

decreased detection of the anaphylatoxin C5a (a marker of complement activation located downstream in the complement cascade) in CFT supernatants from the same experiments (Fig. 1b).

Our *in vitro* results suggest that patients with BP may benefit from off-label LMWH use. Inhibiting ongoing complement fixation and C5a liberation by LMWH may improve skin disease, as suggested in part by BP disease models employing C5a receptor-deficient mice.<sup>9</sup> Such therapy might also help prevent coagulation-related complications in BP,<sup>2,10</sup> but the risk vs. benefit in this regard would have to be carefully studied. LMWHs are generally considered safe therapeutics, although long-term side-effects do include osteoporosis, which is also a side-effect of standard BP therapy with corticosteroids.

One limitation of our *in vitro* study may be the rather supra-physiological concentrations of TS used, but at the same time, a high-titre pool of BP sera was used for CFT, resulting in strong BMZ autoantibody binding. Given that clinically overt disease is seen at considerably lower titres of circulating autoantibodies in patients with BP and that the *in vitro* CFT also works with highly diluted BP sera by extending times of incubation with the fresh complement source (data not shown), we find it conceivable that lower, more physiological TS doses may also be effective, as already suggested in patients with complement-mediated renal disease.<sup>7</sup> In addition, there may be LMWHs other than TS that could inhibit complement better at similar or even lower doses.

In summary, we suggest that patients with BP with complement deposits at the BMZ may benefit from LMWH administration. Positive effects of LMWH may also be observed in other complement-fixing diseases such as mucous membrane pemphigoid, epidermolysis bullosa acquisita, autoantibody-mediated forms of glomerulonephritis and C3 glomerulonephritis. To confirm conclusively the therapeutic potential hypothesized in this report, additional *in vivo* studies employing animal models and randomized controlled trials in patients are warranted.

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## Surveillance for familial melanoma: recommendations from a national centre of expertise

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DEAR EDITOR, An estimated 10% of patients diagnosed with melanoma have a positive family history for this cutaneous malignancy.<sup>1</sup> Familial melanoma is arbitrarily defined as the occurrence of three or more melanomas in multiple members of a family, at least two of which are diagnosed in first-degree

relatives. The pedigrees of these families are compatible with an autosomal dominant mode of inheritance. In a subset of families, clustering is caused by polygenic inheritance or shared ultraviolet radiation exposure patterns among members. The genetic basis of familial melanoma can currently be established in less than half of cases and differs within populations.

The term hereditary melanoma is commonly used when the causative pathogenic gene variant in a family has been identified. Most cases of hereditary melanoma are caused by pathogenic variants in the *CDKN2A* gene, which encodes the p16 and p14 tumour suppressor proteins. Carriers of pathogenic variants in this gene are also at risk of developing pancreatic cancer. For carriers of the p16-Leiden variant in *CDKN2A* (19-base pair deletion in exon 2) the lifetime risk of pancreatic cancer amounts to 18%, but for other inactivating *CDKN2A* variants this risk may be less.<sup>2</sup>

In recent years more melanoma susceptibility genes have been identified, each associated with increased risk of various tumour types in addition to melanoma.<sup>1</sup> Several more candidate genes have been proposed and more await discovery. Surveillance of individuals carrying melanoma susceptibility gene variants increases early detection and treatment outcome.<sup>3</sup> However, it can be difficult, in particular for dermatologists who encounter this condition infrequently, to determine which members of a family should undergo periodic skin examination and other oncological screening procedures. There is a paucity of clinical evidence supporting the benefit of surveillance in genetically defined familial melanoma subgroups. Here we present recommendations of the centre of expertise for familial melanoma in the Netherlands, based on our clinical experience and scarce evidence.

We refer members of families who meet the criteria for a diagnosis of familial melanoma to a clinical geneticist for counselling and genetic testing from the age of 18 years.

Preferably genetic tests are performed on DNA from a family member diagnosed with invasive melanoma. Additionally, we recommend referral of families where two first-degree relatives are diagnosed with melanoma, and families where melanoma and pancreatic cancer are diagnosed. We also recommend clinical genetic consultation for patients with three or more melanomas, patients with melanoma diagnosed before the age of 18 years, patients with multiple BAP1-deficient melanocytic naevi and patients with a combination of melanoma and pancreatic cancer or uveal melanoma.

All individuals at increased risk of melanoma receive oral and written instructions on self-examination of the skin and on sun-protective behaviour. Dermatological surveillance consists of total skin examination with use of dermoscopy and total body photography. Patients are encouraged to visit our clinic if suspicious pigmented skin lesions are noticed, and to abstain from smoking.

Currently we offer high-risk patients genetic testing for mutations in eight established melanoma susceptibility genes using a custom-designed targeted gene panel. For carriers of pathogenic variants in these genes and their first-degree relatives the proposed dermatological and oncological surveillance schedules are presented in Table 1. To carriers of a pathogenic variant in the *CDKN2A*, *CDK4* or *TERT* genes we recommend biannual skin examination. In our centre, first-degree relatives of carriers of these variants undergo annual skin examination from the age of 12 years and second-degree relatives from the age of 20 years.<sup>3,4</sup>

To carriers of pathogenic variants in the *BAP1*, *MITF*, *POT1*, *TERF2IP* or *ACD* genes and their first-degree relatives we recommend annual skin examinations, as melanoma risk for carriers of these gene variants is lower or remains to be determined. To patients and their first-degree relatives with familial melanoma where no DNA testing is performed, where no pathogenic gene variant is detected or where the functional

