Review Article

The evidence for *Mycobacterium avium* subspecies paratuberculosis (MAP) as a cause of nonsolar uveal melanoma: a narrative review

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Background and Objective: Animal microorganisms have been proposed as a cause of human cancers associated with farming, agricultural occupation or residence, and related downstream exposures. Several studies have described uveal melanoma (UvM) as a farming-associated cancer. A possible suspect is the animal microorganism *Mycobacterium avium* subspecies *paratuberculosis* (MAP), the causative agent of paratuberculosis in dairy cows. This microbe is transmitted to humans through various means, including contact with animal faeces, contaminated dust and soil, organic fertilizers, and as workers in slaughterhouses/animal processing facilities. The objective of the current manuscript was to examine the putative association between Mycobacterium avium sub-species paratuberculosis and non-solar UvM.

Methods: Online data sources (PubMed, Scopus, Cochrane Library, and Google) published in English between 1980 to present were searched for key words pertaining to MAP exposure, farming-related occupations and activities, and locations with or in the vicinity of dairy cattle.

Key Content and Findings: While higher than expected rates of eye cancer have been suggested among dairy farmers, with MAP being ubiquitous in their environment, the involvement of MAP in the aetiology of non-solar UvMs (which account for ~97% of UvM cases) remains uncertain.

Conclusions: Alternative explanations exist and future cause-and-effect research is needed to answer this hypothesis. A precautionary approach to exposure continues to be a prudent strategy.

Keywords: Cattle; infectious cancers; paratuberculosis; ocular melanoma; uveal melanoma (UvM)

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Introduction

Uveal melanoma (UvM), also known as intraocular or ocular melanoma, is a rare eye cancer that is distinct from cutaneous melanoma (CM). While both UvM and CM are believed to originate from melanocytes, ultraviolet radiation (UVR) does not have a dominant etiologic role in UvMs that are located in the posterior region of the eye (1,2). The latter area is largely void of sunlight owing to the filtering effect of the cornea, lens, and vitreous (3). This is in contrast to the UV-associated mutational spectrum that characterizes CM, iris cancer (directly exposed to UV-radiation), and epithelial melanomas on the surface skin tissue surrounding the eye (4).

At the molecular level, UvMs are predominately devoid of dipyrimidine site C>T transitions and rarely have mutations in the promoter region of the human telomerase reverse transcriptase (TERT) gene, both of which are attributable to UVR exposure (5). Similar to melanomas presenting in various mucous tissue and non-sun-exposed areas of the body, the etiologic basis of non-solar UvM is unknown.

Several studies have shown an increased rate of eye cancer in farmers (6-12). Zoonoses, infectious diseases that are caused by pathogenic microorganisms and transmitted from animals to humans, have been proposed as possible causes of farming and agriculture associated cancers (13-15). One study showed the highest rate in dairy farmers in particular, although the exact location within the eye was not mentioned (6).

Mycobacterium avium subspecies *paratuberculosis* (MAP) causes Johne's disease or paratuberculosis, a chronic enteropathy of dairy and beef cattle and other ruminants (16-19). MAP is a long-suspected cause of Crohn's disease (20-25). MAP has been implicated in a wide range of autoimmune and neurodegenerative diseases (26-30) and three types of human cancer (31-33).

The literature on the possible relationship between MAP and Crohn's disease has focused on MAP being transmitted to humans through the ingestion of MAP organisms present in vegetables, raw milk (34,35), and MAP organisms that survive pasteurization (36) and are present in retail milk and other retail dairy products (37-39). However, this route of exposure is negligible compared with more concentrated and direct fecal-borne transmission. MAP is heavily excreted in an infected animal's feces or manure (17,40). In the case of UvM, near-field exposure to contaminated airborne dust and soil, manure splatter, flies and other insect carriers, and finger-to-eye contact with fecal material containing the pathogen are believed to be the predominant modes of zoonotic spread among farmers and agricultural workers (41). Particularly concerning are subclinical shedders, animals that appear healthy but are shedding MAP in their manure (42). Overall, >60% of infected cattle will go undetected, even with the most sensitive fecal culture techniques (42). Other considerations include inadequately ventilated animal housing units and poor waste removal systems, increasing the exposure to animal excrement and MAP.

The sizable numbers of MAP organisms in dairy cattle feces have not been appreciated. Two milliliters of manure from a dairy cow infected with MAP can contain 1 million MAP organisms, enough to cause infection in a dairy calf (17). An adult dairy animal infected with MAP excretes 12–14 gallons of such heavily contaminated manure per day, or over 23,000 infectious doses of MAP (43).

