Diabetic retinopathy (DR) is the most frequent cause of blindness in working-age adults in industrialized countries, and its incidence continues to increase. Diabetes affects at least 7% of the adult population, and researchers project that the prevalence will double in the coming decades. Prompt treatment of DR can prevent blindness in more than 90% of cases, but the right treatment depends on a timely diagnosis, and that continues to be a challenge worldwide. Researchers estimate that as many as half of all patients with diabetes remain undiagnosed. In many cases the diagnosis is made only with the onset of complications.

Regular ophthalmic examinations for patients with diabetes are crucial to detect the earliest signs of DR and begin prompt treatment. However, a multitude of barriers keeps many of these patients from receiving the care they need to reduce the risk of blindness, including a lack of qualified ophthalmologists.

Thus, researchers and clinicians alike have been exploring tools that can facilitate ophthalmic examinations in underserved regions. The utility of telemedicine to screen for referable and vision-threatening DR remains under investigation, mainly in developed countries. We wished to explore the feasibility of using a telemedicine screening platform to detect DR in patients in developing nations.

With advances in digital image processing and communications, we believe telemedicine can become a viable screening tool for patients at risk for developing diabetic retinopathy (DR). A deep-learning telemedicine platform designed by the authors achieved statistically significant sensitivities, specificities, and positive predictive values for both referable and vision-threatening DR. A follow-up study is planned to further assess the system’s ability to automatically detect hard exudates and hemorrhages compared with traditional examination techniques.
In this study we collected 9,392 UWF-SLO images of 1,903 eyes of diabetic patients to assess the DL system’s ability to grade images and detect referable and vision-threatening DR (Figure). Retina specialists determined the presence or absence of referable or vision-threatening DR based on the International Clinical Diabetic Retinopathy Disease Severity Scale. The system was then trained to grade and detect signs of DR and then tested via external validation on four different datasets.

For gradeability, the system demonstrated a sensitivity of 86.5% and specificity of 82.1% for the primary validation dataset and > 79.6% sensitivity and > 70.4% specificity for the external validation datasets. As for DR detection in the primary validation dataset, the DL system achieved sensitivities of 94.9% and 87.2%, specificities of 95.1% and 95.8%, and positive predictive values of 98.0% and 91.1% for referable and vision-threatening DR, respectively.

We concluded that our DL system could be an efficient and effective tool to screen UWF-SLO images for signs of referable and vision-threatening DR.

**NEXT STEPS**

Such positive findings led us to plan further studies within a private retina practice in Buenos Aires, Argentina, affiliated with the University of Buenos Aires, and Tel Aviv Sourasky Medical Center. These affiliates will serve as reading centers for images captured by general practitioners caring for patients in areas with no access to specialized ophthalmic care.

During a single visit, asymptomatic patients will undergo a multidisciplinary examination to confirm the diagnosis and clinical staging of diabetes. General practitioners will obtain widefield retinal images during visits and send these images to the reading centers to form the dataset. We plan to enroll approximately 200 patients with diabetes either with (study group) or without (control group) signs of retinal complications. For the study group, any patient with the presence of significant media opacities, with any signs of another eye disease (eg, glaucoma, cataracts), or with previous treatment for DR will be excluded. Those in the control group cannot have any signs of DR, as well as significant media opacities or another eye disease (eg, glaucoma, cataracts).

Using this dataset, we will assess our DL system’s ability to automatically detect hard exudates and hemorrhages—the initial signs of DR—compared with traditional examination techniques.

We will analyze the images manually, then implement a DL algorithm to locate basic elements of the retina and the optic disc for the identification of false positives and for the classification of pathologies according to their severity and the measurement of lesions—often a time-consuming task for clinicians. The system will further detect microaneurysms, hard exudates, and hemorrhages.

To avoid discarding low-resolution images, we plan to develop techniques to improve contrast and reduce noise; this will help specialists better interpret the images and allow them to be included in the automated analysis. Contrast enhancement techniques and restoration algorithms have been used to improve poor quality images, usually due to cataracts. We hope to implement this study at multiple sites around the world, similar to the study previously mentioned.

