Merkel cell carcinoma of the eyelid and periocular region: A review

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Abstract:

Merkel cell carcinoma (MCC) is a rare primary cutaneous neuroendocrine carcinoma with a high mortality rate. It typically affects elderly Caucasians, with a slight predilection for males. It is associated with chronic sun exposure and/or immunosuppression. Almost half of all cases occur on the head or neck and an estimated 2.5%–10% arise on the eyelids or periocular skin. It ranks as the 5th most common malignant tumor at these sites, preceded in frequency by basal cell, squamous cell and sebaceous carcinoma, as well as melanoma. Its clinical presentation as a violaceous nodule/plaque lacks specificity, and it can be mistaken for cysts, chalazia or basal cell carcinomas. Sub-specialized histopathological and immunohistochemical evaluations are required for diagnosis. Clinical staging defines the extent of disease and governs management. This includes surgery and adjuvant radiotherapy for localized tumors and of late, immunotherapy for metastatic disease. Significant advances in our understanding of the dual etiopathogenesis (Merkel cell polyomavirus- and Ultraviolet radiation-induced) and the biology of the neoplasm have been achieved in recent years. Issuing from the tumor's known susceptibility to host immunity, a recent therapeutic breakthrough has occurred whereby immune checkpoint inhibition has been shown to mitigate advanced disease. These factors and the increased global incidence of the tumor have brought it to the forefront of medical attention. This review provides a clinically relevant update on MCC, with special reference to cases arising on the eyelid/periocular region.

Keywords:

Carcinoma, eyelid, Merkel, neuroendocrine, periocular, skin

Introduction

Merkel cell carcinoma (MCC), first described almost 50 years ago, was initially thought to be of sweat gland origin.[1] It was named "trabecular carcinoma" because of its histopathological pattern. Later, similarities were observed between the tumor cells and normal neuroendocrine cells in the skin. This prompted a switch to the eponymous title MCC, in honor of the German investigator Friedrich Merkel who had originally discovered those cells.[2,3] Early on, its predilection for sun-damaged skin of the head or neck of fair-skinned older individuals and its aggressive biological behavior were recognized. In time, its propensity to affect immunocompromised individuals came to light. A scientific milestone in the field occurred in 2008, when the etiopathogenic role of a new polyomavirus Merkel cell polyomavirus (MCPyV) was discovered.[4] Later it became clear that while most cases were linked to this oncogenic virus a minority was a consequence of Ultraviolet (UV) radiation-induced genetic damage.[5,6] Historically, surgery and adjuvant radiotherapy proved relatively effective in the management of localized tumors but the poor response of metastatic disease to cytotoxic chemotherapy provoked ongoing investigation of alternative modalities. This endeavor was recently rewarded by the observation of clinically meaningful responses to immune checkpoint inhibition (ICI) in patients with advanced disease.[7,8] The increased global incidence of MCC during this millennium has piqued further interest in the tumor and factors influencing this trend are a subject of study.[9-12] Herein, it is hoped to crystallize novel developments in the field of MCC and to convey their impact on the subset of tumors arising at periocular sites.

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Epidemiology

Data from Europe, Australia and the USA have shown a substantial increase in the incidence of MCC in recent years[10-13] The rates range from 0.1 to 1.6 cases per 100.000 people per year, being highest in Australia.[13] Of interest, the recorded 95% rise in incidence of the tumor in the USA, between 2000 and 2013, greatly exceeded that documented for melanoma.[9] Individuals of male sex, older age (>75 years) and Caucasian race (particularly those with a history of prolonged sun-exposure) are most susceptible to the disease. Immunosuppressed patients, notably those with (i) chronic lymphocytic leukemia, (ii) a history of organ transplantation or (iii) HIV infection (with reported 30-, 23.8-, and 13.4-fold increases in risk rates respectively) feature significantly in cohorts of cases with MCC.[14-16] Theories to explain the global increase in incidence of the tumor include (i) more refined diagnostic strategies, (ii) improved data collection by cancer registries and (iii) increased life spans in many countries.[16] Epidemiologic data on the subject are generic but they can be compared with information gleaned from a compilation of published cases of MCC of the eyelids.[17] The mean age in this group was 77 years in keeping with the general trend and 6.1% of the patients were immunosuppressed. The predominance of females (64%) in the group runs counter to the male predominance observed generally.