Large dairy farms, known as confined animal feeding operations, may contain 10,000 animals (44). Approximately 70% of all dairy herds (45,46), and 100% of dairy farms in the United States containing over 200 animals (47) have at least one sub-clinically infected animal with high excretion of MAP in its feces, and within herd prevalence rates can reach 100% (48). Regions of a country with multiple large farms can house over 100,000 dairy animals. The manure output of one such region in the USA was described as "equal to the sewage output of the New York City metro system" (49).

MAP excreted in infected animals' feces can resist various environmental conditions such as heat, cold, dryness, and acidic conditions (lower pH) (50-52), and remain in soil (51), dirt and dust (53), in a state of nonreplicating persistence, even when other environmental bacteria are present in the environment. MAP is diffusely present in the soil in countries where MAP infections of domestic ruminants is longstanding, "at a higher rate and wider distribution than expected" (54). MAP is present in natural bodies of water contaminated with manure runoff (55,56).

In this narrative review of the literature, we assessed MAP as a possible zoonotic pathogen, examined sources of MAP exposure, and explored routes of transmission from animals to humans. The aim was to present a balanced philosophical perspective of the hypothetical association between MAP exposure and non-solar UvM (herein simply called UvM unless indicated otherwise). We present the

Table 1 The search strategy summary

Item	Specification
Search date	November 2022
Time frame	January 1980 to present
Data sources	PubMed, Scopus, Cochrane Library, Google
Terms	Uveal melanoma; intraocular melanoma; eye cancer; *Mycobacterium avium* sub-species *paratuberculosis* (MAP); dairy cattle; farming; agricultural occupation or residence; contaminated dust and soil; organic fertilizers; slaughterhouses; animal processing facilities; zoonosis; fecal-borne transmission; infectious disease clusters
Inclusion criteria	Full-length, peer-reviewed manuscripts; English language sources; relevant lay press articles published by established media outlets
Exclusion criteria	Non-English language[†]; abstracts; editorials
Selection process	Two authors independently screened data sources. A third author mediated the process when disagreements occurred

[†], unless translated.

following article in accordance with the Narrative Review reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-2540/rc).

Methods

Based on the several articles documenting an increased rate of eye cancer in farmers (6-11), and particularly dairy farmers (6), a review of the English-language literature from January 1980 to present was conducted to investigate whether there was supporting evidence for MAP excreted in an infected animal's feces as a risk factor for UvM. We searched PubMed, Scopus, the Cochrane library, and Google on key words to identify locations, occupations, and activities associated with an increased rate or clusters of UvM. We then sought papers illustrating possible connections of these occupations, activities, and locations with dairy cattle. In addition, we deliberately sought connections between occupations with an increased risk of UvM and possible MAP exposure. Studies that used well validated assays such as qPCR and Elisa were specifically targeted when addressing MAP-shedders in this analysis (57).

The screening of the literature was independently conducted by two authors (ESP and JTE), with disagreements mediated by a third author (YC). A summary content of the information was compiled by a fourth author (CJ), who also hand-searched the reference lists of the screened articles for relevant papers that were missed in the initial search. The search strategy is summarized in *Table 1*.

Synthesis of the literature

The circumstantial evidence for the possible association of MAP with UvM

We were able to consistently correlate increased rates and clusters of UvM with possible exposure to MAP. Farmers and agricultural workers are exposed to aerosolized microorganisms present in feces or manure (41). Specifically, dairy farmers are exposed to large numbers of MAP organisms as described above, that are readily aerosolized from manure, and coat indoor surfaces of dairy farms (58-60).

The excretion of MAP in an infected dairy animal's feces and the subsequent contamination of underlying soil and nearby water may explain the increased rates of UvM in particular geographic areas and some of the clusters of UvM reported in the literature as described below.

Five cities in Lower Mainland and southeastern Vancouver Island in British Columbia have the highest rates of UvM in Canada (61). This is a region with a great concentration of dairy cattle, approximately 140,000 animals (62,63). In the United States, the incidence for UvM increases disproportionately at higher latitudes (less sun exposure), with the latter region being relatively more populated with dairy farms (64). However, it is important to note that lower latitudes are not devoid of dairy farms and the occurrence of UvM.

