

# Focal Aggregates of Normal or Near Normal Uveal Melanocytes (FANNUMs) in the Choroid. A Practical Clinical Category of Small Ophthalmoscopically Evident Discrete Melanocytic Choroidal Lesions

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## Abstract

Focal aggregate of normal or near normal uveal melanocytes (FANNUM) of the choroid is a term the author has proposed to categorize small melanocytic choroidal lesions that are not detectably thicker than surrounding normal choroid by B-scan ocular ultrasonography. In this article, the author describes the clinical features of small melanocytic choroidal lesions he categorizes clinically as FANNUMs and discusses the presumed compositional spectrum of such lesions. He explains why such lesions should not be categorized uniformly as small choroidal nevi. Lesions of this type are detectable in at least one eye of approximately 25% of light-skinned blue-eyed persons over the age of 50 years. They are frequently multifocal in the affected eye, bilateral, or both.

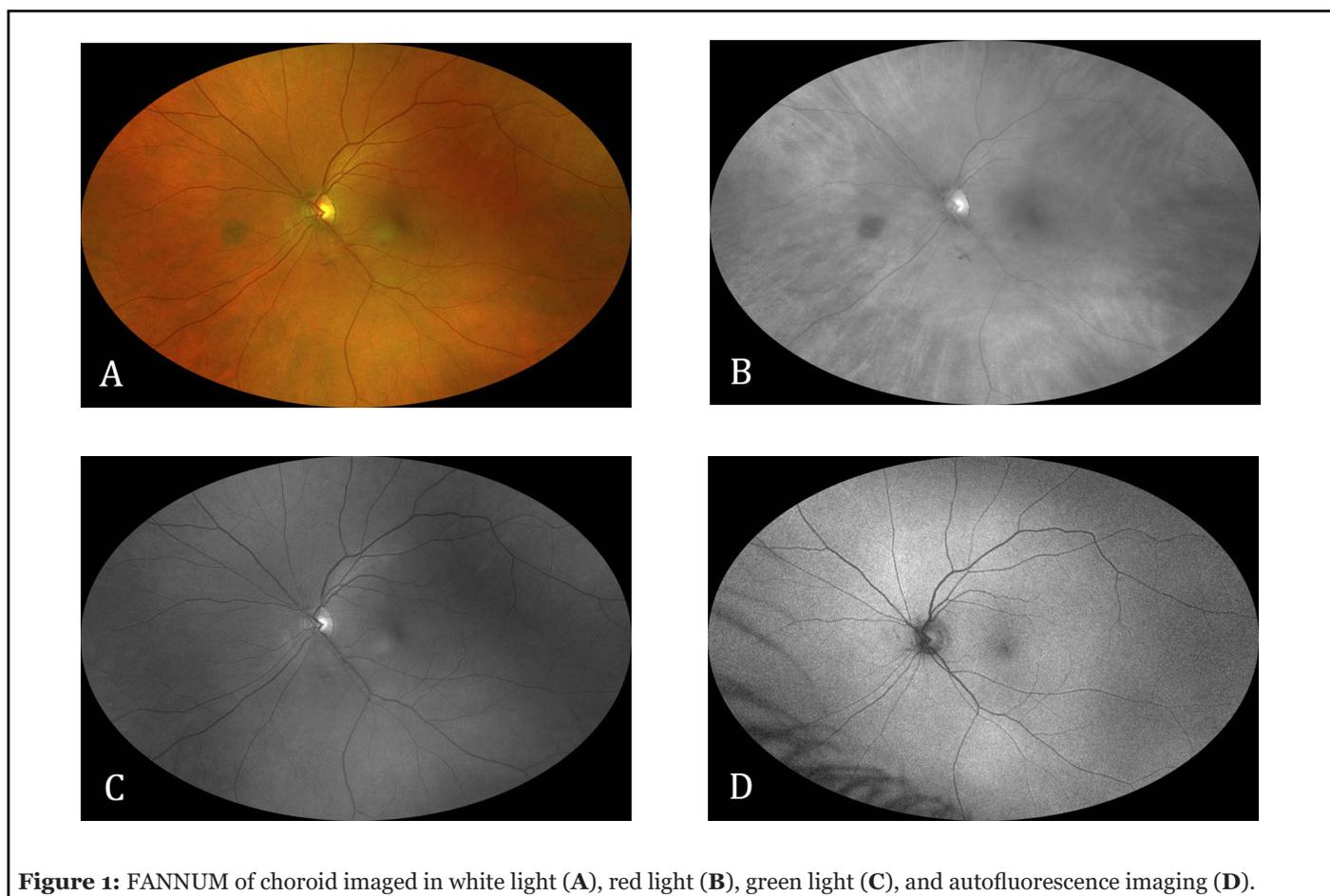
## Introduction

Multiple types of discrete melanocytic choroidal lesions are currently recognized, including benign choroidal nevi, choroidal malignant melanomas, patches of choroidal melanocytosis, and foci of choroidal melanocytes stimulated paraneoplastically by a systemic non-melanoma malignant neoplasm. In 2020, I proposed the term “FANNUM (focal aggregate of normal or near normal uveal melanocytes) of the choroid” [1] to categorize an additional specific type of discrete melanocytic choroidal lesion that exhibits the following clinical features:

- Discrete melanotic (brown, golden-brown, or gray, at least in part) choroidal lesion that is visible on indirect ophthalmoscopy somewhere in the ocular fundus;
- Circular-ovoid-geographic or ribbon-like shape;
- Not measurably thicker than surrounding normal-appearing choroid by B-scan ocular ultrasonography;
- Usually less than about 3.5 mm in largest basal diameter and never more than 5 mm in largest basal diameter if circular-ovoid-geographic in shape;

- Occasionally longer than 5 mm in largest basal diameter if ribbon-shaped and having a smallest basal diameter of less than 1 mm;
- Absence of overlying drusen, retinal pigment epithelial depigmentation and/or clumping (unless these features are also present in the corresponding area of the contralateral fundus), and/or discrete clumps of orange pigment on the surface of the lesion;
- Accentuation when viewed or imaged in red light, disappearance when viewed or imaged in red-free (green) light, and reduced or absent visibility when photographed in white light or by fundus autofluorescence imaging (Figure 1); and
- Lack of appreciable enlargement during short-term follow-up after initial detection.

