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REVIEW

Multimodal Considerations Concerning Basal Cell Carcinoma Clefting – Profile of Structural and Aggressive Traits – Perspectives

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Abstract: Although basal cell carcinoma is a well-known tumor with confirmed clinical and histopathology traits, prognosis factors and treatment options, new facets of this tumor emerge as innovative approach methods develop. Reflectance confocal microscopy (RCM) and optical coherence tomography (OCT) allow a basal cell carcinoma's in vivo analysis of its depth of invasion, tumor margins prior to surgical approach and the tumor's response to a non-invasive treatment, evaluating simultaneously the tumor's vasculature. By RCM and OCT analysis, basal cell carcinoma has registered a groundbreaking discovery regarding a small (but with predictive factor potential) trait – the cleft, developing in between the tumor islands/nodules/chords and the surrounding tumor stroma; it was considered to date as a consequence of the tissue's histopathology processing. RCM and OCT revealed that the "clefting artifact", as it is frequently found in the medical literature, is not actually an artifact of laboratory processing, but a tumor trait found in vivo, with apparent mucin deposits. This review aims at merging the methods of evaluating basal cell carcinoma, both non-invasive (dermoscopy, RCM, OCT) and invasive ones (histopathology – with newly proposed classification), with special emphasis on the cleft issue – its assessment with the aforementioned techniques, with potential implications in the patient's prognosis.

Keywords: basal cell carcinoma, cleft, structural aggressive traits, reflectance confocal microscopy, optical coherence tomography, pathology

Introduction

Basal cell carcinoma (BCC) is one of the most prevalent malignant skin tumors worldwide, having an increasing incidence each year, with variations according to the region. The characteristic-affected population has been represented up until now by the elderly men (having a steep rise in incidence over 40 years of age), with increasing numbers among female patients in the last years, a change reflected in the living style and/or environmental factors' exposure.[1–3] The pathogenesis of BCC is highly complex, with interplay between lifestyle factors, phenotype and genotype, the most important risk factor remaining the ultraviolet (UV) light exposure. The patient's education will play an important role in the future concerning sun exposure and avoidance, with emphasis on (childhood and/or adolescence) protective measures (sun protection creams), the precocious tumor detection and expeditious positive diagnosis, and early treatment measures

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(invasive or not, with updated management alternatives such as Hedgehog pathway inhibitors or immune checkpoint inhibitors).[2,3]

BCC is a skin tumor clinically possessing certain traits which aid in its positive diagnosis, such as the presence of an ulcerated or eroded nodule or papule or plaque, translucency, telangiectasia (dilated blood vessels), pigmentation (black/blue hue) and rolled borders.[1] BCC development is frequently associated with sun exposure, appearing on sun-exposed areas of the face and body; some anatomical areas are considered to be of high-risk, such as facial periorificial zones which frequently develop aggressive types of BCCs.[1,4]

Clinically, BCC should not be confused with a large variety of differential diagnoses which include skin tumors or inflammatory disorders, such as: Darier's disease, adult-onset xanthogranuloma, epidermal cysts, lymphoma, rhabdomyomatous mesenchymal hamartoma, adnexal tumors (having either follicular, sebaceous or sweat gland differentiation), squamous cell carcinoma, Ewing's sarcoma, Merkel cell carcinoma, trichoblastoma, allergic contact dermatitis, irritant contact dermatitis, psoriasis, lymphoepithelioma-like carcinoma, pomade crust, and many others, all of these presenting with traits which could determine a physician to give an erroneous positive diagnosis of BCC.[1,3,5–7]

The positive BCC diagnosis is made on the basis of the clinical traits, the dermoscopic analysis and histopathologic evaluation (considered to be the gold standard and an invasive procedure); other new, emerging non-invasive procedures have been taken into consideration for BCC diagnosis, as indicated below.[8]

