

Differentiating Iris Pigmented Lesions: A Primer

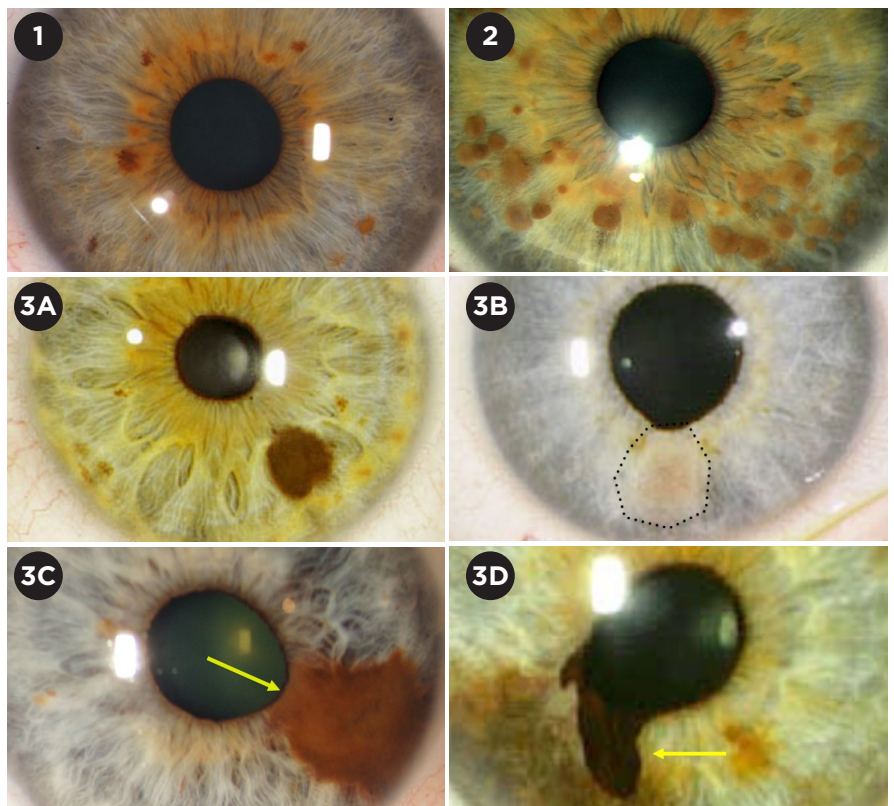
What do you do when a patient walks in with a pigmented lesion on the iris? The first thing that likely runs through your mind is: “What exactly am I looking at, and what risk does it carry?”

Melanocytic growths represent 70% of iris lesions.¹ The six most common types that comprehensive ophthalmologists might see in their offices on any given day, according to Carol L. Shields, MD, are: freckle, nevus, Lisch nodules, melanocytoma, melanocytosis, and melanoma. “The last three are the ones to worry about,” said Dr. Shields, at Wills Eye Hospital in Philadelphia.

Iris Freckle

Iris freckles tend to rest on the iris surface like a flat pancake and are typically multifocal, bilateral, and mostly affect blue and green irides (Fig 1).² “They are not actual masses—just increased melanin pigments associated with UV exposure—so they look very different from benign or malignant tumors in the iris,” said Alison H. Skalet, MD, PhD, at the Casey Eye Institute in Portland, Oregon.

Iris freckles are not typically a precursor to iris melanoma, and patients with freckles don’t need additional follow-up from an ophthalmic standpoint, according to Dr. Skalet. But a recent Australian study showed that having three or more iris freckles is



KNOW YOUR LESIONS. (1) Iris freckles. (2) Lisch nodules. (3A) Pigmented nevus, (3B) nonpigmented nevus, (3C) corectopia, (3D) ectropion.

associated with an increased risk of cutaneous melanoma.³ “I don’t worry about these patients in terms of risk for iris melanoma, but I do refer them to a dermatologist,” said Dr. Skalet.

