical procedures.

**Keywords:** melanoma, dermoscopic examination, reflectance confocal microscopy, cost–benefit, economics, cost analysis, skin cancers

## Introduction

Melanoma has the highest mortality rates among skin cancers and is commonly diagnosed by clinical and dermoscopic examination. However, diagnostic specificity and sensitivity vary according to the medical practitioner’s expertise.<sup>1</sup> False negatives and/or excess unnecessary biopsies greatly impact National Healthcare Systems (NHS).<sup>2–4</sup>

Several non-invasive optical imaging techniques have been developed to increase diagnostic accuracy at earlier stages of disease. Reflectance confocal microscopy (RCM) has already proven useful in increasing non-invasive diagnostic accuracy of melanocytic and non-melanocytic skin cancers, including melanoma.<sup>5–13</sup>

In an era of economic austerity, skin cancer management poses a heavy cost burden on NHSs.<sup>14,15</sup>

Considering the significant expenses involved in diagnosing and treating skin lesions, it is imperative to prioritize public health efforts to implement evidence-based cost–benefit interventions. The adoption of RCM in clinical practice demonstrated a positive impact on the financial burden associated with skin cancer, by reducing excision and biopsy rates and improving early detection of malignant lesions.<sup>16</sup>

In our recent randomized clinical trial, we demonstrated that adjunctive RCM to standard therapeutic care reduces the number needed to excise (NNE) by 43.3% among suspicious lesions compared to dermoscopy alone, thereby greatly reducing unnecessary excisions while assuring melanoma detection at baseline in a real-life setting.<sup>7</sup>

We aim to apply a cost–benefit analysis through a micro-costing approach to results from our randomized clinical trial to demonstrate the economic impact of RCM in routine clinical practice. This model will be applied to regional and national data to estimate wider cost–benefit analyses.

# Materials and Methods

## Data Collection

Data were collected from a prospective, multicenter, two-arm, randomized study conducted in 3 Italian centers between August 2017 and June 2019. Full study details have been previously published.<sup>7</sup> Briefly, patients with equivocal lesions detected during standard therapeutic care, were randomly assigned 1:1 to either standard therapeutic care and adjunctive RCM or standard therapeutic care only. The standard therapeutic care patient pathway included clinical and/or dermoscopic assessment by dermatologists and, based on features observed, the management decision (surgical excision or referral to digital dermoscopic follow-up [DDF]), was made. For patients randomized to the adjunctive RCM arm, the management decision was based on standard therapeutic care with adjunctive RCM evidence. DDF included lesion assessment by standard therapeutic care, with or without adjunctive RCM, at the discretion of the physician and independent of patients’ initial randomization.

## Cost–Benefit Analysis

For each procedure, a cost analysis was performed from the hospital point of view through a micro-costing approach, as reported in Table 1.<sup>17</sup> Procedures were evaluated considering the time-related medical staff expenses and other fixed and variable costs (device, disposables, etc). As no specific reimbursement rate for RCM is assigned in Italy, the cost of RCM examination was calculated with a micro-costing approach, including the depreciation and other fixed and variable costs (technician, disposable, etc), over a 4-year period. Costs and hospital data were provided by the University of Modena

**Table 1** Cost of Procedures as Calculated According to Italian NHS Parameters

Procedure	Identification Code	Actual Cost in Euro	Sub-Cost Analysis in Euro (Source: Policlinico Hospital Modena, it is the Same in All Centers Being a National Based HSC and Same Region)
Dermatologic outpatient exam	DE0001	9.70	Instruments and other fixed costs: 0.03 Personnel: 8.41 (MD=15'; N=5') 15% Hospital Overhead: 1.26
Digital dermoscopy	AN8065	19.84	Instruments (Digital dermatoscope 25,000 Euro per 3200 patients per year) and other fixed costs: 1.95 Personnel: 15.30 (MD=20'; N=20') 15% Hospital Overhead: 2.59

(Continued)

