Horizon Scanning report No. 10

Raman spectroscopy for early detection of skin cancer

July 2012

Methods

Agenas is a public body. Its mission is to promote innovation and development within the Italian national healthcare service and provide an Early Awareness and Alert (EAA) service by Horizon Scanning (HS) activities in the field of new and emerging health technologies.
Agenas serves as a hub for RIHTA, the Italian network for Health Technology Assessment. Agenas develops EAA and HTA projects and initiatives together with RIHTA members (Regional governments, Autonomous Provinces, and Regional Public Health Agencies).

A full description of the methods used for the production of the present HS report can be found at www.agenas.it

This document should be cited as follow:
Migliore A, Bonelli L, Giani E, Romano V. Raman spectroscopy for early detection of skin cancer. Agenas, Agenzia nazionale per i servizi sanitari regionali. Rome, July 2012.

For further information contained in this report please contact:
Agenas – Agenzia nazionale per i servizi sanitari regionali
Sezione Iss – Innovazione, sperimentazione e sviluppo
Via Puglie, 23 - 00187 Roma
e-mail: hta@agenas.it

Limitations

This report is based on information available when the searches were made and does not contain data on subsequent developments or improvements of the evaluated technology. The observations made on effectiveness, safety or cost-effectiveness of the technology evaluated in the report are to be considered temporary.

Authors

This HS report was prepared by:

Antonio Migliore

Luigina Bonelli

Elisa Giani

Valeria Romano

Systematic searches were performed by:

Valeria Romano

Declaration of Conflict of Interest

The authors declare that they will not receive either benefits or harms from the publication of this report. None of the authors have or have held shares, consultancies or personal relationships with any of the producers of the devices assessed in this document.

Acknowledgements

Mauro Picardo *(Istituto Dermatologico San Gallicano, Rome, Italy)*; Thomas Braun *(Verisante Technology Inc.)*; Marina Cerbo *(Agenas, Rome, Italy)*; Tom Jefferson *(Agenas, Rome, Italy)*; Simona Paone *(Agenas, Rome, Italy)*.

Name of the technology/procedure: **Raman spectroscopy for early detection of skin cancer**

Target population

Raman spectroscopy (RS) is indicated for use in the evaluation of skin lesions that may be clinically suspicious for melanoma, squamous cell carcinoma and/or basal cell carcinoma. RS should be used when a medical professional chooses to obtain additional data to rule out one of the above conditions before making a final decision to biopsy [Verisante press release, Nov.2011].

Description of the procedure and technology

The clinical diagnosis of skin cancer is based on visual examination (dermoscopy) followed by biopsy of suspicious lesions. The videodermatoscope (a system including a video-probe that transmits images of the pigmented skin lesion to a color monitor) is commonly used to magnify the lesions for a more accurate examination. Image analysis software contribute in the definition of lesion characteristic and consequently in the diagnosis. As the accuracy of the technique depends on the clinician and is highly variable according to the level of formal training and experience [Lui H, 2012], new methods have been developed. RS is a non-invasive optical method under investigation for cancer diagnosis [Zeng H, 2008]. The Raman spectrum correlates with the molecular vibrations of various tissue biomolecules. The positions and relative magnitudes of spectral peaks correspond to the vibrational energies associated with specific chemical bonds. RS has been shown capable of detecting molecular and/or biochemical changes associated with pathology [Short M, 2006]. In particular, transitions from normal to cancer tissue are associated with differences in chemical structure, which are reflected in the Raman spectra [Gniadecka M, 2004].
Recently a non-invasive optical system based on RS has been developed. It is designed as a tool to aid medical professionals in the assessment of suspect skin lesions for diagnosis as either skin cancer or a benign disorder [Verisante press release, Nov.2011].