Dermoscopy and Other Innovative Non-Invasive Procedures

A well-known, non-invasive, in vivo examination procedure is dermoscopy, having a sensitivity of up to 91.2% and a specificity up to 95%. This allows clinical examination of the lesion's traits which cannot be visible directly (meaning, with the open-eye). In order to make a positive diagnosis of BCC, the following three features have to be found: vascular traits (fine, arborizing, corkscrew/glomerular vessels), pigmented traits (white-shiny areas, alternating with white-reddish areas, and multiple dots-like or ovoid blue-grayish nests) and ulceration. These three traits, associated with melanocytic lesions traits (network-like zones) establish a positive BCC diagnosis. These traits, mixed and matched, give the overall aspect of BCC, with some variability according to the subtype of the tumor, the patient's age, race and gender, the location of the tumor and the existence of pigment in the tumor islands.[9–11]

Currently, there are other new, emerging non-invasive procedures which aid in making a positive BCC diagnosis: the reflectance confocal microscopy (RCM) and the optical coherence tomography (OCT).[8]

RCM is a technology which uses a near-infrared laser in studying a BCC lesion and offers imaging of thin sections from this cutaneous lesion.[8] Besides the characteristics of a BCC's subtype, RCM examination has revealed, in vivo, a somewhat particular trait, considered an artifact in the past: the tumor-stroma separation/cleft which looks like areas of low refractility in-between the tumor mass and the surrounding stroma, thus raising the question whether the mucin found here is the culprit for such separation, and whether this suggests a more aggressive behavior or not.[12]

OCT is a technology which uses infrared light in order to give real-time images of the BCC lesion, based on the sum of the light refractions of the different cutaneous structures with different optical traits; the general characteristics of BCCs under OCT examination are revealed in Table 1 and Figure 1.[8,13,14]

Histopathology

Biopsy of the lesion (either shave, punch or excisional) is of utmost importance when addressing BCC, and, from a histopathological standpoint, the type of BCC and other morphological characteristics have real impact on the patient's prognosis and further therapeutic management.[8,15,16]

In general, BCCs are represented by various-sized groups/nodules of basaloid-looking cells, similar to basal cells found in the first layer of the interfollicular epidermis and/or from the squamous epithelium of the pilosebaceous unit.[8,15] The tumor nodules are characterized by a peripheral palisading of cells (and nuclei) and by a separation space in-between the tumor nodule and the stroma, the latter being considered up until now as an artifact appearing in the course of laboratory processing.[8,12,15] The initial biopsy gives the physician a view of the subtype of BCC with which one deals, and also directs the appropriate treatment; however, in many cases it does not correctly identify the BCC subtype, having

Table 1 BCC Characteristics Revealed by OCT

OCT of BCCs			
General aspects			
Oval-shaped structures ± intensely colored centers	Hyporeflective areas bordering the dermis (dark zones of the lateral tumor border)	Black, cone-shaped areas infiltrating the adjacent dermis	Epidermis with layer disruption
Some BCC subtypes traits			
Nodular BCC		Oval structures with black or dark areas/cysts	
Superficial BCC		Bulges/cones extending from the epidermis into the dermis	
		Dark zone bordering the dermis	
Infiltrative BCC		"A shoal of fish" = dermal, elongated, narrow structures	

Notes: Data from these studies. [8,18,19]
Abbreviations: OCT, optical coherence tomography; BCC, basal cell carcinoma.

a concordance of roughly 54% between the shave specimen subtype and the following full lesion excision; the punch biopsy, though, has better chances of revealing the aggressive pattern of growth in BCCs.[8,15]

In 2021, a group of researchers has proposed a simpler classification for BCC, unifying into a single category of infiltrative BCCs, the following three – infiltrating, micronodular and sclerosing BCC, improving physician concordance