**Table 1** (Continued).

Procedure	Identification Code	Actual Cost in Euro	Sub-Cost Analysis in Euro (Source: Policlinico Hospital Modena, it is the Same in All Centers Being a National Based HSC and Same Region)
Follow-up visit	DE0002	7.78	Instruments and other fixed costs: 0.04 Personnel: 6.72 (MD=12'; N=4') 15% Hospital Overhead: 1.01
Surgical (narrow-margin complete) excision	CH6008	77.83	Instruments and other fixed costs: 37.08 Personnel: 30.60 (MD=40'; N=40') 15% Hospital Overhead: 10.15
Histopathological exam	IS4581	25.87	Instruments and other fixed costs: 10.21 Personnel: 12.21 (MD=11'; T=22') 15% Hospital Overhead: 3.36
Medication/suture removal	CH6082	19.41	Instruments and other fixed costs: 8.61 Personnel: 8.27 (MD=8'; N=15') 15% Hospital Overhead: 2.53
Confocal Microscopy*	-	28.43	Instruments (RCM 100,000 Euro per 1800 patients per year) and other fixed costs: 15.83 Personnel: 8.89 (MD=8'; T=15') 15% Hospital Overhead: 3.71

**Note:** \*ID Code not determined.

**Abbreviations:** MD, medical doctor; N, nurse; T, technician; HSC, Health Care System.

and Reggio Emilia. Involved staff member costs (physicians €27.48/8 min and technician €20.91/15 min) and required consumables (adhesive window €1.94/examination) both for treatment and procedure. The annual amortization cost, with a device purchase cost of €100,000 was determined by considering an operational lifetime of 4 years and the use of the RCM on at least 1800 patients/year. The overhead cost was evaluated for all assessments as 15% of total direct costs for the department. The discount rate was not applied since the analysis was conducted over a one-year period.

Specific RCM physician and technician training costs for image interpretation were not included.

The cost for DDF of dermoscopy was added to all RCM evaluations without excision. For all lesions referred to DDF with changes observed at dermoscopy, surgical excision costs were applied. Indirect costs (working days loss for accessing hospital services, transportation, morbidity, etc) were not considered.<sup>17,18</sup> Average consultation costs for the 2 patient pathways were based on the University of Modena and Reggio Emilia hospital database evidence that 70% of patients undergo consultancies with standard therapeutic care only and 30% with added RCM. The percentage of patients undergoing immediate or deferred excisions was extrapolated from data obtained from our randomized clinical trial.<sup>7</sup> Total costs include surgical excision, medications and histopathology reports, and a follow-up visit.

Given the similarities of available medical resources, clinical and cost–benefit data obtained from our randomized controlled trial<sup>7</sup> and our present analysis were applied to regional and national melanoma incidence estimates to evaluate the impact of adjunctive RCM use in both the hospital and outpatient services. The total number of excisions/year was based on estimates of regional and national new melanoma diagnoses of ~955<sup>19</sup> and 12,700,<sup>19</sup> respectively.

## Statistical Analysis

Absolute and relative numbers were obtained for each tumor. Differences in tumor frequencies in the different patient pathways were evaluated with the Pearson chi-squared test. Diagnostic efficiency was measured with NNE. The NNE was calculated by dividing the total number of excised lesions by the number of confirmed melanomas for both groups. Differences in NNE between the 2 patient pathways were measured with the Kolmogorov–Smirnov two-sample *z*-test.

Perspective estimation of the number of unnecessary excisions and costs saved per year in the region considered the regional population of 4,426,929 inhabitants and national population of 58,850,717.<sup>20</sup>

## Sensitivity Analysis

To explore the uncertainty of the input parameters used and to test the robustness of the model and its results, a deterministic univariate sensitivity analysis was conducted. The analysis involved varying the main input data adopted in the model.

A  $\pm 20\%$  variation in the price of the following was considered:

- Examinations (dermatologic exam with dermoscopy, total body digital dermoscopy, histologic exam, medication suture removal);
- Follow-up visit;
- Surgical excision.

For RCM, price variations of  $+25\%$ ,  $+50\%$ ,  $+75\%$ , and  $+100\%$  were evaluated. Additionally, a  $\pm 20\%$  increase in the number of patients who, after RCM, were referred for surgical excision and those who underwent follow-up visits were considered.