Etiopathogenesis

Despite the eponymous title, normal Merkel cells, (being terminally differentiated), are no longer considered the cell of origin of MCC. The matter remains enigmatic, but hypothetical candidates include epidermal or dermal stem cells, precursors of B lymphocytes (e.g., pro-B/pre-B cells), fibroblasts, and epithelial cells.[16,18,19] A detailed outline of the evidence for and against each of these theories is beyond the scope of this review but a few points deserve mention. On one hand, the immunohistochemical expression of B cell markers (e.g., PAX-5, TdT and immunoglobulins) by a proportion of MCC's supports the "B-cell theory."[19] On the other, the intimate association of a subset of MCC's with squamous cell carcinomas (invoking transformation of malignant keratinocytes to high-grade malignant neuroendocrine cells) lends credence to the "epithelial cell theory."[20]

A dual etiology for MCCs has now been established. MCPyV, a ubiquitous virus prone to re-activation in the elderly,[21,22] is implicated in most cases while UV radiation-induced genetic damage accounts for the remainder.[23] Though often quoted as an 80:20 ratio, the relative proportions of cases in each group varies in different geographic zones. MCPyV is the dominant factor in the northern hemisphere while UV radiation prevails in Australia.[24] Both oncogenic triggers interfere, in different ways, with the same tumor suppressor pathways, thereby promoting malignant growth. In the case of MCPyV, incorporation of the virus in the genome of the tumor cell allows viral antigens to disable the retinoblastoma (RB1) and p53 protein pathways.[25-27] Alternatively, UV radiation causes inactivating mutations in the *RB1* and *TP53* genes, thereby obliterating their functions.[23] This dichotomy in the etiopathogenesis of the tumor is of more than academic interest as it carries several clinical, morphological, and biological implications [Table 1].

Clinical Features

MCCs occur on the head or neck (44%), the limbs (37%), trunk (11%), and less commonly other sites.[14] The neoplasm is often confined to the primary site at presentation, but synchronous nodal and/or systemic metastases are present in approximately one third of cases.[15] The tumor typically occurs as a rapidly growing, painless, violaceous nodule or plaque[28] the features of which are captured by the acronym AEIOU; A = asymptomatic, E = expanding rapidly, I = immune suppression, O = older than 50 years of age and U = UV-exposed site.[29] Tumors arising on the eyelids or periocular region account for 2.5%–10% of all cases.[17,30] An example of a MCC on the eyelid is depicted in Figure 1. Among published cases of MCC of the eyelid[17] the tumors mainly involved the upper eyelid (76%), in contrast to basal cell and squamous cell carcinomas which more commonly arise on the lower lids. A slight predilection for the left eye (34% vs. 27%) has been observed. The lesions arose near the eyelid margin and were often associated with loss of eyelashes, ulceration, and destruction of local structures. The median size of the tumors was 1.5 cm in greatest dimension. The clinical differential diagnoses included cysts, chalazia and basal cell carcinomas.[17] In 6.1% of cases nodal involvement was apparent and in 3% distant metastases were evident. Most periocular MCCs affect the skin of the eyelid but exceptional cases of primary MCC of the conjunctiva, and of the lacrimal gland have been described.[31,32] Metastatic MCC involving the iris and the orbit has also been documented.[33,34]

Histopathological features

MCC is characterized microscopically by a densely cellular tumor in the dermis, usually sparing the epidermis, [Figure 2]. Despite its original title "trabecular carcinoma," a trabecular pattern is rarely observed. Instead, the neoplastic "small blue round cells" are typically arranged in sheets and/or nests. Abundant mitotic figures and scattered apoptotic cells are the norm, while foci of confluent necrosis are often observed. Lymphovascular involvement is a common finding. The subtle interstitial dispersal of tumor cells within the stroma, at some distance from the main mass, can make assessment of surgical margins difficult, particularly on intra-operative frozen sections where crush artifact is a common hindrance to interpretation.[28,35]

The majority of MCCs shows a homogenous neuroendocrine phenotype (pure MCCs) as described above. However, a subset of tumors diverges from this standard, exhibiting

Table 1: Characteristics of Merkel cell polyomavirus+ and Merkel cell polyomavirus- Merkel cell carcinomas