**Table 1** Surveillance recommendations for familial and hereditary melanoma<sup>1-4,6-8</sup>

Gene	Established associated tumour types	Carrier	First-degree relative
<i>CDKN2A</i>	Pancreatic, head and neck cancer, basal cell carcinoma	Skin examination: biannual, from age 12 MRI/EUS pancreas: <sup>a</sup> annual, from age 45	Skin examination: annual, from age 12 <sup>2</sup>
<i>CDK4</i>	—	Skin examination: biannual, from age 12	Skin examination: annual, from age 12
<i>BAP1</i>	Uveal melanoma, mesothelioma, renal cancer, cholangiocarcinoma, meningioma, basal cell carcinoma	Skin examination: annual, from age 20 Eye examination: annual, from age 15 Ultrasound abdomen: biennial (alternating), from age 30 X-ray thorax, MRI abdomen: biennial (alternating), from age 30	Skin examination: annual, from age 20 Eye examination: annual, from age 15
<i>MITF</i>	Renal, pancreatic cancer	Skin examination: annual, from age 12	Skin examination: annual, from age 12
<i>TERT</i>	Bladder, breast, endometrial, lung, ovarian, renal cancer	Skin examination: biannual, from age 12	Skin examination: annual, from age 12
<i>POT1</i>	Glioma, chronic lymphocytic leukaemia	Skin examination: annual, from age 12	Skin examination: annual, from age 12
<i>TERF2IP</i>	—	Skin examination: annual, from age 12	Skin examination: annual, from age 12
<i>ACD</i>	—	Skin examination: annual, from age 12	Skin examination: annual, from age 12
No DNA test performed, or no pathogenic variant detected		Skin examination: annual, from age 12	Skin examination: annual, from age 12

MRI, magnetic resonance imaging; EUS, endoscopic ultrasound. <sup>a</sup>Screening for pancreatic cancer is recommended to carriers of pathogenic variants located in exon 1a, 2 or 3 of the *CDKN2A* gene, affecting the p16 transcript.

consequence of the identified variant is uncertain, we recommend annual skin examination. Identified gene variants classified as uncertain or likely not pathogenic (IARC system class 1, 2 or 3) we consider as not pathogenic.<sup>5</sup>

The proposed dermatological and oncological surveillance schedules are to be considered as a basal frequency. Diagnosis of multiple melanomas, presence of dysplastic naevi, and other factors, could prompt more frequent examinations. Decisions on surveillance and examination frequency should be made on an individual basis by weighing benefits against psychological burden and potential harm from diagnostic procedures. Current and future studies on the absolute risk of various malignancies in carriers of variants in the recently discovered melanoma susceptibility genes will inform these decisions and may lead to modifications of the proposed surveillance schedules and diagnostic procedures. We hope these recommendations will help to improve management of patients with familial and hereditary melanoma.

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## Photoacoustic imaging as an innovative technique for the exploration of blue rubber bleb naevus

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DEAR EDITOR, Blue rubber bleb naevus syndrome (BRBN, Bean syndrome) is a rare vascular malformation (VM) characterized by multiple cutaneous and mucous venous defects disseminated throughout the body. An infringement of mucous membranes is possible with potential complications such as anaemia or haemorrhage.<sup>1</sup> Photoacoustic imaging (PAI) is an emerging technology combining the most compelling features of optical imaging and ultrasound, providing both high optical contrast and high ultrasound resolution at depth in living organisms.<sup>2</sup> PAI offers great potential for noninvasive exploration of tissue, leveraging differences in the optical absorption of underlying tissue components. In particular, oxy- and deoxyhaemoglobin are endogenous absorbers that exhibit specific photoacoustic signals. By using several wavelengths of laser light, relative concentrations of these specific compounds can be determined, providing mapping of total haemoglobin content (HbT) and tissue oxygen saturation (StO<sub>2</sub>) in several tissue layers at submillimetre resolution.<sup>3,4</sup> PAI could be of prime importance for the exploration of VM.

This study reports the use of this new imaging modality, nonionizing and contrast agent free, to monitor the HbT and StO<sub>2</sub> of several BRBN lesions on a 36-year-old patient. The patient presented with BRBN with multiple lesions of the arms, lower limbs and trunk. Doppler ultrasound confirmed the multiple extratruncal low-flow vascular lesions. Ultrasound (B-mode) and PAI were performed using the Vevo LAZR-X system (FUJIFILM VisualSonics, Inc., Toronto, ON, Canada) with a 21-MHz transducer. Three dysplastic sites were scanned – on the left lower limb (Fig. 1a), the left heel and the right forearm (images available on request) – as well as control zones (dermal tissue). The oxyhaemoglobin multispectral PAI mode (750 nm, 850 nm) was used for the evaluation of HbT and StO<sub>2</sub>.

Our results shown that the VM zone on the lower limb (Fig. 1) displayed a very strong photoacoustic signal (Fig. 1c), showing blood accumulation in the lesion area. PAI-derived quantitative values demonstrated significantly higher values of both HbT and StO<sub>2</sub> compared with the contralateral zone ( $\times 2.1$  for HbT and  $\times 1.6$  for StO<sub>2</sub>). In the same way, the VM on the left heel exhibited a clear but heterogeneous photoacoustic signal, illustrating blood accumulation but restricted to a partial zone of the lesion. Quantitative analyses demonstrated higher HbT and StO<sub>2</sub> than in the contralateral zone ( $\times 1.8$  for HbT and  $\times 1.5$  for StO<sub>2</sub>). The PAI results thus illustrated blood accumulation in these two sites, which appeared to be highly oxygenated. Images from other lesions and quantification of HbT and StO<sub>2</sub> measurements are available on request.