Clinical importance and burden of disease

Skin cancers represent the most frequent neoplasia in white populations in many countries worldwide. The three most common subtypes of skin cancer are Basal Cell Carcinoma (BCC), Squamous Cell Carcinoma (SCC) and Cutaneous Malignant Melanoma (CMM). Little is known about the incidence of non melanoma skin cancers (NMSC): studies suggested an increasing incidence trend [Lomas A, 2012]; however, due to current under-registration in most countries (frequently they escape the traditional cancer clinical history), large tumour registry networks [Globocan] do not report incidence and mortality data for NMSC. All skin cancers recognise chronic exposure to solar UV radiation as a key environmental risk factor [Whiteman DC, 2001; Schwartz RA, 2008; Chang YM, 2009; Parkin DM, 2011; Bauer A, 2011]. An important determinant of skin cancer risk is the cutaneous pigmentation and the tanning ability in response to UV radiation exposure [Han J, 2006; Nan H, 2009]. The interaction of environmental and genetic factors also plays a key role in the CMM development. In Italy, in 2003-2005, skin cancers represent around 15% of all cancer diagnosed in both sexes [AIRTUM]. NMSC have a good prognosis as usually are only locally aggressive but represent a considerable economic burden to health services due to their frequency and high

rates of multiple recurrences [Marcil I, 2000]. CMM is potentially the most dangerous form of skin cancer and cause around 90% of skin cancer related mortality. Incidence of CMM is rapidly increasing worldwide and more than 50% of all CMMs are diagnosed within the age 60 years [SEER; Globocan; AIRTUM]. In Italy, in the last two decades the annual incidence of CMM doubled from 6 to 12 cases/100,000 inhabitants (more than 6,000 new cases/year) with a significant north-south gradient (from 15/100,000 to 4/100,000 inhabitants). Mortality is stable around 2/100,000 inhabitants (1,500 deaths per year). In different population's prognosis is slightly better for females than for males [AIRTUM; Joosse A, 2011; Joosse A, 2012] and for people with a higher socioeconomic status [Zell JA, 2008]. In spite of recent impressive developments in systemic therapies for advanced CMM [Eggermont AMM, 2011], the detection and surgical removal of early lesions is still virtually the only curative available approach. However, the observed worldwide increased incidence, mainly of very early CMM stages (AJCC stage IA), associated with only minor changes in mortality suggests some overdiagnosis [Welch GH, 2010; Nørgaard C, 2011]. Accurate identification of skin lesions is essential to ensure that malignancies are identified early and adequately treated. It is as well important that appropriate lesions are submitted for biopsy to decrease the costs and morbidity associated with the unnecessary removal of benign lesions [Tromme I, 2012]. NMSC may mimic or may be mimicked by preneoplastic or frankly benign lesions and differential diagnosis should be established (e.g. superficial BCC from Bowen's Disease, psoriasis, discoid eczema or tinea corporis) or by frankly malignat lesions (Pigmented BCC from nodular melanoma). Dermoscopic vascular patterns of NMSC allow to improve differential diagnosis in non pigmented lesions. Early detection of CMM is a key challenge due to low predictive value of skin examination; in patients with focused symptoms, total body skin examination shows a low rate of false-positive results [Argenziano G, 2012]. The use of dermoscopy in screening campaigns for the early diagnosis of melanoma is increasingly involving routine dermatopathology with smaller and smaller atypical melanocytic lesions. Various instruments based on pigmented skin lesions images' acquisition and elaboration have been developed in an attempt to in vivo establish whether a lesion is a melanoma or not. Although encouraging, the response of these instruments, cannot currently replace the well-established diagnostic procedures.

Products, manufacturers, distributors and approval

We identified only one system for the early detection of skin cancer that is based on RS: the Verisante Aura™ (manufactured by Verisante Technology Inc.). In 2011 the system received CE mark, Health Canada approval and regulatory approval in Australia. The manufacturer stated that the process to obtain the US Food and Drug Administration (FDA) approval started in the same year.

The Verisante Aura™ system comprises a diode laser, an optical fibre and a fibre bundle delivery system, a hand-held Raman probe, a spectrograph, a CCD camera detector, and a computer. A laser beam is delivered to the Raman probe through a single fibre and illuminates a 3.5 mm diameter skin area. The raw signal from the skin, which is composed of the Raman scattering signal and tissue autofluorescence, is collected by the probe and transmitted to the spectrometer through a fibre bundle for spectral analysis. The integrated software contains all calibration procedures and real-time data processing. To take a Raman measurement, the hand-held probe is placed in gentle contact with the target skin site without compressing it. The spectral measurement for a skin lesion takes 1 second and is taken in duplicate by separately measuring each lesion itself and then the normal-appearing surrounding skin from the same anatomic region [Lui H, 2012]. The manufacturer stated that the only two systems being used are at the BC Cancer Agency and at the Skin Care Centre at Vancouver General Hospital (beta units for the field testing of the software/algorithm). The production of the first commercial systems is expected by the end of 2012.