## Results

### Patients, Excised Lesions, and NNE

Study details have been previously described.<sup>7</sup> Briefly, the trial randomized 3165 patients (2017–2019) with a mean follow-up of 9.6 months (SD 6.9; 1.9–37.0). Final diagnostic analysis included 3078 patients; 48 were lost to follow-up and 39 refused excision. Patients were equally randomly assigned to either arm ( $n=1582$  vs  $n=1583$ ). The contribution of enrolled patients was similar among the three collaborating centers.

Notably, in the standard therapeutic care arm, almost all lesions (99.8%) were assigned to surgical excision ( $n = 1579/1582$ ). In the arm with adjunctive RCM, less than half of the patients ( $n = 728$ ; 46.0%) were sent for immediate excision, and the remaining lesions were sent to short- or long-term DDF.

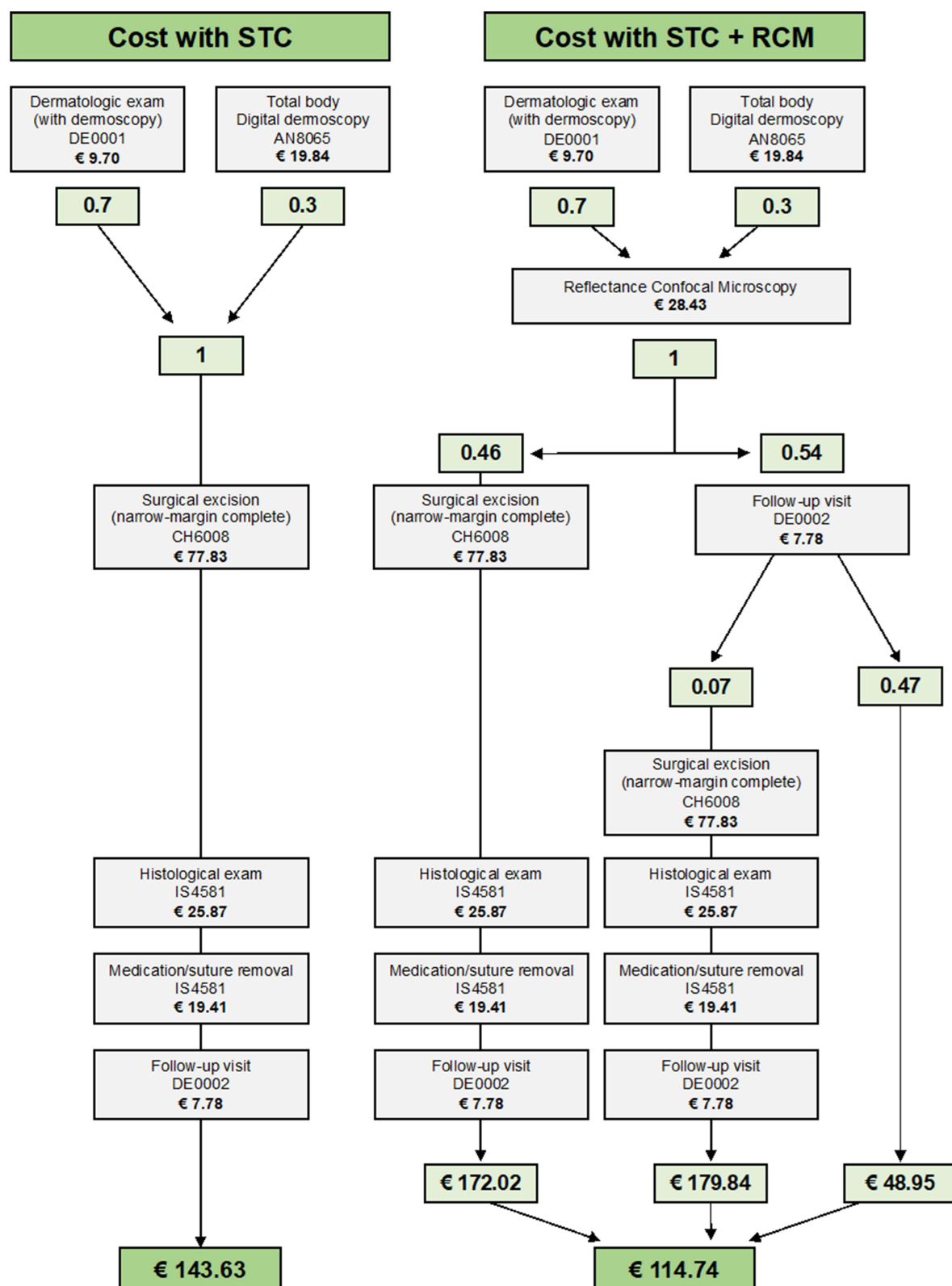
Among all excised lesions ( $n=3165$ ), melanoma was identified in 23.9%, resulting in an overall NNE of 4.2. Slightly more melanomas were diagnosed in the standard therapeutic care arm (51.4%). NNE for standard therapeutic care was 5.3 vs 3.0 with adjunctive RCM.<sup>7</sup>