**FUTURE ASPIRATIONS**

If this DL system proves to be as useful in this real-world setting as it was in our initial study, we hope to eventually use it to provide fully automated detection of DR for those most in need.
In the United States, choroidal nevus—a stable, melanocytic tumor—is found in up to 6.5% of the White population, 0.6% of the Black population, and 2.7% of the Hispanic population.\(^1,2\) Choroidal nevi can grow into melanoma, or they can enlarge slowly over a long period of time without melanoma transformation.\(^3\) Although choroidal nevi can affect vision, most are asymptomatic with little impact on visual function or refractive error. Shields et al evaluated a cohort of 3,422 consecutive eyes with choroidal nevi, categorized as either subfoveal or extrafoveal, and found that the median VA at presentation was 20/20 in both cohorts. However, at the 15-year follow-up, vision loss of ≥ 3 logMAR lines of vision was observed in 26% of eyes with subfoveal tumors compared with only 2% of eyes with extrafoveal tumors.\(^4\) Vision loss due to a subfoveal choroidal nevus is most often related to tumor-induced retinal pigment epithelial (RPE) alterations (especially RPE detachment), lipofuscin pigment, and foveal edema.\(^4\)

Regarding progression to melanoma, Qiu and Shields used the US National Health and Nutrition Examination Survey to identify 5,575 participants 40 years or older and found no association between choroidal nevus and skin melanoma; however, there was a relationship with uveal melanoma.\(^2\) Singh et al retrospectively estimated that one in 8,845 choroidal nevi demonstrated evolution into choroidal melanoma, presuming that all melanoma arises from a nevus.\(^5\) Shields et al longitudinally studied the growth of choroidal nevi into melanoma and found that growth occurred in 2% at 1 year, 9% at 5 years, and 13% at 10 years.\(^6\) Shields and colleagues subsequently identified objective criteria, based on multimodal imaging, to identify at-risk nevi for early treatment.\(^7\)

Choroidal nevi that slowly enlarge without progressing to melanoma are poorly understood. Growth of a choroidal nevus has been considered a key determining feature suggestive of melanoma transformation.\(^8\) However, recent literature shows that some choroidal nevi can enlarge slowly during a patient’s younger years and thereafter remain stable.\(^9\) Here we describe a case of slow enlargement of a benign choroidal nevus. Importantly, this case emphasizes that slow nevus growth in the absence of risk factors can represent benign enlargement, especially in young patients.

**CASE REPORT**

A 28-year-old White woman was diagnosed, using wide-angle imaging, with a choroidal nevus 4 years prior to presentation to our clinic (Figure 1A). The nevus was monitored annually and remained stable for 3 years, according to the referring physician. However, in year 4, enlargement was noted, and the patient was referred for our opinion. Medical and ocular history were noncontributory. Family history revealed cutaneous melanoma in a paternal grandparent.

On examination, BCVA was 20/20 OU. The pupils, IOP, and anterior segment findings were within normal limits in each eye. The left fundus was unremarkable. The right fundus revealed a juxtapapillary pigmented choroidal mass measuring 7 mm in basal diameter, appearing approximately 1 mm larger than was documented 4 years prior (Figure 1B). Fundus autofluorescence (FAF) showed no areas of orange...
pigment or subretinal fluid (Figure 1C). Ultrasonography demonstrated a flat, dense choroidal mass with a thickness of 1.83 mm (Figure 2A). OCT showed an intact retina with no subretinal fluid (Figure 2B). Multimodal imaging revealed only one risk factor: diameter > 5 mm. A diagnosis of benign, slow enlargement of choroidal nevus was made, and observation was recommended.

**DISCUSSION**

Evaluation and imaging are important steps to determine if a choroidal nevus is at risk for progression into melanoma. There are six important risk factors related to the transformation of a choroidal nevus into melanoma, remembered by the mnemonic to find small ocular melanoma doing imaging (TFSOM-DIM), which represents Thickness > 2.0 mm on ultrasonography, Fluid (subretinal) on OCT, Symptoms (VA ≤ 20/50) on Snellen acuity, Orange pigment on FAF, Melanoma acoustic hollowness on ultrasonography, and Diameter > 5.0 mm on fundus photography (Table 1). Each of these risk factors is identified by imaging or visual acuity testing using objective criteria.