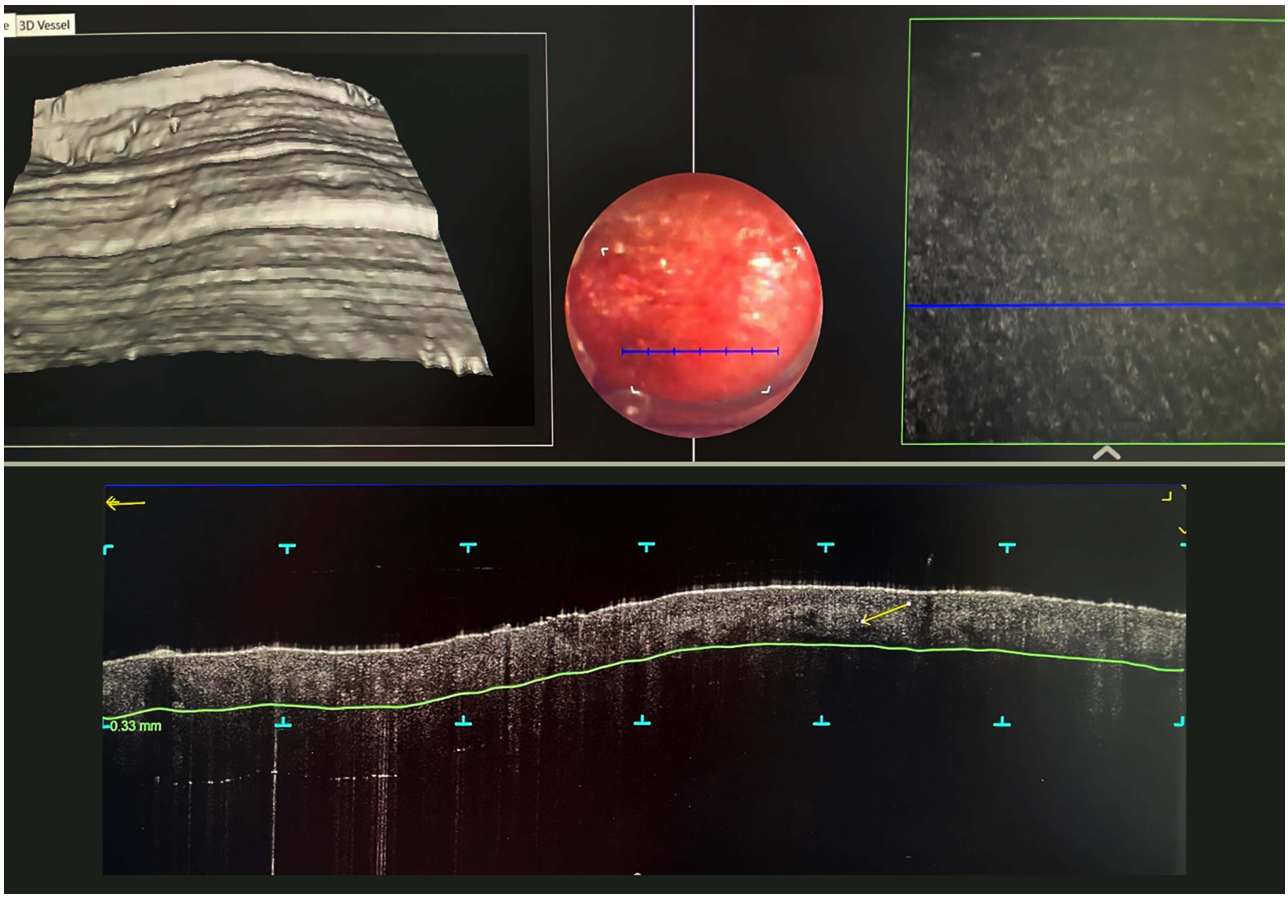

Figure 1 Optical coherence tomography of a superficial basal cell carcinoma – the arrow indicates the cleft.

Table 2 BCC Classification According to Recurrence Risk

Low-Risk BCCs	High-Risk BCCs	
Nodular	Infiltrating	Sclerosing/morphoeic
Superficial		Infiltrating
Pigmented		Micronodular
Infundibulocystic (BCC with adnexal differentiation)	Basosquamous	
Fibroepithelial	BCC with sarcomatoid differentiation	

Notes: Data from these studies.[11–14,20]
Abbreviation: BCC, basal cell carcinoma.