### Regional and National Excision Rate Estimates

We estimated 5062 regional and 67,310 national excisions are performed annually with standard therapeutic care only (NNE = 5.3). With adjunctive RCM, estimates fell to 2865 regional and 38,100 national excisions performed annually (NNE = 3.0), with reductions of unnecessary excisions of 2197 within the regional and 29,210 on a national scale.

### Cost Analysis

The average cost for a standard therapeutic care only consultation was €143.63 and with adjunctive RCM this rate fell to €114.74, see [Figure 1](#). Costs of removing one melanoma with standard therapeutic care only (NNE = 5.3) were calculated to be €904.87, for an estimated overall annual regional cost of €864,150.85 and national cost of €11,491,849.00 (or of €195,271.18 every million inhabitants/year). With adjunctive RCM, the cost of removing one melanoma (NNE of 3.0) was calculated to be €458.96 for an estimated overall annual regional cost of €438,306.80 and national cost of €5,828,792.00 (or €99,043.69 every million inhabitants/year). Overall annual savings with adjunctive RCM to skin cancer diagnostic algorithms were calculated at €425,844.05 for the regional health care system and €5,663,057.00 for Italy (€96,227.49 every million inhabitants/year), see [Table 2](#).



**Figure 1** Diagnostic and management workflow for lesion with cost per procedures. On the left side are indicated the procedures and the cost in current routine setting. On the right side are enlisted the procedures and the costs in a setting with the routine use of reflectance confocal microscopy.

**Table 2** Economic Impact of Routine Use of Confocal Microscopy in Emilia Romagna Region

	Current Cost in Melanoma Diagnosis (Without confocal Microscopy)	Cost with Routinely Use of Confocal Microscopy	Difference
Average cost of procedure	Euro 143.63	Euro 114.74	Euro 28.89
Total costs per melanoma§	Euro 904.87	Euro 458.96	Euro 445.91
Total cost for Emilia Romagna Region x year*	Euro 864,150.85	Euro 438,306.80	Euro 425,844.05
Total cost for Italy x year°	Euro 11,491,849.00	Euro 5,828,792.00	Euro 5,663,057.00
Total cost per million of inhabitants x year°	Euro 195,271.18	Euro 99,043.69	Euro 96,227.49

**Notes:** § Calculated as the “cost per procedure” x “number of procedures needed for one melanoma”. In our setting, it resulted that 6.3, without RMC, or 4.0, with RCM, procedures are required to diagnose a melanoma, supposing that all suspicious lesions (including 5.3 (without RMC) or 3.0 (with RCM) benign lesions, corresponding to the NNE value, +1 melanoma) are referred to one of the two workflows. \* Total predictable melanomas (including in situ) x Emilia Romagna Region x year = 955 in a population of 4,426,929. Total predictable melanomas (including in situ) x Italy x year = 12700 in a population of 58,850,717.