Product name [Manufacturer]	Distributor	CE Mark	RDM	FDA
Verisante Aura™ [Verisante Technology Inc.]	Verisante Technology Inc.	☑	☐	☐

Setting

The Verisante Aura™ system can be used in both generalist and specialist clinics.

☐ Home	☐ Hospital	☑ Outpatient
☐ Accident and Emergency	☐ Other:	

Roll out in Italy

At the time of writing (July 2012) Verisante Technologies Inc. has no distributors for Italy. No systems are operating in any Italian hospital.

☑ Pre-marketing	☐ On the market for 1-6 months	☐ On the market for 7-12 months
☐ On the market for more than 12 months	☐ Not identified	

Comparators

As RS is a means for assisting the evaluation of suspect skin lesions, its use can be considered as additional to the current diagnostic pathway (the primary diagnosis of skin cancer is made by visual examination by the dermatologist/general practitioner; the definitive diagnosis requires excision of the suspect lesion, biopsy and full pathology) [Lui H, 2012]. The Verisante Aura™ system is thus complementary to other non-invasive evaluation techniques. Several dermoscopy-based systems have been developed and tested in the past decade. All of them were aimed at differentiating cutaneous melanoma from non neoplastic pigmented lesions [Lui H, 2012]. These systems should be considered as “competitors” of the technology assessed and not proper comparators.

Effectiveness and safety

We carried out searches on EuroScan and CRD (DARE & HTA) databases (10th May 2012) looking for documents published in Italian and English on the non-invasive diagnosis of skin cancer, and Raman spectroscopy. No documents were found.
We searched the major databases: Medline (21st June 2012), EMBASE (28th June 2012) and the Cochrane

Library (11th May 2012) looking for studies, published in Italian or English, reporting on effectiveness and safety in all kind of patients (humans) in which skin lesions clinically suspicious for melanoma, squamous cell carcinoma and/or basal cell carcinoma have been evaluated by using the Verisante Aura™ system. The search results (n = 97) were screened reading title and abstract. One citation was considered eligible for full text analysis [Lui H, 2012].

The study by Lui et al. 2010 [Lui H, 2012] was performed in Canada, at the Vancouver General Hospital Skin Care Centre, using an integrated real-time Raman system developed in-house (a prototype of the Verisante Aura™ system). Between 2003 and 2011, Raman spectra were acquired from 1,022 separate benign and malignant skin lesions from 848 patients. Among these the following were selected: (a) malignancies and premalignancies that require treatment: melanoma, SCC, BCC, and actinic keratosis and (b) benign conditions that can visually mimic skin cancer: seborrheic keratosis, atypical nevi, melanocytic nevi (junctional, compound, and intradermal), and blue nevi. The final data set thus consisted of 518 validated lesions from 453 subjects (224 male, 229 female), aged 18 to 94 years (median, 61 years).

The diagnostic performance of the system, defined as "discrimination ability", was assessed in the following three dichotomous groupings based on clinical relevance: i) cancerous and precancerous lesions (malignant melanoma, BCC, SCC, and actinic keratosis) *versus* benign conditions (atypical nevi, blue nevi, compound nevi, intradermal nevi, junctional nevi, and seborrheic keratosis); ii) melanoma (all forms, melanoma) *versus* benign pigmented skin lesions (atypical nevi, blue nevi, compound nevi, intradermal nevi, junctional nevi, and seborrheic keratosis); iii) melanoma (all forms, melanoma) *versus* seborrheic keratoses. The following parameters were calculated: the receiver operating characteristic (ROC) AUC; positive predictive value (PPV), negative predictive value (NPV), skin biopsy ratio (number of negative biopsies that are conducted for each true-positive biopsy showing skin cancer) at sensitivity levels of 90%, 95%, and 99%, respectively.