Feature	MCPyV+	MCPyV−
Gender	Female > male	Male > female
Anatomic distribution	Limbs>Head and neck	Head and neck > limbs
Geographic distribution	US and Europe (+++)[a]	Australia (+++)
Morphology	Pure	Pure and combined
IHC	Classical[b]	Classical or aberrant
Immune response	TILS (+++)	TILS (+)
Prognosis	Better	Worse
Response to ICI	Favorable	Favorable
Genetics	Mutational burden-low	Mutational burden-high
	Rec mut RB1 and TP53-absent	Rec mut RB1 and TP53-present
	UV mut sign-absent	UV mut sig-present

[a]The designation (+++), (as opposed to [+]) is used to semi-quantitatively represent frequency of occurrence, [b]The classical pattern of IHC is CK20+, synaptophysin+. MCPyV+, neurofilament +, CK7−and TTF-1. Variations on this pattern are considered aberrant. MCPyV: Merkel cell polyomavirus, IHC: Immunohistochemistry, TILS: Tumor infiltrating lymphocytes, ICI: Immune checkpoint inhibition, RB: Retinoblastoma, TTF: Thyroid transcription factor, CK: Cytokeratin

neuroendocrine and various other phenotypic elements.[20] These hybrid neoplasms, termed "combined MCCs," most often comprise malignant squamous epithelial nests admixed with the neuroendocrine population of cells. The two morphologically distinct variants of MCC differ in terms of viral status, most pure MCCs being MCPyV-positive and all combined MCCs being MCPyV-negative.[36] Examples of pure and combined MCCs are depicted in Figure 3.

Several malignant tumors are represented microscopically by proliferations of "small blue rounds cells" hence, a diagnosis of MCC cannot be based on routine microscopy alone.[16,28,36] The differential diagnosis includes primary and metastatic neoplasms such as melanomas, lymphomas, other neuroendocrine or nonneuroendocrine small cell undifferentiated carcinomas and sarcomas (particularly cutaneous Ewing's or Ewing's-like sarcomas).[37] Of the metastatic tumors in the differential diagnosis, distinction between a deposit of small cell carcinoma of the lung and MCC is the most common diagnostic quandary.

Immunohistochemical Features

Immunohistochemistry (IHC) is essential for the diagnosis of MCC. This evaluation is best performed in the hands of a pathologist with expertise in dermatopathology as pitfalls in interpretation can occur. The classical IHC profile of MCC is well known, but these tumors can show staining patterns which overlap with those of their morphological mimics (e.g., lymphomas and Ewing's sarcoma).[38-40] Moreover, a subset of them (particularly MCPyV-negative tumors) can be immunophenotypically aberrant.[41,42] Hence, application of a comprehensive IHC panel, incorporating stains with expected positive and negative results, is imperative.

Historically, combined expression of neuroendocrine markers (e.g., chromogranin A or synaptophysin) and basic epithelial stains was used to make the diagnosis of MCC.[43-45] In that context a paranuclear dot pattern of positivity for broad spectrum keratins (e.g., AE1AE3) was regarded as specific for MCC. More recently, IHC panels of greater diagnostic specificity are employed.[46,47] These incorporate antibodies that are usually positive in MCC (e.g., cytokeratin 20 [CK20], chromogranin or synaptophysin, CM2B4 [recognizing MCPyV viral antigens] and neurofilament), as well as those expected to be negative (CK7 and thyroid transcription factor protein 1). The latter stains are usually positive in small cell carcinoma of the lung. Other site-specific markers of visceral neuroendocrine carcinomas can be added to the panel to exclude cutaneous metastases from such sources. An example of the classical immunohistochemical profile of MCC (pure, MCPyV-positive) is illustrated in Figure 4. Two new antibodies useful in the context of MCC have been identified. The first is special AT-rich sequence-binding protein-2, shown to be highly specific for MCC.[46,47] The second is insulinoma-associated protein 1, known to be highly sensitive for detection of MCC in sentinel lymph nodes, but lacking specificity as it also marks other neuroendocrine tumors.[48] In the final analysis, integration of histopathology, IHC, clinical factors and imaging studies is necessary to establish a final diagnosis.