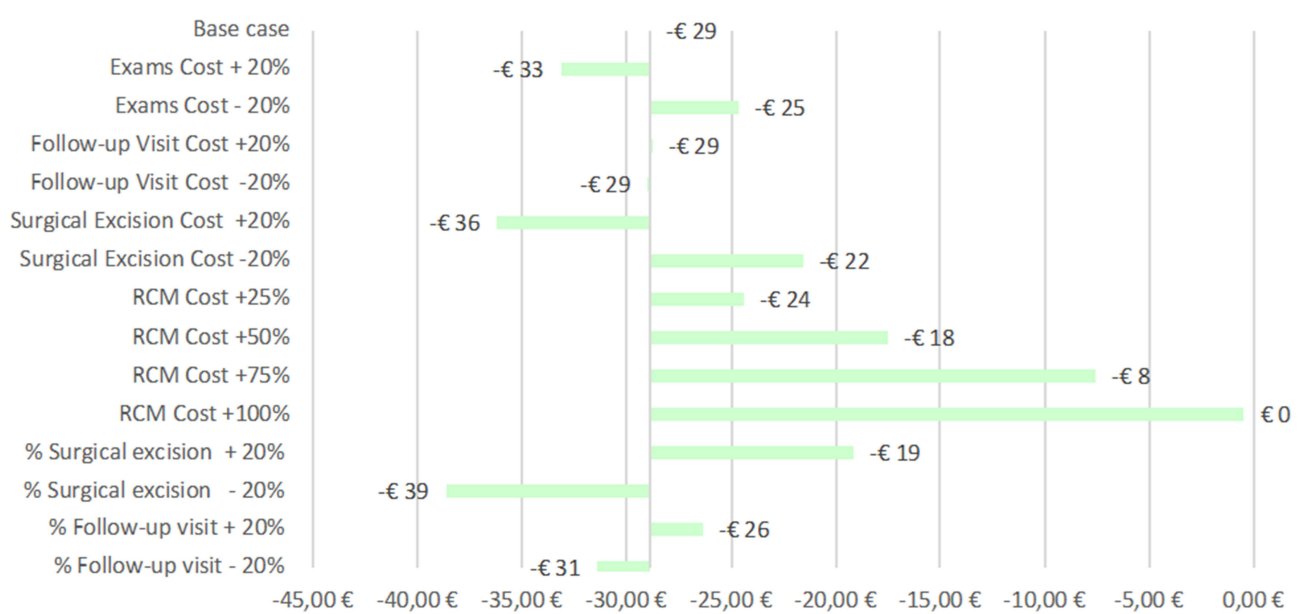
### Cost–Benefit Ratio

Considering a saving of €445.91 for the identification of one melanoma and a cost for an adjunctive RCM procedure of €114.74, an overall benefit–cost ratio in the hospital setting is 3.89 (445.91/114.74). With a basal saving of €28.89, for every €1 spent for an RCM procedure, a benefit of €3.89 is achieved.

### Sensitivity Analysis

The robustness of the study results was demonstrated by the outcomes of the conducted sensitivity analysis. In all proposed scenarios, the cost savings generated by adopting Reflectance Confocal Microscopy compared to the standard of care were confirmed.

As shown in Figure 2, the economic savings increase with the rise in the cost of surgical excision and the decrease in the number of patients undergoing surgical excision. Another parameter that significantly influences the analysis is the cost of RCM. As the price of RCM increases, the economic savings decrease.



**Figure 2** Cost Sensitivity Analysis for the Adoption of RCM in Melanoma Diagnosis.

## Discussion and Conclusions

Previously, we demonstrated a notable impact on the number of unnecessary excisions. We now provide evidence of a cost–benefit advantage for local, regional, and national health care through the routine adoption of adjunctive RCM to standard therapeutic care in a real-world clinical setting. Our evidence is based on data obtained from a randomized clinical trial in a real-world clinical, multi-center scenario.<sup>7</sup>

During our randomized controlled trial, 54 patients randomized to adjunctive RCM and assigned to DDF were lost to follow-up. As these patients did not access the follow-up and therefore did not undergo any excision, for the economic analysis, patients were classified as “without any change at DDF”. Therefore, these patients did not impact our study from an economic point of view; however, any procedure-risk analyses should consider these patients as potential missed melanoma diagnoses.