Table 3 Clinically Relevant BCC Subtypes and Their Morphological Traits

Clinically Relevant BCCs	Histopathology Traits
Nodular	Deep dermis extension of malignant basaloid cells arranged as large nests/islands with peripheral palisading and central, disorganized cell arrangement with apoptotic cells; tumor-stroma separation (clefts), mucoid or myxoid stroma with spindle cells (sometimes with a keloidal or collagenous aspect), ± amyloid deposits secondary findings: centrally located mature keratin areas (keratotic), cystic degeneration (cystic/nodulocystic), cribriform display of tumor cells (adenoid)
Superficial	Superficial dermis extension of malignant basaloid cells connected to the epidermis and arranged as small islands/lobules with peripheral palisading, with myxoid stroma and a lichenoid, chronic, band-like inflammatory infiltrate ± multicentric tumor ± associated patterns: micronodular, nodular, or infiltrating
Infiltrating	Deep dermal or hypodermal small/thin irregular islands/nests/chords of malignant tumor cells (1 to 8 cells in thickness), sometimes angulated with apparent permeating invasion pattern, bordered by a narrow margin of stroma, parted by normal collagen, rarely with tumor-stroma clefting
Infundibulocystic (with adnexal differentiation)	Has follicular, apocrine, eccrine or sebaceous gland differentiation matrical differentiation = presence of shadow cells infundibulocystic variant = small infundibular cyst-like spaces in the basaloid nodules sebaceous differentiation = mature sebocytes eccrine/apocrine sweat gland differentiation = ductal structures (+ decapitation secretion = apocrine differentiation)
Basosquamous/metatypical	Features common to both BCC and squamous cell carcinoma, with transitioning zones in-between tumor nests of basaloid cells are intermingled with eosinophilic, atypical squamous cells which are focally or diffusely distributed in the tumor mass highly cellular stroma (most often), fibrotic
Fibroepithelial (fibroepithelioma of Pinkus/Pinkus tumor)	Narrow strands of intermingling malignant basaloid cells set in a reticular pattern, with epidermal link, inside a fibroblastic stroma. ± basaloid islands (rarely)
With sarcomatoid differentiation (metaplastic carcinoma)	Malignant basaloid cells resting in a sarcomatous stroma with variable histology the stromal malignant mesenchymal component: leiomyosarcoma, osteosarcoma, chondrosarcoma, rhabdomyosarcoma, pleomorphic undifferentiated sarcoma.

Notes: Data from these studies.[11–14,20]
Abbreviation: BCC, basal cell carcinoma.

in reporting this type of tumors and making this classification more practical, with a better highlighting of the high-risk tumors with deep involvement. The subtypes of BCC that remained valid in the classification were infiltrative, nodular, superficial, infundibulocystic, basosquamous, with sarcomatoid differentiation, and fibroepithelial.[16] Furthermore, BCC types can be classified into two main groups, low-risk and high-risk ones, respectively, according to the recurrence risk of this tumor (Tables 2 and 3).[16–20]

The Cleft Issue

What is "the cleft" or "clefting" or "the clefting artifact"? For some BCC subtypes, such as nodular BCC, the separation between the malignant tumor nodules and the surrounding stroma (meaning the cleft) is a characteristic trait, either seen as an empty space or an area with a bluish material (hyaluronic acid); it can also be visible in superficial BCC and it was considered to be a retraction artifact during the histopathology laboratory routine practices, the fibromyxoid stroma retracting itself from the tumor nodules. For other types of BCC, such as morpheaform/sclerosing having a more fibrotic stroma and aggressive behavior, retraction spaces are usually absent.[12,21]

Then…

The BCC's basal lamina has been an issue to discuss even since the 1980s (and, indirectly, has also been the BCC clefting).[22] The basement membrane is a thin layer of extracellular matrix underlying epithelial cells, separating them from and also connecting them to the stroma or interstitial matrix.[23] In 1980, Tosca et al concluded that basement membrane antigenic loss (meaning the bullous pemphigoid antigen) is a general and early trait of neoplasia, being directly linked to the characteristic neoplastic cell's loss of control, making it able to further disseminate and metastasize.[22]

In a study done by Stanley et al, the BCC's basal lamina was characterized by using indirect immunofluorescence studies and it was found to be made up from laminin, type IV collagen and bullous pemphigoid antigen; the first two display a linear, continuous pattern, while the latter has a rather discontinuous and linear pattern, or it is even absent. This matter is a specific defect of BCC, the normal epidermal cells being able to synthetize it. Other epidermal tumors, such as benign ones (trichoepithelioma, wart, seborrheic keratosis, cylindroma) or malignancies (squamous cell carcinoma – keratoacanthoma-like, superficially invasive or invasive one), do not have this particular trait, presenting all three antigens in their basal lamina which surrounds the epithelial tumor nests, as well as in the normal epidermis.[22,24]