A recent report describes three clusters or "geospatial accumulations" of UvM in the United States (65). The first mentioned cluster ranged from 5 to 22 cases (65), located in a predominately rural region (66). Three of the cases

attended a high school that was built in 2001 (66), but was previously "farmland and open fields" (66). The type of farms in the area were dairy farms (67). Conceivably, this cluster was related to the dense contamination with MAP of the ground underlying the high school, ground that went from being heavily MAP contaminated, but unoccupied, to the site of the school.

The second United States cluster consisted of 14 cases along the northern stretch of the Susquehanna River in the state of New York (65). This stretch of the Susquehanna River houses a dense concentration of dairy cattle, over 110,000 animals (68). On a related note, increased rates and clusters of MAP-associated illnesses, e.g., Crohn's disease and ulcerative colitis (69), have previously been reported in relation to the presence of possibly MAP-infected dairy cattle, sheep, and non-domestic ruminant animals adjacent to rivers and streams. These clusters have occurred in Cardiff, United Kingdom (56,70), Spokane, Washington (71-73), Northport, Washington (74-77), Plains, Montana (78), and Forest, Virginia (79). The concentration of MAP from natural bodies of water, first by floating to the top of the body of water owing to MAP's hydrophobic cell wall, and then by the scavenging bubble - jet drop bursting mechanism, has previously been described (78). In particular, the area of British Columbia described above consists of an island surrounded on two sides by narrow straits, across from a section of land with multiple lakes and rivers.

The third United States cluster occurred at a regional university, with the reported number of cases ranging from 6 (65) to 36 (80). Three of the women lived in the same dormitory room, suggesting exposure to a common source of aerosolized MAP, perhaps the shower water (81,82). An idiopathic inflammatory bowel disease (IBD) cluster has previously been described in three college roommates (83). Although the beef and dairy industries have had a historic economic presence (84) and collocation near the university (85), the association with MAP exposure is circumspect. One case was involved in "the reconstruction of dormitories" (65), possibly related to the generation of MAP contaminated dirt and dust when two residence halls were built in the mid-1990s (86). However, it is not clear if, and to what degree MAP exposure occurred, as the individual was not tested for the presence of this organism.

The increased rate of UvM in male athletes and sportsmen (87) is consistent with the presence of MAP in the soil in countries where MAP infection of domestic ruminants is longstanding (54). The increased rates of glioblastoma (32) and amyotrophic lateral sclerosis (28,88) in outdoor athletes associated with possibly MAP contaminated soil has previously been discussed.

There is an increased rate of UvM in welders and metal workers (10,89-93). UVR has been proposed as the cause of the increased rate of UvM in welders (89). However, UVR, either UVA, UVB, or UVC, is unable to reach the choroidal layer of the eye and has not been consistently correlated with UvMs (93,94). A possible explanation may be the presence of MAP in metalworking fluid, which is known to be contaminated with bacteria (95), including mycobacteria (96-99). Aerosolization is a known mechanism of increasing the concentration of mycobacteria present in liquid (100-102).

The increased rate of UvM in occupational cooks (89,103,104) and workers in the leather industry (10,105) and a cluster of three UvM cases in a rural community where a rendering plant was located (106) are consistent with the presence of MAP in an infected animal's tissues and fluids, including blood (107-114).

Possible explanations for the racial difference in patients with UvM

An epidemiologic feature of UvM is their almost exclusive occurrence in non-Hispanic Whites and Hispanic Whites, in persons with white skin (115). Mackintosh proposed that the melanin and melanosomes conferring skin color develop as defenses against bacteria and fungi, in particular noting that "animal husbandry practices…will further determine local parasite pressures" (116). Hurbain and colleagues demonstrated that the individual melanosomes that are the predominant melanosome type in non-white skin function as antibacterial degradative organelles (117). In contrast, the melanosome clusters that are the predominant melanosome type in white skin have no effect on bacteria (117).

Choroidal tuberculomas, a rare location of miliary tuberculosis, are thought to result from hematogenous dissemination after entry of *Mycobacterium tuberculosis* organisms into the bloodstream at the level of the pulmonary alveoli (118). Miliary tuberculosis occurs at a much higher rate in black than white patients (119). The contrast with white-skinned UvM patients suggests that MAP organisms are getting to the uveal layer of the eye, not from hematogenous dissemination to the eye after the inhalation of aerosolized MAP organisms, but by the penetration of aerosolized MAP organisms through the white skin of the face and eyelid. MAP organisms may be able to penetrate white facial and eyelid skin more easily than non-white

facial and eyelid skin. Note that the aerosolized potentially MAP contaminated metalworking fluid is being sprayed right at a welder's face. Depending on the sport, the faces of outdoor athletes are directly contacting possibly MAP contaminated soil and dirt within their playing fields. On the other hand, given the rarity of UvM, it is not likely that MAP readily penetrates either white or black skin, and that once it has penetrated through skin, there is a paucity of evident suggesting an ocular tropism.