Lisch Nodule

This is a hereditary condition that

tends to manifest by age 5. It can be a marker for neurofibromatosis type 1 (NF1). Lisch nodules typically are a tan color (even on a brown iris), bilateral, multifocal, and about 1 mm in diameter with tiny seeds around them (Fig. 2). “You want to check the patient’s skin for neurofibromatosis features and ask about neurofibromatosis in the family,” said Dr. Shields. Lisch nodules can be associated with choroidal freckling. They do not turn into melanoma.

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MD, PHD.

Iris Nevus

The chubby cousin of the iris freckle, an iris nevus appears as a pigmented (Fig. 3A) or nonpigmented (Fig. 3B) spot, typically about 3 mm in diameter and with an inferior clock-hour position. They penetrate the iris stroma, often distorting its architecture, and may be associated with corectopia (pulling on the pupil, altering its shape; Fig. 3C) or iris ectropion (Fig. 3D), according to Dr. Skalet. If you see corectopia or iris ectropion, it must be a nevus or something worse, she said.

A 2009 meta-analysis found that iris nevus has a 1.53 odds ratio for association with uveal melanoma.⁴ “It is a marker that tells us we should dilate these patients at least once a year to check the back of the eye for melanoma,” said Timothy S. Fuller, MD, at Texas Retina Associates in Dallas.

Iris Melanocytoma

A “bigger and badder” subtype of iris nevi is melanocytoma, said Dr. Shields. This tends to have a dark brown, homogeneous appearance with a granular surface and often a little bit of seeding around it. It can be very large, especially in children (Figs. 4A, B) and is associated with secondary glaucoma (11% at five years).⁵ “Melanocytoma carries only a small risk for growth into melanoma, but it is frequently mistaken for melanoma,” she said.

Iris Melanocytosis

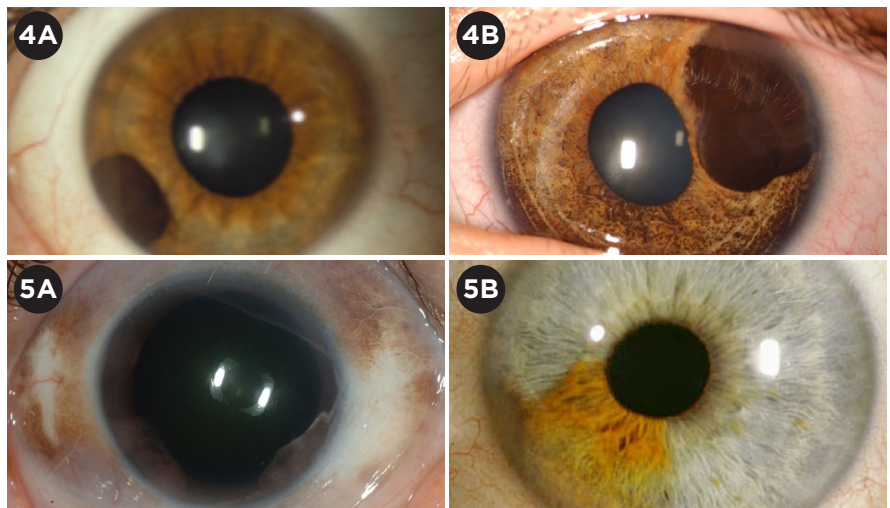
When a patient walks in with one green iris and one brown iris, or one light brown and one dark brown, the darker iris could have melanocytosis, which

ABCDEF Guide

Clinical factors predictive of nevus growth to melanoma:

- A Age \leq 40 years
- B Blood in the anterior chamber
- C Clock-hour inferior
- D Diffuse configuration
- E Ectropion
- F Feathery margins

SOURCE: Shields CL et al. *Ophthalmology*. 2013;120(4):766-772.



MANIFESTATIONS. (4A, B) Iris melanocytoma. (5A, B) Iris melanocytosis

is a congenital condition in which the uvea gets too much pigmentation, putting the eye at risk for melanoma, said Dr. Shields. Melanocytosis can be complete (Fig. 5A) or sectoral (Fig. 5B) and is characterized by mammillations, appearing as tiny micronodules within the pigmented area. Scleral and uveal pigmentation are hallmarks and sometimes there is skin pigmentation around the eye. “Make sure you lift the lids and check if the patient has scleral pigmentation; that will nail the diagnosis,” Dr. Shields said.