In 1984, Mérot et al described the cleft as being a dynamic process by involving a degenerative phase of the palisading tumoral basal cells. As such, yet again with the help of indirect immunofluorescence studies, they have found that two antigens – collagen IV and laminin, were found only on the stromal side of the cleft when the peritumoral cleft was present, while in cases where the cleft was not present, these antigen deposits were found as linear, continuous deposits surrounding the tumor nests. At the same time, the bullous pemphigoid antigen, which was present in a continuous and/or discontinuous pattern along the basement membrane of the tumor islands in cases where the cleft was missing, was absent where the cleft was present, raising the question whether it plays a role in the cleft formation.[25] In fact, an important role in bullous pemphigoid antigen production by the BCC tumor cells might be the epithelial-stromal interaction; this antigen production is involved in basal cell differentiation, but its defective synthesis is present in BCC, thus impairing their maturation.[24,25]

The 1989 study by Basset-Séguin also supports the finding in regard to the antigenic alteration of the bullous pemphigoid antigen (from the lamina lucida) inside the tumor island's basement membrane (significant reduction or even total absence), with the normal presence of laminin and type IV collagen antigens. The idea that malignant keratinocytes do not produce certain antigens – such as bullous pemphigoid antigen, is further supported.[22,24–26]

C3d,g is a fragment of the third complement component and it is normally present in the epidermal basement membrane, more specifically, the lamina densa. In the BCC's basement membrane, C3d,g is significantly diminished or even absent, just like in the case of the bullous pemphigoid antigen, revealing a more complex series of changes at this level of the malignant tumor islands. Moreover, each subregion of the basement membrane presents its own changes: lamina lucida, with the reduced/absent bullous pemphigoid antigen; lamina densa, with the KF-1 antigen reduction and the C3d,g reduction/absence (at the base of the lamina densa and within the sublamina densa region).[26]

Puizina-Ivić et al, in their study from 2008, have highlighted the role of Bcl-2 in BCC variants and squamous cell carcinoma. Bcl-2 is very important in cell death regulation, protecting the cell against it and against apoptosis. Concerning the nodular, adenoid and cystic variants of BCC, the peripheral palisading of tumor cells proved to have intense immunoreactivity, ensuring the extension of the tumor. Another BCC subtype, the morpheaform one, proved

reduced immunostaining intensity, showing high proliferation rates and the origin in the basal keratinocytes (as squamous cell carcinoma, for example, is negative for Bcl-2).[27]

In 2018, Hirakawa et al concluded that besides collagen IV, nidogen-1 (a main structural component of the normal basement membrane of the epidermis) has a role in BCC (but also actinic keratosis and squamous cell carcinoma) tumor development, being increased in the BCC's basement membrane and in the surrounding stroma, with patterns similar to collagen IV. A possible explanation could be the fact that the stromal cells (such as fibroblasts) surrounding the tumor islands start to produce basement membrane components, as a reactive response to the tumor islands, and thus making and acting like a restrictive enclosure, limiting the tumor at its primary development site. Cancer-associated fibroblasts have been reported as having a possible role in malignant tumor development and progression. Fibroblasts surrounding BCC might produce more nidogen-1, and, alongside other basement membrane components, might be involved in limiting its progression, infiltration and metastatic potential.[23]

...and Now

The now available, novel in-vivo evaluation techniques such as RCM and OCT (both based on the backscattering of light and used either as separate clinical evaluation techniques, or as an integrated one, complementing each other) have highlighted the fact that "the artificial cleft" might not be secondary to routine processing or to the reduced adhesiveness of the tumor, but that rather it is a BCC "structure" (or BCC trait) which is present in the patient's skin, prior to excision and processing.[12,28] RCM allows for an increased image resolution to be obtained, while OCT has a minimum resolution and is considered to have a lowered specificity and sensitivity. A combination of RCM-OCT ensures the highest rates of a BCC entire volume examination, being also a good tool in studying the subtype of BCC examined (with excellent results regarding the infiltrative component which indicates high risk, with same terminology as in the histopathological examination – angulation, small nests or chords), while OCT alone does not have the necessary resolution for cellular-level studying.[12,28]