Results from grouping i) – Cancerous and precancerous skin conditions (n = 232) versus benign skin lesions (i.e. noncancer; n = 286): the ROC AUC was 0.879 (95% CI, 0.829–0.929, P < 0.001). At a sensitivity of 90%, the overall specificity was more than 64%, with a PPV of 67% and NPV of 89%. The estimated biopsy ratio was 0.5:1.

Results from grouping ii) – Melanoma (n = 44) versus nonmelanoma pigmented skin lesions (n = 286): the ROC AUC was 0.823 (95% CI, 0.731–0.915, P < 0.001). The biopsy ratio ranged from 5.6:1 to 2.3:1 for sensitivities corresponding to 99% to 90% and specificities from 15% to 68%, respectively.

Results from grouping iii) – Melanoma (n = 44) versus seborrheic keratosis (n = 114): The ROC AUC was 0.898 (95% CI, 0.797–0.999, P < 0.001). The biopsy ratio ranges from 2.2:1 to 0.9:1, for sensitivities ranging from 99% to 90% and specificities of 25% to 68%.

The authors found evidence to support the use of RS for guiding skin cancer diagnosis at different levels of clinical interest with the ROC AUCs ranging above 0.82. The observed benign/malignant biopsy ratio was far lower than that observed in a pure clinical setting [Cohen MH, 1991; Westerhoff K, 2000] or with the complementary use of devices [Westerhoff K, 2000]. RS could be considered as a "second expert opinion" when cutaneous biopsy is indicated on the basis of clinical evaluation.

We also searched in the clinicaltrial.gov database (14th May 2012): no pertinent clinical trials were found. The manufacturer stated that at the time of writing (July 2012) there are no running registers for data collection.

Potential benefits to patients

The technology guides skin cancer diagnosis at different levels of clinical interest (i.e. malignant/premalignant versus benign; melanomas versus benign pigmented lesions, melanomas versus seborrheic keratoses). Use of this technology may reduce the number of unnecessary biopsies [Lui H, 2012].

☑ Mortality reduction or increased survival	☐ Reduction of the morbidity	☐ Improved quality of life (patient/users)
☐ Improved patient monitoring	☑ Other: Early diagnosis	☐ Not identified

Cost of the technology / procedure

The Verisante Aura™ system needs disposable tips (one per patient) and a filtered light to be used during the scanning procedures. Everything is provided by the manufacturer. We contacted the manufacturer (Verisante Technology, Inc.) for the following price list (all prices are exclusive of VAT):

- Verisante Aura™ device plus filtered light: € 60,000;
- Disposable tip: € 10.

As the technology is additional to the current diagnostic pathway for skin cancer, its introduction will be linked to new costs (i.e. acquisition of the technology) at a first instance. However, potentially, its use will contribute to the reduction of the number of biopsies performed and this will be translated in avoided costs. At the time of writing (July 2012) no economic evaluations have been performed on the use of the Verisante Aura™ system.

☐ Increased costs compared to alternative treatments	☐ Increased costs due to increased demand	☐ Increased costs due to the required investments
☑ New costs	☐ Other:	☐ Not identified

Potential structural and organisational impact

Structural impact

The Verisante Aura™ system has no relevant structural impact. It needs to be used in a windowless examination room with no light sources (they may interfere with the signal that is being acquired).

☐ Increase in requirement of instruments	☑ Always be used	☐ Can be used only under specific circumstances
☐ Decrease in requirement of instruments	☐ Other:	☐ Not identified

Organisational impact

According to the manufacturer, any medical professional can use the Verisante Aura™ system; it only requires one person to operate. A general practitioner, with less expertise in skin cancer detection, may use the device to screen for skin cancer to refer suspicious lesions to a dermatologist; a dermatologist, who has extensive experience in skin cancer detection, may use the device to decide on which lesions a biopsy needs to be performed. The manufacturer anticipated that local distributors will be directly trained and final users (i.e. medical professionals) will receive training from the latter, without any further cost. At the time of writing (July 2012) studies reporting the learning curve in using the Verisante Aura™ system are not available.