In the remainder of this article, I explain why I regard such lesions as a distinct clinical diagnostic category of discrete melanocytic choroidal lesions and why I advocate against classifying such lesions routinely as small choroidal nevi.



**Figure 1:** FANNUM of choroid imaged in white light (A), red light (B), green light (C), and autofluorescence imaging (D).

## Normal Choroid and Normal Choroidal Melanocytes

The choroid is a complex three-dimensional portion of the uvea composed principally of blood vessels, stromal cells (fibrocytes), extracellular collagenous matrix, nerve fibers, and uveal melanocytes. Uveal melanocytes are distributed widely throughout the choroid; however, they are not distributed uniformly in all portions of the choroid. They tend to be more concentrated in the outer choroid than in the inner choroid [2] and most concentrated in the lamina fusca (the interface between the outer choroid and inner sclera), especially at foraminal sites of penetration of the short ciliary arteries posteriorly, the long ciliary arteries and nerves in the horizontal midline of the fundus in the nasal and temporal midzone areas, and the vortex veins at the midzonal-peripheral fundus interface in the four quadrants [3].

Normal choroidal melanocytes of several distinct morphological types have been described [4]. All of these histomorphological uveal melanocytic types exhibit bland nuclei without prominent nucleoli on histopathological preparations stained with hematoxylin and eosin. All of these uveal melanocytic types possess the capability

of producing melanin pigment that accumulates in the cell's cytoplasm. The most common type of normal uveal melanocyte in the choroid in light-skinned, blue-eyed persons is the spindle shaped (dendritic) melanocyte. In contrast, the most common uveal melanocytic type in the choroid of dark-skinned, dark brown-eyed persons is the plump rounded (polyhedral) melanocyte. Persons of intermediate skin pigmentation and intermediate eye color tend to have an admixture of these two principal cell types. The two principal morphological types of uveal melanocytes differ substantially in the number and size of the melanin granules they produce and contain and the timing of melanin appearance in the cytoplasm of those cells. Most normal dendritic uveal melanocytes produce little if any melanin during the first few years of life but then start to do so as the person ages [4,5]. In contrast, plump polyhedral uveal melanocytes appear to produce melanin very early in life and tend to have their cytoplasm filled with numerous relatively large melanin granules already in infancy. Because plump polyhedral uveal melanocytes are substantially larger than dendritic melanocytes, choroid containing plump polyhedral uveal melanocytes is usually slightly thicker than choroid containing an equivalent number of dendritic uveal melanocytes [4].

In light-skinned individuals having comparable amounts of retinal pigment epithelial pigment, three different patterns of choroidal pigmentation have been noted [6]. Individuals with predominantly plump polyhedral uveal melanocytes tend to have dark choroidal pigmentation characterized by visibility of large choroidal blood vessels that are lighter in color (red-orange) than the associated choroidal stroma (brown to dark gray). Individuals with predominantly dendritic uveal melanocytes tend to have light choroidal pigmentation characterized by visibility of large choroidal blood vessels that are darker than the associated choroidal stroma (yellow). Individuals having a combination of plump polyhedral and dendritic uveal melanocytes tend to have intermediate choroidal pigmentation characterized by limited contrast between the choroidal blood vessels and the associated choroidal stroma.

In some persons, a portion of the choroid but not the entire choroid contains a dense congenital collection of darkly pigmented plump polyhedral uveal melanocytes indistinguishable histomorphologically from normal choroidal melanocytes that populate the choroids of dark-skinned persons [4]. The portion of the fundus that contains such cells is darker than the surrounding uninvolved choroid, at least in persons with light or intermediate choroidal pigmentation and the hypermelanotic area is likely to be evident ophthalmoscopically as a patch or sector of choroidal melanocytosis in such persons. In some persons, such a patch of partial choroidal melanocytosis is associated with partial or sectoral scleral and iridic melanocytosis [7]; however, in others the choroidal melanocytosis appears to be an isolated feature. In our published articles on isolated choroidal melanocytosis [8,9], my coauthors and I restricted this diagnosis to “flat” melanocytic choroidal lesions  $\geq 5$  mm in largest basal diameter. We did so to distinguish them from most true choroidal nevi, which are almost always  $>1$  mm thick if they are  $>5$  mm in largest basal diameter. While some patches of choroidal melanocytosis can involve more than half the choroid, we fully expect some foci of isolated choroidal melanocytosis to be substantially smaller than 5 mm in largest basal diameter. Unlike dendritic choroidal nevi and most choroidal melanocytomas, small foci of isolated choroidal melanocytosis are likely to be evident in the fundus at birth. While the involved choroid in such cases can be slightly thicker than adjacent uninvolved choroid when evaluated by OCT with enhanced depth imaging, most lesions of this type are not detectably thicker than normal surrounding choroid by B-scan ultrasonography.