RCM has revealed that the BCC tumor islands have areas of low refractility, separating them from the surrounding stroma and deposits such as mucin might be found here.[12] Table 4 presents some RCM and histopathological characteristics correlation for the superficial subtype of BCC. Some features, such as streaming of the epidermis, are highlighted by RCM evaluation and offer more information on BCC morphology, without being specific for a certain subtype. This trait is evidenced by the nuclei of the spinous layer keratinocytes which are elongated and oriented in the same axis; moreover, large, plump, bright cells are also found and are considered to be melanophages.[29]

A study done by Ulrich et al has found that between the histopathological measurement of mucin deposits (done with special stains such as Alcian blue) and the dark areas' diameter there is good correlation. However, they have also highlighted that in between RCM and histopathological examination there were some variations, including the morphological presence of wider cleft-like spaces which were not observed at RCM, thus reflecting the already emerged theory

Table 4 Superficial BCC - RCM and histopathology evaluation

Superficial BCC Type	
RCM evaluation	Histopathological evaluation
Multiple, small islands of basaloid cells with multilobular architecture	Small nests of basaloid cells connected to the epidermis
Peripheral palisading of nuclei	Peripheral palisading
Highly refractile fibrous tissue – superficial dermis, bright inflammatory cells, telangiectasia	Fibrous stroma (±mucin), marked inflammatory infiltrate (lymphocytes, histiocytes, ±melanophages)
Peritumoral dark spaces	Cleft formation
Dark silhouettes	Hypopigmented variant of BCC

Note: Data from Sahu et al.[30]
Abbreviations: RCM, reflectance confocal microscopy; BCC, basal cell carcinoma.

about clefting being an artifact of laboratory processing.[12] Of high interest was a finding by Gill et al who reported a false-positive result on RCM-OCT, a finding which was positive only on OCT due to the fact that the image was outside the field of view of the RCM examination. The image described some angulated chords and/or nests which surrounded a very well-structured tumor nodule, the team considering these (on histopathological examination) as being peritumoral areas with fibrosis, thick collagen bundles, an increased number of blood vessels and inflammation. However, a false-negative histopathological examination cannot be excluded, the peritumoral cleft still being a questionable issue.[28]

Sahu et al have also used a combination of RCM and OCT in order to visualize the cellular structure and to evaluate the depth of BCCs; they have also evaluated amyloid and mucin deposits which can be found in such tumors, further correlating them histopathologically. Amyloid deposits are seen under RCM-OCT investigation as areas of amorphous, hyperreflective, homogenous material, which is placed intra- or peritumorally, while mucin is seen as hyporeflective areas (inside the tumor nodules or peritumorally), as stated before. An important aspect with prognostic significance is the fact that amyloid and/or mucin deposits have been observed in less aggressive forms of BCC, such as the nodular BCC. This raises a red flag for the physician so that such deposits be searched for, in order to establish a better further management of the patient's case.[30]

Other theory concerning BCC talks about the "angiogenic switch", meaning the predominance of pro-angiogenic factors which determine the development of new blood vessels, an important step in tumor development and progression. A higher microvascular density is correlated with higher levels of vascular endothelial growth factor (VEGF) in BCC, with a following remodeling of the extracellular matrix. BCCs have really low metastasis rates, although the vascular architecture is enriched, having increased numbers of vessels which are more dilated and irregular. Could angiogenesis be a regulating system for BCC aggressiveness? It remains a subject for further research as novel imaging tools such as RCM and OCT can ensure an in vivo examination of tumor vessels, without compression artifacts.[31,32]

Conclusion

RCM, OCT or both combined are new in-vivo investigating techniques for the dermatologist, with better outcomes and procedure steps concerning the patient, evaluations which can be reproduced, are cost-effective and which avoid invasiveness. At the same time, these techniques can offer a clear image of the tumor margins, prior to the surgical excision and can monitor the tumor's response to a non-invasive treatment with vasculature observations.

Abbreviations

BCC, basal cell carcinoma; UV, ultraviolet; BCCs, basal cell carcinomas; RCM, reflectance confocal microscopy; OCT, optical coherence tomography; VEGF, vascular endothelial growth factor.

Data Sharing Statement

The information will be granted access to under reasonable request.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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