The diagnostic safety of the adjunctive RCM and delaying lesions to DDF were found to be acceptable, with none of the melanomas identified during follow-up with a thickness >0.5mm. These results should be considered together with the 1.2% of patients who refused excision and the 1.5% of patients lost to follow-up.

As expected, the number of melanocytic and non-melanocytic excisions is considerably lowered with the introduction of adjunctive RCM. We observed nearly half of the number of excised lesions compared to those excised with standard therapeutic care only. The economic benefit estimates of the introduction of adjunctive RCM evaluation for suspicious lesions suggest a saving of €96,227.49 every million inhabitants per year in a real-world setting.

Overall, these data induce some clinical considerations, which may be translated into considerations for clinical practice and the development of institutional pathways. The most immediate is that the introduction of new technologies into diagnostic workflows, proven to be effective, safe, and cost-beneficial, represents a mid- to long-term advantage for both patients and health system sustainability. Cost–benefit analyses obtained from randomized clinical trials performed in real-world settings can assess new technologies’ effectiveness and costs, thereby providing strong evidence of both patient and cost benefits.

Avoiding unnecessary excisions poses benefits for both patients and NHS costs and requires skin cancer-focused education and experience. Our previous local provincial analysis reported that approximately half of the local population refers to outpatient services, where the overall NNE was 19.41.<sup>16</sup> The annual costs compared to estimates with adjunctive RCM were >2-fold (Table 3). These data show that a real-world setting with dermatologists who are not dedicated or technologically equipped for skin cancer management may have a 3-time higher cost impact compared to experts, and up to 12 times higher impact compared to centers with adjunctive RCM. This impact was recently reported as even greater by Bucchi et al who analyzed evolving trends in skin biopsy in Italy. Authors reported biopsy rates of approximately 75-fold higher than the number of total malignant melanomas.<sup>4</sup> Dermoscopy culture and specific training in RCM

**Table 3** Economic Impact of Routine Use of Confocal Microscopy in Emilia Romagna Territorial Service

	Current Cost in Territorial Service (Pellacani et al 2015 <sup>16</sup> )	Cost with Routinely Use of Confocal Microscopy	Difference
Average cost of procedure	Euro 143.63	Euro 114.74	Euro 28.89
Total costs per melanoma§	Euro 2931.49	Euro 1376.88	Euro 1554.61
Total cost for Emilia Romagna Region x year*	Euro 2,799,572.95	Euro 1,314,920.40	Euro 1,484,652.55
Total cost for Italy x year°	Euro 37,229,923.00	Euro 17,486,376.00	Euro 19,743,547.00
Total cost per million of inhabitants x year°	Euro 632,616.30	Euro 297,131.06	Euro 335,485.24

**Notes:** § Calculated as the “cost per procedure” x “number of procedures needed for one melanoma”. In Pellacani et al 2015, it resulted that 20.41 procedures are required to diagnose a melanoma, supposing that all suspicious lesions (including 19.41 benign lesions, corresponding to the NNE value, +1 melanoma) are referred to Territorial Service with no RCM adoption. In our setting, it resulted that 12.0 procedures are required to diagnose a melanoma, supposing that all suspicious lesions (including 11.0 benign lesions, corresponding to the NNE value, +1 melanoma) are referred to Territorial Service with the adoption of RCM. \* Total predictable melanomas (including in situ) x Emilia Romagna Region x year = 955 in a population of 4,426,929. Total predictable melanomas (including in situ) x Italy x year = 12700 in a population of 58,850,717.

interpretation should be favored, with dedicated centers made widely available to increase accessibility and equity in patient care.

The routine adoption of non-invasive techniques may also optimize patient compliance whilst continuing to assure patient safety. In the standard therapeutic care arm, almost all patients with suspicious lesions are immediately sent for surgical excision. However, biopsy is an invasive procedure, associated with complications and psychological patient stress. Our data report that 23 patients in this study arm refused excision. However, with adjunctive RCM, the percentage of patients who refused excision fell to 10. This reduced number may be associated with the higher level of physicians' diagnostic assurance.