## Abnormal Choroidal Melanocytes and Lesions They Form

Morphologically abnormal (atypical) uveal melanocytes

are also present in the choroid of some but not most eyes, almost always in the context of focal aggregates categorized as melanocytic neoplasms. The vast majority of such cells are only slightly atypical compared with normal choroidal melanocytes and most are categorized histopathologically as nevus cells [4]. Nevus cells are believed to have undergone slight mutations that influence both their cytomorphology and reproductive capacity [10]. Focal melanocytic neoplasms composed of such cells are categorized clinically and histopathologically as choroidal nevi. Choroidal nevus cells exhibit slightly larger nuclei than normal uveal melanocytes and occasionally exhibit a small but discrete nucleolus; however, they do not exhibit anaplastic features and almost never exhibit any evident mitotic figures. Choroidal nevi can be composed of atypical uveal melanocytes of several types [11]; however, most are composed of spindle-shaped dendritic uveal nevus cells, plump polyhedral uveal nevus cells, or a combination of these two cell types. In general, dendritic choroidal nevus cells tend to contain relatively few and small cytoplasmic melanin granules while plump polyhedral uveal nevus cells tend to contain numerous large cytoplasmic melanin granules; consequently, choroidal nevi composed almost exclusively of dendritic uveal nevus cells tend to be relatively hypomelanotic, those composed almost exclusively of plump polyhedral uveal nevus cells tend to be darkly melanotic, and those composed of an admixture of the two cell types tend to exhibit intermediate pigmentation. Benign melanocytic choroidal tumors composed exclusively of plump polyhedral uveal melanocytes (a feature of such tumors that can only be determined by histopathologic study) are commonly referred to as choroidal melanocytomas [4]. Although there is some controversy regarding the appropriate classification of choroidal melanocytoma cells (i.e., are they “typical” uveal melanocytes or “atypical” magnocellular nevus cells), I have decided to categorize choroidal melanocytomas as a distinct subtype of choroidal nevus for the purposes of this article.

Most choroidal nevi that are detected ophthalmoscopically are thicker than surrounding normal choroid but  $<1$  mm in maximal thickness and also  $<3.5$  mm in largest basal diameter [11]. In their classic histomorphological study of 102 small melanocytic choroidal lesions the authors classified as choroidal nevi, Naumann and coworkers [11] indicated that two-thirds of the lesions they encountered were detectably thicker than surrounding normal choroid.

Some investigators have suggested that a melanocytic choroidal lesion should be at least 0.35 mm [12] or 0.5 mm [13] in largest basal diameter to be categorized as a choroidal nevus. These authors have not explained why they specified these arbitrary lower boundaries of lesion size or indicated how they would categorize a melanocytic

choroidal lesion that is smaller than this. To my knowledge, no pathologists or clinicians have ever specified a minimal required thickness for categorizing a small melanocytic choroidal lesion as a nevus. At issue here is whether a small collection of uveal melanocytic cells that is not large enough to form a distinct three-dimensional “tumor” should ever be classified clinically as a choroidal nevus. Nevertheless, in my opinion, most small melanocytic choroidal lesions that are well-defined and detectably thicker than normal surrounding choroid by B-scan ultrasonography should be categorized as choroidal nevi. In contrast, those that are poorly defined and not detectably thicker than surrounding normal choroid by B-scan ocular ultrasonography should be categorized as FANNUMs.

A particular type of uveal melanocytic lesion that is commonly noted in eyes of light-skinned persons is the lesion categorized as the iris freckle [14]. Lesions of this type are focal collections of only slightly atypical uveal melanocytes on the anterior (exterior) surface of the iris stroma with possible slight partial thickness extension into the underlying anterior iris stroma. Iris freckles are observed in one or both irides of approximately 50% of light skinned persons. While similar lesions are believed to occur commonly in the outer (exterior) layers of the choroid [15], lesions of this type are not identified clinically or pathologically in most persons.

In some eyes, aggregates of clearly abnormal choroidal melanocytes exhibiting anaplastic features form malignant neoplasms categorized as choroidal malignant melanomas. Anaplastic choroidal melanocytes tend to have even larger nuclei and more prominent nucleoli than nevus cells, and cells of this type frequently exhibit mitotic figures. Tumors composed of anaplastic choroidal melanocytes can be relatively uniform in morphology or quite heterogeneous in size and shape (pleomorphism). Malignant choroidal melanocytes (malignant melanoma cells) differ substantially in the amount of melanin contained in their cytoplasm: some contain numerous large melanin granules that give them a dark brown color while others contain few or no evident melanin granules and are classified as amelanotic. Most choroidal malignant melanomas are dark brown, at least in part; however, approximately 10% of choroidal malignant melanomas are predominantly amelanotic clinically and histopathologically and at least 25% exhibit heterogenous pigmentation in different areas. Almost all melanocytic choroidal lesions diagnosed clinically as choroidal malignant melanomas and confirmed pathologically as such have been > 1 mm in maximal thickness and >5 mm in largest basal diameter, thus putting them outside the range of size I specified above for FANNUMs of the choroid.

Choroidal malignant melanomas may be either primary (i.e., arising within the choroid) or metastatic (i.e., arising from an extraocular primary site [usually the skin] and involving the choroid via hematogenous spread). Of these two types, primary choroidal malignant melanomas are much more common than metastatic ones. Nevertheless, the cumulative lifetime incidence of choroidal malignant melanoma in light-skinned persons has been estimated to be no higher than 1 in 2,000 to 1 in 2,500 persons. While some primary choroidal malignant melanomas may arise from previously normal-appearing uveal melanocytes, most appear to arise from a preexistent benign choroidal nevus [16].