Prognosis

The clinical stage of the tumor is the main prognostic indicator for MCC.[15] In general, 65% of patients exhibit local disease at presentation, 26% have nodal involvement and 8% have systemic metastases. The corresponding 5-year survival rates are 51%, 35% and 14%, respectively. Currently, the 8th Edition of the tumor, node and metastasis staging system (TNM8) forms the basis for this process. Two versions of TNM8 exist, one published by the Union for International Cancer Control,[49] favored in the UK and the second by the American Joint Committee on Cancer (AJCC), favored in the USA.[50] These are comparable and they provide a framework for evaluating the dimensions of the primary tumor, the extent of involvement of local structures and quantification of nodal and/or systemic metastases, if present.

Each version provides specific staging systems for MCCs (regardless of site) and for eyelid carcinomas (regardless of histopathological type). The former is more commonly used by anatomical pathologists and the latter by ophthalmic pathologists. Good correlation between the AJCC T categories, derived either from the staging template for MCCs or for eyelid carcinomas, with outcomes in patients with periocular MCCs has been recorded.[51] Irrespective of which system is employed, it is important that the maximum clinical dimension of the tumor (in millimeters) and the clinical status of the regional lymph nodes (occult or detectable) be conveyed to the pathologist and/or multidisciplinary team to enable accurate staging. Moreover, in keeping with recommendations for staging of MCC in general,[16,52] evaluation of sentinel

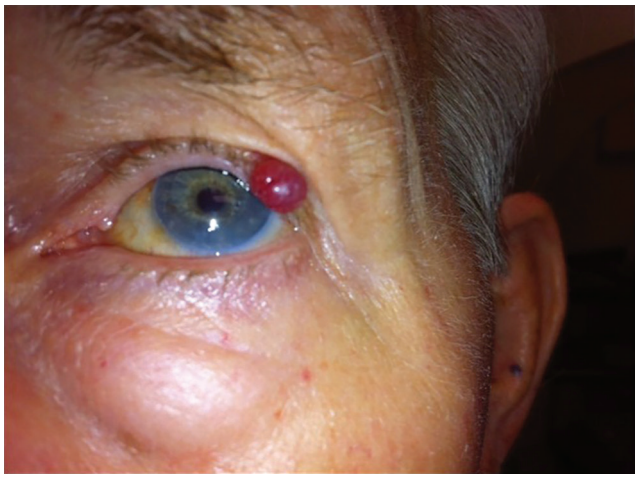

Figure 1: Clinical image of a Merkel cell carcinoma characterized by a violaceous nodule involving the margin of the left upper eyelid of an elderly man. This figure is reproduced by kind permission of Elsevier having featured originally as Figure 1a in our article "Fleming KE, Ly TY, Pasternak S, Godlewski M, Doucette S, Walsh NM. Support for p63 expression as an adverse prognostic marker in Merkel cell carcinoma: Report on a Canadian cohort. Hum Pathol 2014;45:952-60. doi: 10.1016/j.humpath. 2013.12.008. Epub 2014 Jan 8. PMID: 24746200"

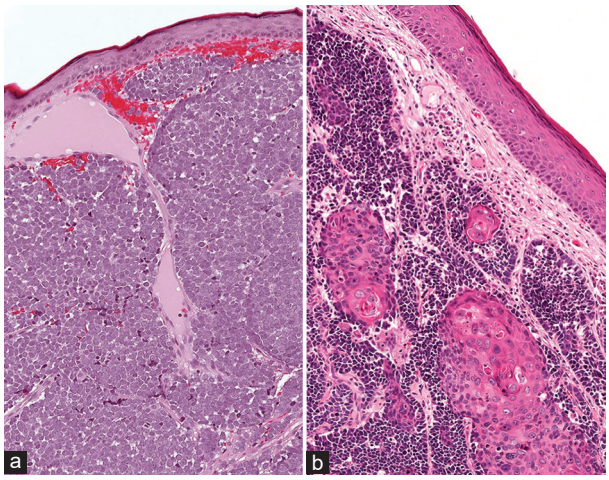

Figure 3: Photomicrographs of a pure (a) and combined (b) Merkel cell carcinoma seen at high magnification. The monomorphous "small blue round cell" neuroendocrine features of the pure tumor are in contrast to the mixed appearance of the combined tumor which exhibits pink squamous and blue neuroendocrine elements. This figure is reproduced by kind permission of Elsevier having featured originally as Figures 1b and 2 in our article "Fleming KE, Ly TY, Pasternak S, Godlewski M, Doucette S, Walsh NM. Support for p63 expression as an adverse prognostic marker in Merkel cell carcinoma: Report on a Canadian cohort. Hum Pathol 2014;45:952-60. doi: 10.1016/j.humpath. 2013.12.008. Epub 2014 Jan 8. PMID: 24746200"

lymph nodes with IHC, to facilitate sub-categorization of nodal status in tumors affecting the eyelids and periocular region is advisable.