☐ Increase in the number of procedures	☐ Re-organisation required	☑ Training required for users
☐ Reduction in the number of procedures	☐ Other:	☐ Not identified

Conclusions

Even if the device is CE marked, it is not commercially available for clinical use (testing of the first beta unit is ongoing in Canada; the production of the commercial version is expected in the second semester of 2012). The advantages of this new technology (e.g. short examination time, diagnostic performance higher than other competitor technologies) seem to be concrete but have been proved in just one cohort of patients, within a single-centre non-comparative study carried out using a prototype device, published by the inventor, and for which the manufacturer covered the publication costs. Further evidence is needed before giving guidance on the use of the final commercial version of the system. In particular, comparative data should be generated within the framework of independent, multi-centre, multi-operator clinical studies (to compare the standard diagnostic pathway without the new technology versus the standard diagnostic pathway with the new technology). No considerations about costs can be made. One of the most important gains would be the reduction of the number of biopsies performed but such analysis needs more generalisable results from clinical studies.

Future prospects

Together with diffuse reflectance spectroscopy and fluorescence spectroscopy, RS has the potential to become an important optical tool in the field of clinical oncology. Significant progress has been made in the discriminating abilities of the various techniques between normal and cancerous tissue and the field is rapidly evolving. In the next decade, a translation of this technology into clinical practice is expected. Prospective analyses of spectroscopy systems, as well as in vivo clinical trials in humans, have recently been initiated [Evers DJ, 2012].

Evidence searches

Searches of the databases were carried out between 10th May 2012 and 28th June 2012, using the following keywords to indicate:

- ***the technology of interest:*** *Raman spectroscopy, non-invasive skin cancer diagnosis, multimodality skin cancer diagnosis, Verisante, Aura, imaging, diagnosis.*
- ***the pathology of reference:*** *melanoma, basal cell carcinoma, squamous cell carcinoma, suspect lesions, pre-cancer, Raman spectra, Raman spectroscopy.*

Bibliography

Verisante press release, Nov.2011: http://www.verisante.com/news/68/ce-mark-for-verisante-aura-opens-doors-to-massive-european-market/

Lui H, Zhao J, McLean D, Zeng H. Real-time Raman Spectroscopy for In Vivo Skin Cancer Diagnosis. Cancer Res. 2012 May 15;72(10):2491-500.

Zeng H, Zhao J, Short M, McLean DI, Lam S, McWilliams A, et al. Raman spectroscopy for in vivo tissue analysis and diagnosis, from instrument development to clinical applications. J Innov Opt Health Sci 2008;1:95–106.

Short M, Lui H, McLean DI, Zeng H, Alajlan A, Chen XK. Changes in nuclei and peritumoral collagen within nodular basal cell carcinomas via confocal micro-Raman spectroscopy. J Biomed Opt 2006;11: 034004.

Gniadecka M, Philipsen PA, Sigurdsson S, Wessel S, Nielsen OF, Christensen DH, et al. Melanoma diagnosis by Raman spectroscopy and neural networks: structure alterations in proteins and lipids in intact cancer tissue. J Invest Dermatol 2004;122:443–9.

Lomas A, Leonardi-Bee J, Bath-Hextall F. A systematic review of worldwide incidence of nonmelanoma skin cancer. Br J Dermatol. 2012 May;166(5):1069-80.

Globocan - Cancer Incidence, mortality and Prevalence Worldwide in 2008. http://Globocan.iarc.fr

CI5 - Cancer Incidence in five continents. http://ci5.iarc.fr/CI5plus/ci5plus.htm

Whiteman DC, Whiteman CA, Green AC. Childhood sun exposure as a risk factor for melanoma: a systematic review of epidemiologic studies. Cancer Causes Control. 2001; 12: 69-82.

Schwartz RA, Bridges TM, Butani AK, Ehrlich A. Actinic keratosis: an occupational and environmental disorder. J Eur Acad Dermatol Venereol. 2008; 22:606-15.

Chang YM, Newton-Bishop JA, Bishop DT, Armstrong BK, Bataille V, Bergman W et al , A pooled analysis of melanocytic nevus phenotype and the risk of cutaneous melanoma at different latitudes. Int J Cancer 124: 420-428; 2009.

Parkin DM, Mesher D, Sasieni P. 13. Cancers attributable to solar (ultraviolet) radiation exposure in the UK in 2010. Br J Cancer. 2011;105 Suppl2:S66-9.