Unfortunately, no currently available non-invasive clinical technology allows one to determine whether the uveal melanocytic cells comprising a small melanocytic choroidal lesion are normal uveal melanocytes, atypical but benign uveal melanocytes (nevus cells), or anaplastic uveal melanocytes (uveal malignant melanoma cells). Because of this, lesion size (particularly its thickness) is generally used by clinicians as a surrogate for cytologic nature of the component cells and associated clinical features (including secondary serous subretinal fluid over, adjacent to or surrounding the lesion, clumps of orange lipofuscin pigment on the surface of the lesion, drusen overlying the lesion, disruption and clumping or fibrous metaplasia of the retinal pigment epithelium overlying the lesion, visual symptoms attributable to the lesion, and absence versus presence and time course of lesion enlargement if the lesion is monitored without intervention) are commonly used to subcategorize small melanocytic choroidal lesions as nevi or melanomas [5]. Some small melanocytic choroidal lesions exhibit “overlap features” and should probably be categorized as intermediate or borderline tumors; as a practical matter, most ocular oncologists who encounter such a tumor are likely to err on the side of classifying the tumor as malignant.

Cytomorphology of choroidal melanocytes comprising a focal aggregate of those cells may not be satisfactory evidence that those melanocytes are typical (i.e., normal uveal melanocytes) or atypical but benign (i.e., uveal nevus cells). In all probability, there is considerable morphological overlap between normal cells stimulated in some way by local microenvironmental factors in the choroid and slightly atypical uveal melanocytes due to minor cytogenetic mutations that have altered both their morphology and reproductive capacity. Ophthalmic pathologists forced to classify a melanocytic choroidal lesion composed of slightly atypical-appearing uveal melanocytes based exclusively on their cytomorphology are more likely to categorize that lesion as a choroidal nevus than as a focal aggregate of normal choroidal melanocytes.

Most ophthalmologists who detect a discrete melanocytic choroidal lesion are likely to categorize that lesion clinically (at least initially) as either a choroidal nevus or a choroidal malignant melanoma. Many articles addressing the issue of differential diagnosis of these two types of choroidal melanocytic lesions have been published, and a discussion of this differential diagnosis is beyond the scope of this article. As mentioned above, however, not all discrete melanocytic choroidal lesions fall neatly into one of these two categories.

## **Evidence That FANNUMs of Choroid Exist**

Multiple studies intended to determine the prevalence of melanocytic choroidal nevi have been performed and reported over the past 50 years. Choroidal nevi are acknowledged to be much more common in light-skinned persons than in dark-skinned ones [4]. Consequently, all prevalence studies of choroidal nevi that have been reported to date have evaluated populations that are overwhelmingly light-skinned. Choroidal nevi are also generally acknowledged to be substantially more common in older adults than in young persons. Prevalence studies that have surveyed persons from infancy to older adulthood have generally observed an extremely low rate of small melanocytic choroidal lesions in infants and young children, a higher but still quite low rate in young adults, and substantially higher rates among older adults [5]. While most infants and children do not undergo a comprehensive fundus examination looking for identifiable fundus abnormalities, some do. For example, many infants and children regularly undergo multiple ophthalmic screening evaluations, often under general anesthesia, to look for fundus disorders such as retinopathy of prematurity or retinoblastoma. If a discrete melanocytic choroidal lesion were present in such children, it is likely that it would be noted by the ophthalmoscopic examiner. Yet, extremely few such children have ever been noted to have even a single discrete melanocytic choroidal lesion in one eye [5]. Most of the melanocytic choroidal lesions that have been identified in such children have been foci of choroidal melanocytosis [17] (either isolated [8,9] or part of sectoral or generalized ocular melanocytosis [7]). Similarly, fundus examinations in individuals in the age range 10 to 20 years only rarely identify any discrete melanocytic choroidal lesions [5]. Those that were not evident ophthalmoscopically at birth but are noted within the first two decades of life are likely to be focal aggregates of normal or slightly atypical uveal melanocytic cells consisting of a relatively high proportion of densely pigmented plump polyhedral uveal melanocytes. The majority of small discrete melanocytic choroidal lesions do not appear until middle age or older adulthood [5]. This appearance of most small melanocytic choroidal lesions later in life is consistent with gradual accumulation of intracytoplasmic melanin pigment within dendritic uveal

melanocytic cells that eventually makes focal aggregates of such cells visible ophthalmoscopically.

Let's look at the results of several frequently cited prevalence studies of choroidal nevi. In 1973, Ganley and Comstock [18] reported finding at least one choroidal nevus in at least one eye in 3.1% of 287 normal, predominantly light-skinned persons evaluated by prospective direct and/or indirect ophthalmoscopy. In 1965, Hale, Allen and Straatsma [19] reported finding at least one choroidal nevus (detected by observing a transillumination shadow of the lesion in the ophthalmic pathology laboratory prior to globe sectioning) in at least one eye in 8.6% of 152 light-skinned persons whose eyes were evaluated in an autopsy study. And in 1998, Sumich, Mitchell and Wang [13] reported finding at least one choroidal nevus in at least one eye in 6.5% of 3,583 light-skinned persons evaluated in a prospective fundus photographic study. Differences in methods of lesion detection and diagnostic criteria for counting a particular lesion are believed to explain most of the differences in the prevalence rates reported by these studies. In all three studies, the vast majority of affected persons had a single detected lesion in only one eye. The American Academy of Ophthalmology, in its Basic and Clinical Science Course, has endorsed the figure of 8% as a satisfactory estimate of the true prevalence of choroidal nevi in light-skinned adults [20].