A recent case report hinting that MAP organisms may be getting to the eye from the surface of the face describes an individual living on an animal farm (of "sharps and pigeons", not dairy cattle) who developed a UvM in his left eye several years after "light blunt trauma" to that eye (120). Nontuberculous mycobacterial ocular infection is associated with surgery of and biomaterials in the cornea and sclera (121), but there are no other reports of UvM associated with trauma to the affected eye.

Once MAP organisms have penetrated through the white skin of the face and reached the uveal layer of the eye possibly within facial blood vessels, MAP organisms may be able to invade the choroidal melanocytes of the eyes of white-skinned persons more easily than the eyes of nonwhite-skinned persons. A frequently cited study (122) demonstrated that the eyes of persons with black skin have a significantly greater amount of protective choroidal melanin than the eyes of persons with white skin. The literature is not clear on the total choroidal melanin in persons of Asian descent, but the low incidence of UvM in Asians suggests a comparably large total choroidal melanin content as in persons with black skin (115).

Mackintosh's hypothesis regarding melanin and melanosomes as antibacterial substances and organelles also may explain why UvMs often occur in persons with blue eyes. Larger individual melanosomes have more melanin than smaller ones and so are better antibacterial degradative organelles. Brown-eyed choroidal melanocytes have the greatest number of and largest individual melanosomes, blue-eyed choroidal melanocytes the least number of and smallest individual melanosomes (123).

Melanocytes are the malignant cell type in CMs and UvMs (124,125). Studies have demonstrated MAP's ability to invade human macrophages (126), human enterocytes (127), human monocyte-derived dendritic cells (128), and human small intestinal goblet cells (129,130). However, the ability of MAP to invade human melanocytes and cause their proliferation has not been tested.

Although intermittently reported in the literature (131-133), it is important to rule out CM that has metastasized to the eye when studying UvM, as the former is predominantly associated with sun exposure (134). The differentiation of primary and metastatic melanoma poses difficulties, especially when the diagnosis of UvM may occur up to 15 years following the original skin diagnosis (135,136). In many cases, patients may be asymptomatic, suggesting an under ascertainment of CM that has spread to the eyes (137). On the other hand, mutations in the CDKN2A gene may represent a common genetic predisposition to both CM and UvM (138).

Possible animal models, the implications to humans, and the potential for therapy

Canine melanomas including UvM have been proposed as models of human melanomas (139). The proposed association between MAP and UvM suggests that canine UvMs may be good models for human UvM because canine UvMs also may be caused by MAP. Dogs manifest near-field exposure by putting their noses and faces into MAP contaminated soil, with MAP organisms theoretically penetrating their facial skin. This is analogous to outdoor "athletes and sportsmen" (87) who place their faces into MAP contaminated soil, and dairy farmers exposed to aerosolized MAP contaminated feces spraying their face. The same is true for welders having aerosolized MAP contaminated metalworking fluid reaching their faces.

The proposed association implies that evidence of MAP infection may be present in human UvM lesions and patients. Researchers have developed methods of detecting MAP in human tissue (140), blood (141), and feces (142,143). These identification methods can be applied to human UvM patients. A similar methodology could also be developed to test for MAP in dogs with UvMs.

MAP-associated Crohn's disease can be treated with anti-MAP antibiotics (144-149). The triple antibiotic drug formulation, known as RHB-104, has been observed to have important bactericidal action against MAP in the treatment of Crohn's disease (150). However, the therapeutic effect may not be solely attributable to a decrease in MAP viability, as this antibiotic therapy also reverses pro-inflammatory responses in lipopolysaccharide (LPS)-induced macrophages.