Bauer A, Diepgen TL, Schmitt J. Is occupational solar ultraviolet irradiation a relevant risk factor for basal cell carcinoma? A systematic review and meta-analysis of the epidemiological literature. Br J Dermatol. 2011;165:612-25.

Han J, Colditz GA, Hunter DJ. Risk factors for skin cancers: a nested case-control study within the Nurses' Health Study. Int J Epidemiol. 2006; 35: 1514-21.

Nan H, Kraft P, Hunter DJ, Han J. Genetic variants in pigmentation genes, pigmentary phenotypes, and risk of skin cancer in Caucasians. Int J Cancer. 2009; 125: 909-17.

AIRTUM 2009: New incidence and mortality data 2003-2005 (Associazione Italiana Registri Tumori). http://www.registri-tumori.it/cms/it

Marcil I, Stern RS. Risk of developing a subsequent nonmelanoma skin cancer in patients with a history of nonmelanoma skin cancer: a critical review of the literature and meta-analysis. Arch Dermatol 2000; 136: 1524.

SEER (Surveillance, Epidemiology and End Results): http://seer.cancer.gov

Joosse A, de Vries E, Eckel R, Nijsten T, Eggermont AM, Hölzel D, Coebergh JW, Engel J; Munich Melanoma Group. Gender differences in melanoma survival: female patients have a decreased risk of metastasis. J Invest Dermatol. 2011; 131: 719-26.

Joosse A, Collette S, Suciu S, Nijsten T, Lejeune F, Kleeberg UR, et al . Superior Outcome of Women With Stage I/II Cutaneous Melanoma: Pooled Analysis of Four European Organisation for Research and Treatment of Cancer Phase III Trials. J Clin Oncol. 2012 Apr 30.

Zell JA, Cinar P, Mobasher M, Ziogas A, Meyskens FL Jr, Anton-Culver H. Survival for patients with invasive cutaneous melanoma among ethnic groups: the effects of socioeconomic status and treatment. J Clin Oncol. 2008; 26:6 6-75.

Eggermont AMM, Robert C. New drugs in melanoma: It's a whole new world. Eur J Cancer, 2011; 47: 2150–2157.

Welch GH, Black WC. Overdiagnosis in Cancer. J Natl Cancer Inst 2010;102:605–613.

Nørgaard C, Glud M and Gniadecki R. Are All Melanomas Dangerous? Acta Derm Venereol 2011; 91: 499–503.

Tromme I, Sacré L, Hammouch F, Legrand C, Marot L, Vereecken P, et al. Availability of digital dermoscopy in daily practice dramatically reduces the number of excised melanocytic lesions: results from an observational study. Br J Dermatol. 2012 May 7.

Argenziano G, Zalaudek I, Hofmann-Wellenhof R, Bakos RM, Bergman W, Blum A, et al Total body skin examination for skin cancer screening in patients with focused symptoms. J Am Acad Dermatol. 2012; 66: 212-9.

Cohen MH, Cohen BJ, Shotkin JD, Morrison PT. Surgical prophylaxis of malignant melanoma. Ann Surg. 1991; 213:308–14.

Westerhoff K, McCarthy WH, Menzies SW. Increase in the sensitivity for melanoma diagnosis by primary care physicians using skin surface microscopy. Br J Dermatol 2000;143:1016–20.

Evers DJ, Hendriks BHW, Lucassen GW, Ruers TJM. Optical spectroscopy: current advances and future applications in cancer diagnostics and therapy. Future Oncology, March 2012, Vol. 8, No. 3, Pages 307-320.

Glossary

AJCC: American Joint Commission on Cancer.

AUC: Area under the curve.

BCC: Basal cell carcinoma.

CCD: Charge-coupled device.

CI: Confidence interval.

CMM: Cutaneous malignant melanoma.

CRD: Centre for Reviews and Dissemination.

FDA: Food and Drug Administration.

NMSC: Non melanoma skin cancer.

NPV: Negative predictive value.

PPV: Positive predictive value.

RDM: Medical device Repertory (http://www.salute.gov.it/dispositivi/paginainternasf.jsp?id=499&menu=repertorio).

ROC: Receiver operating characteristic.

SCC: Squamous cell carcinoma

VAT: Value added tax.