In spite of the information contained in the preceding paragraphs, two prospective indirect ophthalmoscopic studies of light-skinned persons, one reported by Gass in 1977 [5] and the other reported by me in 2020 [1], identified at least one small melanotic and presumably melanocytic choroidal lesion in at least one eye in approximately 34% of light-skinned, blue-eyed persons over the age of 50 years. As in the previously mentioned prevalence studies, the majority of affected persons in both the Gass and Augsburger studies also had a single lesion in one eye. Unlike the previously mentioned prevalence studies, however, both Gass and I identified a relatively large proportion of patients with at least one such lesion in both eyes (about 20%) or multiple lesions in one or both eyes (also about 20%).

While Gass categorized all of the melanotic choroidal lesions he identified in his study as choroidal nevi [5], I expressed my doubt about the reliability of his categorization of the "excess lesions" (i.e., the proportion of cases above the 8% prevalence rate mentioned in the preceding paragraph) and suggested that some if not most of these excess lesions were likely to be something other than choroidal nevi [1]. If these "excess lesions" weren't choroidal nevi, then what were they? In my opinion, lesions of the type whose diagnostic criteria I've specified above as FANNUMs of the choroid are almost certainly a heterogeneous group of melanocytic lesions, most of which

are likely to be either very small choroidal nevi analogous to iris freckles or focal aggregates of normal uveal melanocytes (FANUMs). A small but indeterminate proportion of such lesions (particularly ones that are evident at birth) could be tiny foci of isolated choroidal melanocytosis. In our published articles on isolated choroidal melanocytosis [8,9], my coauthors and I restricted the diagnosis of isolated choroidal melanocytosis to “flat” melanocytic choroidal lesions  $\geq 5$  mm in largest basal diameter. We did so to distinguish them from most true choroidal nevi, which are almost always  $>1$  mm thick if they are  $>5$  mm in largest basal diameter. While some patches of choroidal melanocytosis can involve more than half the choroid, we fully expect some foci of isolated choroidal melanocytosis to be substantially smaller than 5 mm in largest basal diameter. Unlike dendritic choroidal nevi, most choroidal melanocytomas and virtually all foci of isolated choroidal melanocytosis are likely to be evident in the fundus at birth. While the involved choroid in such cases can be slightly thicker than adjacent uninvolved choroid when evaluated by OCT with enhanced depth imaging, most lesions of this type are not detectably thicker than normal surrounding choroid by B-scan ultrasonography.

## Factors Influencing Ophthalmoscopic Visibility of Thin Melanocytic Choroidal Lesions

In my opinion, the following factors all have an impact on the ophthalmoscopic visibility of discrete melanocytic lesions of the choroid:

- **Thickness of the focal aggregate of choroidal melanocytes**

The thickness of a given melanocytic choroidal lesion depends on both the size of the individual uveal melanocytes comprising the lesion and the number of cells that are present in the focal aggregate. A focal aggregate of uveal melanocytes that is only a few cells thick in cross section is less likely to be evident than one that is multiple cells thick. Because many if not most choroidal nevi and melanocytomas and virtually all choroidal malignant melanomas that are detected ophthalmoscopically are three-dimensional neoplasms that occupy full-thickness choroid and are detectably thicker than surrounding normal choroid, such tumors are more likely to be detected ophthalmoscopically than are melanocytic choroidal lesions occupying only a limited cross-sectional portion of the choroid.

- **Abruptness of lesion margins**

A focal aggregate of uveal melanocytic cells may be well-defined or poorly-defined. A well-defined aggregate of

uveal melanocytic cells generally occupies full-thickness choroid with possible sparing of the choriocapillaris and is appropriately categorized as a tumor. In contrast, a poorly-defined aggregate of uveal melanocytic cells frequently involves only partial thickness choroid with a tendency to involve the outer choroid rather than the inner choroid. A poorly-defined partial thickness choroidal melanocytic lesion is less likely to be evident ophthalmoscopically than a well-defined full-thickness melanocytic choroidal tumor.

- **Extent of melanin pigment within the component cells**

The amount of melanin pigment (both the number and size of the melanin granules) within the melanocytes that comprise a discrete small melanocytic choroidal lesion clearly influences the ophthalmoscopic visibility of such lesions. As mentioned earlier, this feature is in turn dependent on the type of uveal melanocytes comprising the lesion: discrete choroidal lesions composed of normal dendritic uveal melanocytes, dendritic uveal nevus cells, or spindle shaped uveal melanoma cells are likely to contain relatively few, small melanin granules and be relatively hypomelanotic while ones composed principally or exclusively of plump polyhedral uveal melanocytes, plump polyhedral nevus cells, or plump polyhedral malignant melanoma cells are likely to contain relatively numerous, large melanin granules and be darkly hypermelanotic.

- **Amount of melanin within retinal pigment epithelial (RPE) cells**

The amount of melanin within retinal pigment epithelial cells influences the visibility of the choroidal vasculature on ophthalmoscopy and white light fundus photography (a feature termed “fundus tessellation”) [21]. The number and size of melanin granules within retinal pigment epithelial cells of a given individual tend to be relatively uniform in different areas of the fundus in both eyes. Eyes of persons with considerable pigment within their retinal pigment epithelial cells tend to have limited fundus tessellation while those of persons with a limited amount of melanin within their retinal pigment epithelial cells tend to have pronounced fundus tessellation. The choroid in eyes with pronounced fundus tessellation has been shown to be thinner on average than that in eyes with limited or no fundus tessellation [21]. Focal aggregates of normal or near normal uveal melanocytes are more likely to be visible on ophthalmoscopy in tessellated fundi than in non-tessellated ones.