In this patient, all imaging risk factors were absent except for nevus diameter > 5.0 mm. Based on the mean 5-year estimates, patients with one risk factor have an overall 11% rate of growth into melanoma. Furthermore, tumor diameter > 5.0 mm was found to be the weakest risk factor (P = .0275; hazard ratio, 1.84). Thus, cautious observation was advised for our patient with the intent to treat if further growth or development of other factors was observed.

Choroidal nevus with growth into melanoma tends to occur with a mean 1.0 mm/year diameter growth rate and 0.5 mm/year increase in thickness, often with development of other features such as subretinal fluid (63%), orange pigment (40%), and acoustic hollowness (30%). Benign choroidal nevus enlargement, however, is a relatively slow process with a mean diameter increase of only 0.06 mm/year. In a study of 284 choroidal nevi, researchers observed 31% of the nevi with very slow enlargement on follow-up over a mean 15 years. Enlargement was inversely related to age, with 54% of nevus growth observed in patients < 40 years, 34% in patients ≥ 40 years.

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**TABLE. CHOROIDAL NEVUS TRANSFORMATION INTO MELANOMA IN 2,355 CASES**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Letter(s)</th>
<th>Mnemonic</th>
<th>Representation</th>
<th>Hazard ratio (95% CI) by multivariable analysis</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor thickness: &gt; 2 mm vs ≤ 2 mm</td>
<td>T</td>
<td>To</td>
<td>Thickness &gt; 2 mm by ultrasonography</td>
<td>3.80 (2.22–6.51)</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>Fluid subretinal: Cap vs none ≤ 3 mm from nevus vs none</td>
<td>F</td>
<td>Find</td>
<td>Subretinal fluid by OCT</td>
<td>3.00 (1.77–5.09)</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>Symptoms: visual acuity loss 20/50 or worse vs better</td>
<td>S</td>
<td>Small</td>
<td>Symptoms, vision loss by Snellen</td>
<td>2.28 (1.28–4.04)</td>
<td>.0050</td>
</tr>
<tr>
<td>Orange pigment: present vs absent</td>
<td>O</td>
<td>Ocular</td>
<td>Orange pigment by fundus autofluorescence</td>
<td>3.07 (1.65–5.74)</td>
<td>.0004</td>
</tr>
<tr>
<td>Melanoma acoustic density: hollow vs solid</td>
<td>M</td>
<td>Melanoma</td>
<td>Melanoma hollow by ultrasonography</td>
<td>2.10 (1.31–3.37)</td>
<td>.0020</td>
</tr>
<tr>
<td>Tumor diameter: &gt; 5 mm vs ≤ 5 mm</td>
<td>DIM</td>
<td>Doing IMaging</td>
<td>Diameter by photography</td>
<td>1.84 (1.07–3.17)</td>
<td>.0275</td>
</tr>
</tbody>
</table>

between 41 and 60 years, and 19% in patients > 60 years. We speculate that benign nevus enlargement may be more common in young adults. Most notably, patients with slow enlargement of choroidal nevus demonstrate further stability without the development of melanoma features over a mean follow-up of 15 years.

In this case, the patient had only one risk factor, a basal diameter of 7 mm, with slow nevus enlargement of approximately 0.25 mm/year. Although this is faster than most nevi enlargement, it is slower than melanoma growth. Thus, we recommended cautious observation with long-term follow-up. This case highlights that slow growth of choroidal nevus, especially in young patients, is not a definitive sign of melanoma transformation.

Clinicians must assess all six risk factors of choroidal nevus when making a judgment regarding the potential for future growth, keeping in mind that a subset of patients might show slow enlargement of nevus without risk factors and without transformation into melanoma. For those patients, observation may be a suitable management option.


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