Bacterial inflammation and UvM

A key mechanism of bacterial infection as a cause of cancer

is the induction of inflammation (151). Regions of persistent inflammation instigate regenerative cell division with an increased occurrence of point mutations, deletions, and/or translocations (152). This 'disordered cell differentiation' in the form of inflammation in turn prompts 'a cycle of cell damage, repair, and compensatory proliferation,' believed to underlie cancer development (152-154). The microenvironment of UvM in essence is an inflammatory phenotype, characterized by various lymphocytes, macrophages, heightened HLA class I/II expression, and the presence of Tregs, which may explain the lack of an efficient antitumor immune response (155). Additionally, the increased cellular production of macrophage-attraction molecules in UvM leads to an expanded population of myeloid immature cells that suppress immune responses and facilitate the development of new blood vessels needed to nourish tumor growth (156). MAP possesses these bacterial properties and has been proposed to cause the angiogenesis and lymphangiogenesis of Crohn's disease (157).

MAP also is associated with small-bowel inflammation among cattle, with a trophic affinity for the mucosa of the distal small intestine (158,159). Indeed, there is a striking pathognomic similarity between human Crohn's disease and paucibacillary Johne's disease of dairy cattle (and related ruminants), with both regarded as inflammatory paratuberculosis attributable to MAP infection (22,160). While more than 90% of dairy herds in US farms have infected animals, MAP often remains undetected owing to the low sensitivity of diagnostic testing, especially in the case of early-stage disease (161). Farm animals such as dairy cows, sheep, and goats may serve as an unwitting reservoir for frequent and persistent MAP infections. In many cases, infected animals do not manifest clinical symptoms for years, yet shed MAP in their feces (162).

The immediacy of humans with environmental MAP exposure, whether on a farm, in contact with contaminated soil, organic fertilizers, and/or agricultural runoff of fecal material, poses a risk for inflammatory-related cancers such as UvM. Exposure is further exacerbated owing to the spore-like resistance of MAP to disinfectants, chlorination (used to treat municipal water supplies), and pasteurization (159). While the organism has been detected in cow mammary glands, dairy products, and human breast milk, the levels for the most part are minute and relatively insignificant compared with direct fecal sources (which we again posit to primarily underlie UvM risk) (163). Overall, 80–90% of cancers are estimated to be caused by exogenous environmental factors including bacteria, with certain types of cancer more or less susceptible to specific exposures (164).

In addition to producing toxins that induce inflammation and disrupt normal cell growth, bacteria may play a role in directly damaging DNA, mimicking other known carcinogens and tumor promoters (165). Bacteria and similar microbes may act in a "hit-and-run" fashion with the initial cellular transformation occurring years prior to the presentation of cancer (166). Presumably by the time that the cancer first appears, the infection has long been cleared, making it difficult to establish a causal relationship.

Eye lysozyme levels and routes of infection have been explored as another mechanism of relevance to MAP. At the site of infection, lysozyme hydrolyses glycosidic bonds and degrades peptidoglycans in bacterial cell walls. Based on radial immuno-diffusion, increases in the level of lysozyme in inflammatory conditions such as sarcoidosis, latent tuberculosis, and syphilis have been observed in patients with ocular involvement (164). Comparable aspects could underlie the putative association of MAP and UvM.

Limitations

The association of MAP with UvM has not previously been proposed. There are, therefore, no studies documenting the presence of MAP organisms in UvM lesions. The studies mentioned in this perspective were observational in nature. As such, they are prone to various sources of epidemiologic bias (e.g., poor recall, residual confounding, collider effects, or the lack of adjustment for key outcome-related variables). Many of the studies were poorly powered to detect meaningful statistical differences or were inappropriately analyzed with respect to post hoc subsets of the data. Inconsistencies in the literature also may be explained by selection bias, misclassification error, and/or reverse causality.

The association between MAP exposure and UvM, while suggestive, is uncertain. Alternative and equally plausible explanations may underlie the association. For example, the article citing a link between UvM and the leather industry also mentions dry cleaning and glass manufacturing as possible occupations connected with this cancer (105). In the case of welder exposure to bacteria in water, a just as likely risk factor is intense light. Working outdoors and exposure to UV radiation likewise may explain risk attributable to farming and outside athletic activities. However, it is important to note again that sun exposure, in contrast to CM, is an unproven risk factor for UvMs presenting in the posterior region of the eye (9,167).

Chemical fertilizers, ammonium nitrate, and various military exposures are other plausible agents that may underlie risk and should be considered when interpreting findings (140-142). The reader is reminded that association does not prove causation.