- **Topographical location of the melanocytic choroidal lesion in the fundus**

Although the amount of melanin within retinal pigment epithelial cells of a given person tends to be relatively

constant regardless of fundus topographical location, the retinal pigment epithelial cells in the posterior fundus tend to be more columnar than those in the peripheral fundus while those in the peripheral fundus tend to be more broad-based and flatter. Because of this, the number of melanin granules through which light must pass to reach and be reflected from the choroid during ophthalmoscopy tends to be greater per unit area in the macula than in the periphery. Consequently, visibility of choroidal blood vessels and focal aggregates of uveal melanocytes tends to be higher, on average, in the peripheral fundus than in the posterior fundus.

Readers should keep in mind that a focal choroidal lesion that is only about 0.3 to 0.5 mm thick may be clearly “detectably thicker” than normal surrounding choroid by ocular ultrasonography if it is located in the fundus midzone to periphery but not detectably thicker than normal surrounding choroid if it is located in the posterior fundus. This is because normal choroid varies greatly in thickness depending on the topographical region of the fundus. Normal choroid is generally acknowledged to be thickest posteriorly (i.e., in the macular and juxtapapillary regions of the fundus), thinnest in the peripheral fundus, and intermediate in thickness between the posterior and peripheral fundus in normal subjects of all ages. Over the years, many attempts have been made to estimate the normal spectrum and central tendency of choroidal thickness in “normal” persons of various age groups. Investigators who have measured choroidal thickness in the ophthalmic pathology laboratory post-enucleation or post-mortem have determined the average thickness of the posterior choroid to be about 0.22 mm and that of the peripheral choroid to be about 0.1 mm [22]. Obviously, such measurements are likely to underestimate the *in vivo* choroidal thickness because of the loss of blood pressure and consequent reduced filling of choroidal blood vessels. Since the advent and improvements in optical coherence tomography (OCT), multiple investigators have attempted to measure normal posterior choroidal thickness using this technology. Posterior choroidal thickness in “normal” subjects has been shown to be slightly greater in young persons than in older ones and varies considerably with axial length and refractive status of the eye (thinner for eyes with axial myopia, thicker for eyes with axial hyperopia). Using this technology, typical measurements of subfoveal choroidal thickness are from about 0.31 to 0.36 mm in relatively young persons (mean age 37 years) [23], from about 0.25 to 0.30 mm in slightly older persons (mean age 51 years) [24], and from about 0.23 to 0.27 mm in older subjects (mean age 66 years) [25]. Unfortunately, this technology is not applicable currently to measurements of normal choroid in the fundus midzone and periphery.

Investigators who have measured choroidal thickness in

portions of the choroid involved by ocular melanocytosis have shown the involved choroid to be about 23% thicker on average than comparably located portions of the choroid in the uninvolved eye [26]. The greater thickness of the involved choroid in such cases appears to be due to the substantially greater size of the plump polyhedral melanocytes that are densely packed with melanin granules in the involved areas.

A focal aggregate of uveal melanocytes (normal, atypical but benign, atypical or malignant) that is visible ophthalmoscopically but does not replace full thickness choroid at its fundus location is unlikely to thicken the choroid substantially enough at that site to be detectable by conventional B-scan ultrasonography (whose reproducibility for thickness measurement of discrete choroidal lesions is at best about 0.3 mm). A lesion that does not thicken a tissue as thin as the choroid would not normally be categorized as a “tumor” (i.e., a three-dimensional mass). Because the choroid is generally substantially thicker posteriorly than peripherally, an aggregate of uveal melanocytes would have to be substantially thicker posteriorly than in the peripheral fundus to be detectably thicker than surrounding normal choroid. To be detectably thicker than normal-appearing surrounding choroid, a small melanocytic choroidal lesion in the posterior choroid might have to be 0.4 mm thick or thicker. In contrast, a discrete choroidal lesion in the peripheral choroid might be detectably thicker than normal surrounding choroid even if it is only 0.2 mm thick.

- **Grade of normal choroidal pigmentation**

The number and size of melanin granules within normal uveal melanocytes tend to vary greatly from person to person. As I mentioned earlier, the proportion of normal uveal melanocytes of different types and the number and size of melanin granules in the cytoplasm of those cells influence whether the choroid appears darkly pigmented, lightly pigmented, or intermediate in pigmentation. Focal aggregates of normal dendritic uveal melanocytes, which are likely to contain a relatively sparse concentration of small intracytoplasmic melanin granules, may be evident on ophthalmoscopy as relatively hypomelanotic lesions in some eyes with dark choroidal pigmentation. In contrast, lesions of this type may not be as apparent in eyes with intermediate or light choroidal melanocytic pigmentation. Conversely, focal aggregates of normal plump polyhedral uveal melanocytes, which are likely to contain a relatively dense concentration of large intracytoplasmic melanin granules, may be evident on ophthalmoscopy as darkly pigmented choroidal lesions in most eyes with light choroidal pigmentation and some eyes with intermediate choroidal pigmentation but virtually invisible in eyes with dark choroidal pigmentation.

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- **Age of subject and refractive status of affected eye**

Older persons and individuals with axial myopia are likely to have a thinner choroid than younger persons and non-myopic individuals. Consequently, a melanocytic choroidal lesion that is 0.3 to 0.5 mm in maximal thickness is more likely to be detectably thicker than surrounding normal choroid in older and myopic persons. In addition, a number of clinical conditions have been associated in recent years with choroidal thickening (pachychoroid) and thinning (leptochoroid). A discussion of these various conditions and an explanation of how they are believed to influence choroidal thickness are beyond the scope of this presentation. The important concept is that any condition that thickens the choroid is likely to make a small aggregate of choroidal melanocytic cells less evident on B-scan ultrasonography and any condition that thins the choroid is likely to make a small aggregate of choroidal melanocytic cells more evident on B-scan ultrasonography.