Melanocytosis carries a 1 in 400 risk for melanoma among Caucasians, according to Dr. Shields. Melanoma can develop in the uvea, the orbit, or the meninges, so patients need to be monitored in all those sites. “The best way is to get magnetic resonance imaging (MRI) of the head and orbit, but no one has established guidelines on how frequently to do so. In our office, we do an MRI every three to five years,” said Dr. Shields.

Iris Melanoma

To predict iris nevus growth into melanoma, Dr. Fuller relies on the ABCDEF Guide (at left).⁶ “I highly recommend posting the guide in your exam rooms for reference. If your patient meets even just one of those criteria, your index of suspicion for melanoma should go way up,” said Dr. Fuller. The three strongest predictors are diffuse configuration followed by clock-hour inferior and blood in the anterior chamber.⁶

Clinical features. Iris melanomas are typically larger and more vascular than nevi. Depending on location, they may be associated with ectropion uveae or sectoral cataract, according to Dr. Skalet. When she sees seeding on the surface of the iris stroma or within the angle (especially if associated with increased intraocular pressure), extrascleral extension, or progressive growth, she worries about the melanoma spreading.

“In addition to the nodular pattern of growth, comprehensive ophthalmologists need to be aware that thin, diffuse iris melanomas exist and carry risk for spread outside the eye. These tumors are often associated with elevated intraocular pressure,” said Dr. Skalet.

To biopsy or not? Melanoma is sometimes confirmed with fine-needle aspiration biopsy, but most ocular melanomas are diagnosed clinically; it’s not standard to do a needle biopsy for diagnosis of iris melanoma, said Dr. Skalet.

Biopsies can be tricky and carry a risk of bleeding and potentially seeding the tumor. “Even when biopsy is performed by a skilled ocular oncologist who sees these cases regularly, it’s not unusual to get a nondiagnostic read because the lesions tend to be fairly small,” Dr. Fuller explained.

That said, for cases in which it’s difficult to make a clinical diagnosis, a biopsy can be helpful for two reasons. First, cytology indicates whether the tumor is a nevus or melanoma. Second, molecular prognostic testing—when it is a melanoma—helps predict how

aggressive the cells in the tumor might be. “The gene expression profiling test was developed for tumors in the back of the eye, so we’re extrapolating when we use it for tumors in the iris,” said Dr. Skalet, “but there is an ongoing study that includes iris melanomas, and the researchers are looking at the outcomes for patients based on the gene expression profile result.”

Mission Critical: Get Baseline Images

“When a comprehensive ophthalmologist sees a patient with a pigmented iris lesion, I can’t stress enough how important it is to get a good photo to serve as a baseline,” Dr. Fuller said. He recently had a female patient in her 60s with a very large pigmented iris lesion. When she was examined at the slit lamp, he was sure she had a melanoma that needed treatment. But, thankfully, the patient had a slide from the 1970s when the spot was first seen by a diligent ophthalmologist who documented it, and it hadn’t grown at all. Based on that, he

could spare the patient from radiation, monitoring the lesion closely instead.

“Taking photographs and getting imaging is critical. Notes are not as reliable as an image. You need concrete evidence of what the lesion looked like at point A so that you can refer back to it at point B if you become concerned that it has grown,” said Dr. Skalet.

Imaging starts with slit-lamp measurements. If there is any appearance of dimension or depth to the lesion, it’s advisable to perform ultrasound biomicroscopy to precisely measure the size of the lesion, check for ciliary body involvement, and look for spontaneous vascular movement, which would suggest melanoma—as well as doing gonioscopy to check for any pigment in the angle, which further suggests melanoma, said Dr. Skalet.