Apart from clinical stage, other factors known to have a negative impact on prognosis include increased age, immunosuppression, male sex and an origin of the tumor on

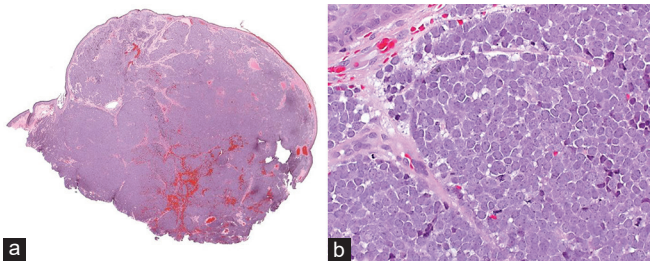

Figure 2: Photomicrographs at scanning (a) and high (b) magnification of the Merkel cell carcinoma depicted in Figure 1. The lesion is characterized by a cellular dermal nodule, sparing the epidermis and exhibiting features of a malignant, undifferentiated, "small blue round cell tumor."

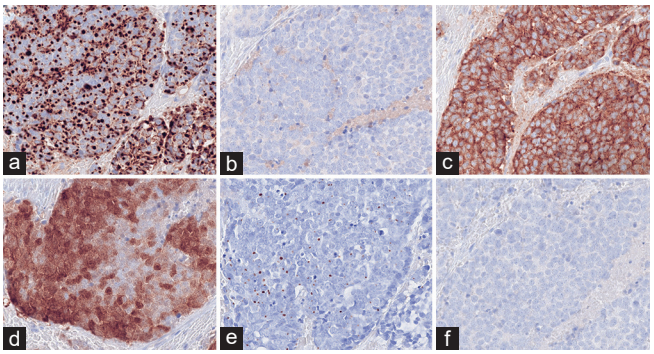

Figure 4: Photomicrographs illustrating the classical immunohistochemical profile of a Merkel cell polyomavirus -positive Merkel cell carcinoma. The sequence is as follows: Cytokeratin20 - positive (paranuclear dot pattern) (a), cytokeratin7 – negative (b), synaptophysin - positive (c), CM2B4 - positive (reflecting nuclear expression of Merkel cell polyomavirus) (d), neurofilament – positive (dot-like) (e), thyroid transcription factor protein 1-negative (f). Positivity for cytokeratin 7 and thyroid transcription factor protein 1 would be expected in metastatic small cell carcinoma of the lung

the head/neck.[15] Hence, MCCs of the eyelid and periocular region are inherently impacted by the latter high-risk factor. Other variables have also been shown to influence outcome. Most important among these is the viral status of the tumor. Earlier data in this regard have been conflicting, largely due to differences in methodology used to detect the virus. However, the favorable impact of viral positivity on outcome has now been convincingly demonstrated[53] and it has been shown to be a prognostic variable independent of clinical stage and immune status.[54] For practical clinical purposes positivity for MCPyV can reliably be demonstrated by IHC (CM2B4 antibody).[54] Data pertaining to the proportions of MCCs of the eyelid and periocular region exhibiting viral positivity are not available. However large studies have shown that MCPyV-negative tumors show a predilection for the head/neck while MCPyV-positive tumors are more commonly observed on the limbs.[55-57]

The presence of brisk tumor infiltrating lymphocytes, particularly when harboring abundant CD8+ (suppressor/cytotoxic) T cells, has been associated with a better outcome.[58,59] This observation concurs with the known immune susceptibility of the tumor, which, at the ultimate

degree, can result in complete spontaneous regression of the neoplasm.[60] Examples of this phenomenon have been recorded in MCCs of the eyelid and periocular skin.[61,62] The observation of lymphovascular involvement by the primary tumor is also of prognostic relevance and should be documented in pathology reports. While several isolated studies have shown associations between different microscopic variables and disease outcome, only those of broadly accepted importance are incorporated in standardized pathology reporting guidelines.[63,64]