As I mentioned earlier, many normal uveal melanocytes, especially dendritic ones, do not produce much melanin pigment during the first decade of life and usually produce only a limited amount of melanin during subsequent decades of life. Focal aggregates of uveal melanocytic cells in older individuals are more likely to be evident as discrete melanotic choroidal lesions because of the gradual increase in intracytoplasmic melanin within those cells as a function of age.

### **Determining Whether a Small Melanocytic Choroidal Lesion Should be Categorized as a FANNUM**

In my opinion, one should only categorize small melanocytic choroidal lesions that are not detectably thicker than the surrounding normal choroid as FANNUMs of the choroid. If one detects a small, presumably melanocytic choroidal lesion he or she believes might be a choroidal FANNUM, the first thing the examiner must do is determine whether or not the choroidal lesion is “detectably thicker” than the surrounding normal choroid.

One can frequently recognize slight focal thickening of a small melanocytic choroidal lesion ophthalmoscopically by observing shifts in curvilinear inner retinal light reflections around the choroidal lesion induced by slight rapid changes in position of the illuminating beam of the indirect ophthalmoscope or the condensing lens. Visualization of inner retinal reflections of this type is enhanced when the fundus is examined in monochromatic green (red-free) light [27]. Retinal reflections of this type around a small melanocytic choroidal lesion can sometimes but not always be appreciated on fundus

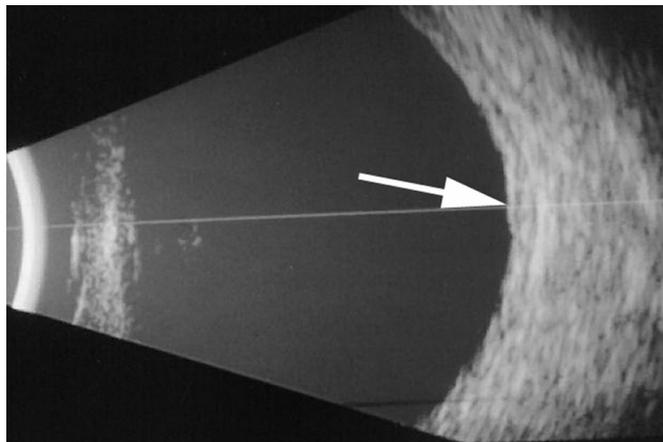
photographs. The brilliance of inner retinal reflections tends to decrease with advancing age, so such reflections may not be apparent around some choroidal lesions that are detectably thicker than surrounding normal choroid in some older individuals.

Based on ophthalmoscopy, some examiners indicate in their notes that a localized choroidal lesion they observed is “flat”. While most readers are likely to equate the term “flat” with “not detectably thicker than surrounding normal choroid”, these two terms are not precisely equivalent. Because of the arc-chord relationship that exists for a thin tissue such as the choroid in eyes that have a radius of curvature that greatly exceeds the maximal thickness of the normal choroid [28], a focal choroidal lesion could be both “flat” relative to the examiner and substantially thicker than surrounding normal choroid at the same time [29]. Because of this, I believe that an objective method of assessing the absence versus presence of detectable focal thickening of a small melanocytic choroidal lesion is appropriate in every case.

The standard for detection of slight focal thickening of a small melanocytic choroidal lesion (if it is present) that I recommend is B-scan ocular ultrasonography. Ocular B-scan ultrasonographic images provide cross-sectional views of the retina-choroid that are quite sensitive for detecting very slight but detectable focal choroidal thickening corresponding to an observed small melanocytic choroidal lesion (Figure 2). Satisfactory B-scan images can be acquired to evaluate detectable focal thickening of small melanocytic choroidal lesions located in all regions of the fundus and regardless of optical media clarity versus clouding.

Detecting slight focal thickening of a small melanocytic choroidal lesion by B-scan ocular ultrasonography is not the same thing as measuring that choroidal lesion’s thickness. Reliable measurement of thickness of small melanocytic choroidal lesions <0.5 mm in thickness by ocular ultrasonography is effectively impossible. In my experience, the reproducibility of measurements of thickness of small choroidal lesions by ocular ultrasonography is only about  $\pm 0.3$  mm. Because this value is greater than the normal choroidal thickness in most areas of the fundus and because ultrasound measurements of thickness of small choroidal lesions usually include the thickness of the overlying retina, one must realize that such measurements may well be greater than the lesion’s true thickness by 50% or more.

In recent years, optical coherence tomography (OCT) with enhanced depth imaging (EDI) has been used to measure the thickness of many discrete melanocytic choroidal lesions [30]. For small melanocytic choroidal lesions in the posterior fundus in eyes with clear optical media,



**Figure 2:** B-scan ocular ultrasonographic image showing a very small melanocytic choroidal lesion (at arrow) that is detectably thicker than surrounding normal choroid. This type of lesion would be classified as a choroidal nevus, not as a FANNUM of the choroid, because of its detectable focal thickness.

EDI-OCT provides images and measurements of choroidal lesion thickness that are far more precise and reproducible than those provided by B-scan ocular ultrasonography. Because EDI-OCT images of a small melanocytic choroidal lesion show clear separation between retina and choroid, estimates of thickness of small but detectably thicker than surrounding normal choroid lesions provided by EDI-OCT are almost always substantially less than the measurements of the same lesions provided by US. Unfortunately, currently available OCT technology does not provide satisfactory images of most midzonal choroidal lesions or of any peripheral fundus lesions and ones in eyes with cloudy or opaque optical media. Consequently, OCT is not an appropriate current means for detecting absence versus presence of detectable thickening of most small melanocytic choroidal lesions.