Increased diagnostic accuracy with adjunctive RCM is expected to greatly impact the phenomenon of "false positive" diagnoses. Recently, there has been much discussion around a potential cycle of increasing melanoma "overdiagnosis" due to the adoption of lower thresholds for referring patients to a dermatologist for evaluation, and by dermatologists to refer to biopsy.<sup>21</sup> Interestingly, if future longer-term follow-up of our study participants confirms ongoing non-malignant diagnosis, the slightly higher number of melanomas identified with standard therapeutic care only (294 vs 278) may support the presumed dermatologists' lower threshold in sending patients to biopsy, as sustained by Welch et al.<sup>21</sup> Welch suggests that the solution may be in the reduction of screening visits. However, we firmly believe in enhancing diagnostic accuracy of the general practitioner in the triage of skin lesions in routine clinical practice and through the adoption of adjunctive RCM in the dermatological setting.<sup>4,22</sup>

The discussion around the plausibility of adjunctive RCM in a clinical setting considers both clinical and economic aspects, with the plausibility of health technology requiring robust evidence.<sup>23</sup> In addition to the clinical advantages of improved diagnostic precision and safety, already provided by our previous publication, the estimated costs provided by our current study underline the direct and indirect savings associated with the adoption of adjunctive RCM.<sup>7</sup>

Our analysis is principally limited by assumptions. We assumed similar costs among the participating centers as they are all located in the same Italian region. However, the cost estimates provided in our study were estimated in a specific clinical, ethnical, and geographical area, with specific healthcare policies. Other real-world settings are likely to have variations in these factors that could influence health technology assessments and relative reimbursement outcomes.<sup>24</sup> Moreover, there is currently a limited pool of experienced RCM readers in both hospitals and outpatient services, and different expertise and dedication to dermoscopy use, with costs and learning curves associated with doctor and technician RCM training, and neither of these aspects were considered in the current study.<sup>9</sup> However, prior to our randomized study, almost all NNEs available in literature have been based on retrospective analyses, with inherent limitations of validity. Future cost-effectiveness research should provide a comprehensive evaluation of complementary costs either encountered (eg foregone wages, travel expenses, and costs covered by family members) or avoided by the patient with the diagnosis of a benign lesion following adjunctive RCM assessment.

We have demonstrated that both in a randomized clinical trial<sup>7</sup> and a real-life setting,<sup>16</sup> the adoption of adjunctive RCM in routine clinical practice offers overall economic advantages for health systems, whilst maintaining patient safety, reducing unnecessary surgical exposure, and potentially increasing patient adherence. In this time of economic austerity, economic sustainability studies of non-invasive, advanced technologies in routine melanoma detection are essential.

## Synopsis

**Question:** Is adjunctive reflectance confocal microscopy in real-world, routine clinical practice economically viable?

**Findings:** Our cost–benefit analysis, conducted with a micro-costing approach, applied to prospectively collected data from a multicenter, two-arm, randomized study estimates that adjunctive reflective confocal microscopy in skin cancer diagnostic settings offers an overall cost–benefit ratio.

**Meaning:** For every €1 spent on reflectance confocal microscopy, there is a benefit of €3.89.

## Data Sharing Statement

Giovanni Pellacani had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Data collection was conducted by Silvana Ciardo and Laura Mazzoni and data analysis was

also conducted by Shaniko Kaleci and Johanna Chester. The data are not available since the economic analysis was conducted using aggregated data.

## Ethics

IRB approval status: Reviewed and approved by Italian Ministry of Health (NET-2011-02347213) 18/February 2013; Modena Ethics Committee (Prot. No. 3844/C.E.) 09/October/2014.

Clinicaltrial.gov listing: NCT04789421

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## Disclosure

The authors have no conflict of interest to declare. Giorgio Lorenzo Colombo and Giovanni Pellacani shared last-coauthorship.

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