Monitoring Schedule

Monitoring depends on how long a lesion has been there. If a patient’s spot has never been seen before, and it has one or more risk factors, Dr. Fuller

brings the patient back in about two to three months. If there’s no growth at that point, he’ll extend it to four to six months, then eventually to a year, which is the longest he would recommend for follow-up. If the patient comes in with a photo from a couple years back and there’s no growth, then Dr. Fuller is comfortable starting him/her out with a six- to nine-month follow-up and subsequently extending it out to a year.

Low Threshold for Referral

Comprehensive ophthalmologists should know that ocular oncologists are willing to give a second opinion on any pigmented lesion at any time, according to Dr. Fuller, who hopes that they have a low threshold for sending patients to an ocular oncologist for a second opinion. “With melanoma, more than

An Iris Lesion May Be Melanoma If . . .

- there is evidence of growth
- the tumor has intrinsic vessels
- there is seeding on the iris or in the angle
- the tumor is more than 3 clock hours
- the tumor is invading the ciliary body
- there is elevated intraocular pressure or seeding in the angle

other cancers we deal with, size matters!” said Dr. Shields. “Ocular oncologists are familiar with all the risk factors and can pick up on a melanoma when it’s still tiny, hiding out as a nevus.”

1 Shields CL et al. *Ophthalmology*. 2012;119(2):407-414.

2 Kliman GH et al. *Am J Ophthalmol*. 1985;100(4):547-548.

3 Laino AM et al. *Br J Dermatol*. 2018;178(5):1119-1127.

4 Weis E et al. *Ophthalmology*. 2009;116(3):536-543.e2.

5 Demirci H et al. *Am J Ophthalmol*. 2005;139(3):468-475.

6 Shields CL et al. *Ophthalmology*. 2013;120(4):766-772.

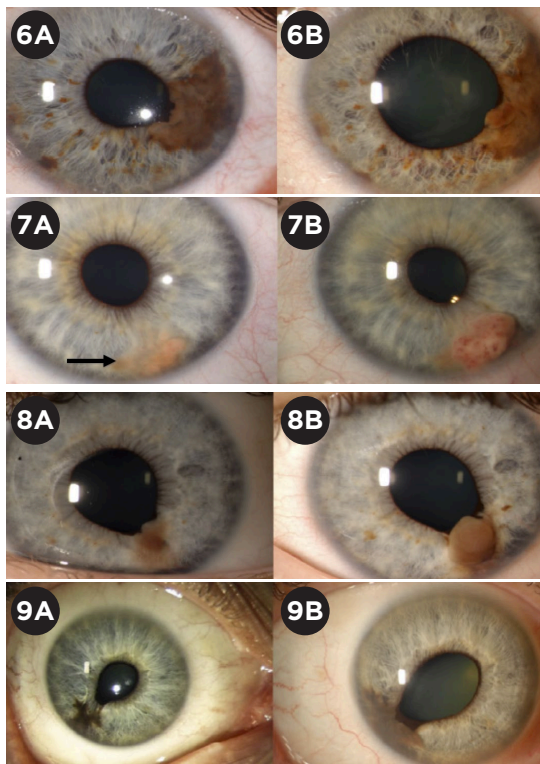
Dr. Fuller is an ocular oncologist with Texas Retina Associates in Dallas. *Relevant financial disclosures: Castle Biosciences: C.*

Dr. Shields is chief of the ocular oncology service at Wills Eye Hospital and professor of ophthalmology at Thomas Jefferson University in Philadelphia. *Relevant financial disclosures: Aura Biosciences: C.*

Dr. Skalet is an ocular oncologist and associate professor of ophthalmology at the Casey Eye Institute at Oregon Health & Science University in Portland. *Relevant financial disclosures: Castle Biosciences: C.*

See disclosure key, page 10. For full disclosures, view this article at aao.org/eyenet.

EXTRA MORE ONLINE. For a video of Dr. Shields discussing this topic, visit aao.org/1-minute-video/is-it-iris-freckle-nevus-melanoma.



ABCDEF PREDICTORS OF GROWTH. (6A,B) Age, diffuse, ectropion. (7A,B) Age, blood, clock-hour inferior. (8A,B) Clock-hour inferior, ectropion. (9A,B) Age, blood, clock-hour inferior, diffuse, ectropion, feathery.