The second thing an examiner must do is verify the clinical “dormancy” of a choroidal melanocytic lesion he/she has categorized on initial examination as a choroidal FANNUM. Lesions of the following types might be categorized clinically as choroidal FANNUMs when they are first detected ophthalmoscopically but should not continue to be regarded as FANNUMs once progression is detected during follow-up:

Primary extra-ocular malignant melanoma metastatic to the choroid may be detected when the metastatic lesion or lesions are in the size range consistent with choroidal FANNUMs; however, most such lesions are likely to enlarge substantially during relatively short-term follow-up. Furthermore, multiple other metastatic sites of malignant melanoma are likely to be detectable during systemic staging evaluation. Fortunately, lesions of this type are extremely rare.

A primary choroidal malignant melanoma that arises from previously normal choroidal melanocytes or from a tiny choroidal nevus may become evident ophthalmoscopically when it is in the size range consistent with my definition of choroidal FANNUM’s; however, such a lesion would be expected to enlarge progressively post-detection and become detectably thicker than surrounding normal choroid during relatively short-term follow-up. Once such progression is documented, the clinical diagnosis of choroidal FANNUM should be rejected.

Focal aggregates of paraneoplastically stimulated choroidal melanocytes (FAPSUMs) are choroidal melanocytic lesions composed of uveal melanocytes stimulated paraneoplastically to proliferate by some substance elaborated by a primary extra-ocular non-melanoma systemic malignant neoplasm [31]. The component cells may appear normal, slightly atypical, or frankly malignant. While all melanocytes within the uvea are likely to be stimulated in this disorder, most affected persons exhibit one or more discrete darkly melanotic choroidal lesions in both eyes, at least when the disorder is detected initially. Most individuals who have developed this syndrome have been middle aged or older when the choroidal lesions were first detected. The melanocytic choroidal lesions generally enlarge progressively during relatively short-term follow-up and are frequently accompanied by a prominent reticular accumulation of orange lipofuscin pigment in the posterior to midzonal fundus. Fortunately, lesions of this type are also exceedingly rare.

Assuming that a discrete small melanocytic choroidal lesion that is not measurably thicker than surrounding normal choroid remains stable ophthalmoscopically long-

term post-detection, that lesion should continue to be regarded as a choroidal FANNUM.

## Alternative Terminology

When my coworkers and I first described lesions we now call FANNUMs of the choroid, we referred to such lesions as “choroidal melanocytic clusters (CMCs)” [8]. While we continue to use this alternative term internally in charts of our Ocular Oncology Service patients, we prefer the term FANNUMs of the choroid in publications and presentations for the following reasons: (1) the term “FANNUM” expresses the possibility that some lesions of the type we are describing in this article are composed of normal uveal melanocytes while others are composed of abnormal (slightly atypical but non-malignant) uveal melanocytes (i.e., are nevi) while the term “CMC” does not; and (2) some ophthalmologists we’ve encountered have misconstrued the word “cluster” in “choroidal melanocytic clusters” to mean either (a) occurrence of a number of similar cases in different patients during a relatively limited time interval [e.g., 32] or (b) the presence of multiple lesions of identical histologic features limited to a localized area of the fundus of an individual patient [e.g., 33].

We also considered the term “choroidal freckle” for such lesions. However, we object to this term for the following reasons: (1) the term “freckle” has been used by dermatologists and dermatopathologists for many years to refer to a clinically evident cutaneous macule, usually located in a frequently if not chronically sun-exposed site, that is due to a localized increase in melanin production by normal melanocytes in the basal layer of the epidermis without any corresponding localized increase in melanocyte number [4]; application of the term “freckle” to the choroidal lesions I’ve defined in this article is likely to confuse some pathologists about the nature of these ocular lesions; (2) the term “freckle” is already entrenched in ophthalmology as a descriptive term for small melanocytic lesions of the iris [14]. Although the cells comprising such lesions appear to be normal uveal melanocytes histologically, they have been shown to be slightly atypical and therefore consistent with nevus cells by electron microscopy [34]. While some FANNUMs are likely to be similar histopathologically to iris freckles, some are almost certainly composed of entirely normal uveal melanocytes; and (3) many ophthalmologists already use the term “choroidal freckle” as a surrogate term for a choroidal nevus [35].

## Conclusion

A considerable number of small melanocytic choroidal lesions detectable by indirect ophthalmoscopy fall into the category of FANNUMs of the choroid, as defined by the diagnostic criteria specified in this article. While some

of these lesions are undoubtedly tiny choroidal nevi, tiny choroidal melanocytomas, and small foci of isolated choroidal melanocytosis, some of them are likely to be focal aggregates of normal uveal melanocytes (FANUMs). While tiny choroidal nevi, tiny choroidal melanocytomas, and small foci of ocular melanocytosis all are likely to pose a low but non-negligible cumulative lifetime risk of transformation to uveal malignant melanomas [36], focal aggregates of normal uveal melanocytes are unlikely to pose a similar transformative risk. Ophthalmologists should recognize the distinct character of choroidal FANNUMs and attempt to categorize such lesions they encounter as such and not classify them uniformly as choroidal nevi.

Because the precise nature of choroidal FANNUMs cannot be determined clinically, lesions of this type should be documented when they are detected initially and then reevaluated periodically to be certain they are remaining stable or to detect enlargement should it occur. If enlargement of a fundus lesion categorized initially as a FANNUM of the choroid should occur, especially if that enlargement occurs over a relatively short time interval and especially if it is accompanied by development of “detectable thickening” of the lesion by ocular ultrasonography, choroidal FANNUM should be eliminated from the differential diagnosis and an alternative more appropriate diagnosis applied to the choroidal lesion.

## Author’s Conflicts of Interest

None.

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