While examples exist in the noninfectious disease epidemiologic literature of well-recognized clusters, discovery in other cases is usually attributable to chance. The artifactual construction of borders in time and space (104) and multiplicity concerns likely underlie the increased incidence of UvM in reported clusters (94). Clusters of UvM also may be attributable to familial cases BAP1 tumor predisposition syndrome (168-170). However, in comparison with somatic mutations, germline BAP1 mutations in the 3p21 chromosomal region occur infrequently in UvMs (171-173). Barring direct evidence of exposure within multiple clusters, one is advised to carefully interpret the reliability of evidence from MAP-UvM clusters.

Although UV radiation is the most likely cause of iris tumors located in the anterior region of the eye, this does not preclude MAP as a risk factor. However, if this bacteria is involved in the development of iris cancer, one would expect a relatively higher frequency than for posteriorly located UvMs, given the closer proximity of the former to surface of the eye (implying more direct exposure to the microbe). However, iris cancers only account for 3% of UvMs (174). In general, a spatial predilection for cancer is poorly understood, with tissue heterogeneity, genetics, sex, and race being possible underlying explanatory factors (175-178). A temporal causal dominance of UV radiation over MAP exposure also might explain the etiology of iris cancer, although supportive proof for this theory is not evident in the literature.

The intermixing eyelid, orbital, and intraocular cancers in studies of UvM is another potential limitation. While primary intraocular cancers in adult patients are predominately melanomas, eyelid and orbital malignancies may include lymphomas, keratinocyte carcinomas, and other histologic subtypes (179).

Conclusions

To date, there is a paucity of data to support a cause-and-effect basis for MAP in the etiology of non-solar UvMs located in the posterior (dark) region of the eye. Neither animal nor human studies provide sufficient proof, vis-à-vis direct exposure, for such an association. MAP infection has never been observed in the posterior region of the eye nor 'conclusively' proven to cause cancer in any organ system. Furthermore, the literature is largely void of evidence that MAP can persist in this immune privileged site and subsequently induce malignant mutations in effector cell types (i.e., melanocytes of the eye).

Oncologic inflammatory responses evoked by MAP likely are co-incidental versus inductive. Equating immune reactivity during tumorigenesis with chronic immune dysregulation remains dubious—with the latter being pathognomonic of the mucosal instability and uncontrolled immunological stasis in IBD. Unlike CM, UvM remain relatively resistant to immune checkpoint blockade drugs (3). A reverse causality explanation also cannot be ruled out, wherein UvM might induce inflammation antecedent to infection.

Doubts persist and a precautionary approach to MAP exposure continues to be a prudent strategy in the prevention of UvM. Conceivably, factors associated with UvM could interact in a multifactorial and synergistic fashion with MAP, to evoke or reinforce a carcinogenic effect. Genetics and metabolomics may play a contributory role, with UvMs manifesting driver mutations in GNAQ and GNA11, rather than BRAF mutations (146,180). Additionally, miR-155 (an endogenously expressed, noncoding RNA) is believed to function as a tumor promotor in UvM, potentially increasing cell proliferation and tumor invasion autonomous of solar exposure (181).

However, with the exception of tumors restricted to the iris (which account for only ~3% of cases) and those driven by germline MBD4 mutations, most UvMs are sporadic and have a low mutational burden (4,174). A unified UV-related pathogenetic basis for UvMs, comparable to CM, has yet to be elucidated for this cancer (182,183). Interestingly, ciliochoroidal UvMs are predominately associated with light-colored eyes and typically manifest A>T mutations, characteristic of a pigment dependent etiology (2).

Posteriorly located UvMs of the eye may be characteristic of non-sun exposed, primary gastric melanomas (184). Melanomas also are known to occur on the soles of feet, subungual areas, and various mucous membranes. These sites manifest divergent mutation patterns and other features that are independent of, or less susceptible, to solar radiation (185,186). Nonetheless, it remains difficult to believe that a bacterial infection invading from the outside environment would be able to affect the choroid, cause an inflammatory response, and be involved in the development of UvM without histologic evidence of granulomatous

inflammation or mycobacteria. Additional study is needed to better delineate this possibility, in light of the extensive vascular supply of the choroid.

The association of MAP with non-solar UvMs remains an unanswered question. In this paper, we aimed to provide a thought-provoking synthesis of the literature, with the intent of generating future research ideas and questions. New directions and the development of novel approaches to this topic are welcome. This will aid the understanding of neoplastic disease etiology and further elucidate the role of bacterial infections on human health and life. However, until new proof is forthcoming, there is a paucity of methodologically rigorous evidence to support either a direct or indirect causal link between MAP exposure and UvM, as well as any other infectious agent.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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