Treatment

Wide local excision has long been the cornerstone of treatment for localized MCC[16,28,65] and to date most tumors (85%) involving the eyelid have been managed in this way.[17] Adjuvant radiotherapy is of proven effectiveness in reducing the incidence of local (and/or locoregional) recurrence of the tumor.[16,28,66] This modality has been employed to date in a minority (36%) of reported MCC's of the eyelid.[17] Cytotoxic chemotherapy for advanced disease has historically yielded poor results and was used in only a small proportion (7%) of cases of MCC in the periocular region.[17] Recently ICI has superseded use of traditional chemotherapy.[7,8,28]

Local recurrence of MCC following primary excision has been observed in up to 30% of cases and tumors on the eyelid are no exception.[17] A clear consensus on the optimal size of surgical margins remains elusive and measurements ranging from 1 to 3 cm have been proposed for MCC in general.[65] Unfortunately, studies evaluating the efficacy of different margins have often failed to take the impact of adjuvant radiotherapy into consideration. In clinical settings where significant functional and cosmetic factors are at stake, a tissue-sparing surgical approach is desirable. In a recent review of MCC of the eyelid a margin of 0.5 cm has been quoted as appropriate for tumors at this site.[17] Support for narrow excision of a localized MCC, in combination with adjuvant radiotherapy, has recently been published.[67] The latter study of 188 cases of MCC showed that even in patients with high-risk tumors (e.g., higher clinical stage) and in the context of narrow (or even positive) surgical margins, the risk of local recurrence was significantly less in the "combined surgery with adjuvant radiotherapy" group than in the "surgery alone" group. No difference in MCC-specific survival was observed between the two groups. The authors proposed a helpful treatment algorithm as a guide for clinicians. Considering the functional and cosmetic factors pertinent to surgery on the eyelid and periocular region further exploration of this approach would seem worthwhile. Moreover, it would obviate the need for intraoperative evaluation of surgical margins which is fraught with technical and interpretative difficulties.

The formerly dismal prospects for patients with metastatic MCC have been significantly improved by the advent of ICI.[7,8,16,28] Antibodies such as anti-PD-1 and/or anti-PD-L1 act to block mechanisms of tumoral immune-evasion (such as the PD-1/PD-L1 pathway) and unleash an individual's host response to the neoplasm. Clinical trials have shown favorable and sustained anti-tumoral responses to these agents, in both chemo-refractory advanced disease (objective response rate of 32%) and as first line treatment in patients with metastatic disease (objective response rate of 56%).[68-70] The superiority of first line treatment over that employed in chemo-refractory cases has now been confirmed.[71] Moreover, response rates have proven to be independent of the viral status of the tumor.[16] ICI has now been approved for use in the setting of advanced MCC by regulatory agencies in many countries.[8,11,16] Although clinical trials specifically addressing their safety and efficacy in relation to MCC of the eyelid or periocular region have not been performed, the data in general is promising and has been used to promote their use at this site.[72]

The above breakthrough notwithstanding, clinical limitations of ICI include (i) an approximate 50% treatment failure rate, (ii) immune-related side effects of therapy and (iii) the relative contraindication to its use in patients with autoimmune disease or those on immunosuppressive therapy.[16] These shortfalls have provoked a search for predictive biomarkers of responsiveness to ICI.[23,73] They also underline the need for continuing investigation of alternative or complimentary therapies for this disease. A plethora of such studies, at translational and clinical levels are underway, primarily focusing on a range of immunotherapies and genetically targeted therapies.[16]

Summary and Conclusion

In the half-century since the discovery of MCC remarkable advances in our understanding of the pathogenesis, biology and treatment of the tumor have been realized. Its dual viral and UV radiation-induced pathways speak to the fact that it represents a final common pathway of two tumors and the implications of this duality continue to unfold. Many developments in the field are meritorious but the improvement in patient care achieved via ICI is foremost among them. Future endeavors will focus on (i) determining the cell (or cells) of origin of the tumor, (ii) continued mining of biological details of the neoplasm in search of new therapeutic opportunities and (iii) a pursuit of biomarkers of responsiveness to help customize treatment.

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Conflicts of interest

There are no conflicts of interest.

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