

Normative Databases for SD-OCT: Only Part of the Story

Databases have their place, but individual serial measurements are the gold standard for tracking disease.

BY GLENN J. JAFFE, MD

Normative databases have been used since the early days of time-domain (TD) optical coherence tomography (OCT) for the purpose of comparing the characteristics of an individual patient to a population-wide norm. The normative database allows the clinician to tell at a glance whether a particular patient's retinal dimensions fall within normal limits. It is important, however, for the clinician to understand what normative databases can and cannot do, and to be aware that the information they provide has certain limitations.

TD-OCT, introduced to ophthalmology in the 1990s,¹ provided 2-D cross-sectional images of the fundus that served almost as "in vivo biopsies" to provide clinicians with important information on the morphology of the retina and other structures in the posterior pole of the eye. The introduction of spectral-domain OCT (SD-OCT) technologies brought advances in the diagnostic value of OCT, including higher resolution and faster acquisition of images, and as a result more accurate portrayals of retinal morphology and pathology.²

However, with the introduction of these improvements, we also saw a proliferation of OCT technologies, as each manufacturer developed its own SD-OCT software and methods of delineating and defining posterior segment structures. This meant that each system now had its own normative database, based on its own cohort of "normal" or representative subjects.

While normative databases can be useful in a number of contexts, there are caveats that clinicians must bear in mind when using them. First, as mentioned, measurements cannot be compared across platforms because each technology's normative database is derived from a different population. Second, and just as important, there are demographic variations within populations that may not be represented in the overall norms presented by these normative databases—for example, differences among racial or ethnic groups, and differences between the sexes. This article explores these caveats and con-

cludes with some remarks on ways in which normative databases can be of value to the clinician and researcher.

VARIATIONS WITHIN, BETWEEN POPULATIONS

Normative databases for SD-OCT are based on studies of patient populations that provide benchmarks against which to compare the characteristics of an individual patient. These tools are used in 2 broad contexts: Retina specialists are generally more interested in database parameters pertaining to retinal or macular thickness, while those who treat glaucoma and other diseases of the optic nerve generally use database information relating to retinal nerve fiber layer (RNFL) thickness and ganglion cell complex thickness. As a retina subspecialist, I am in the former camp, although I also understand the significance and use of the RNFL and ganglion cell complex information. Increasingly, I have been using this information in my own practice, and, conversely, glaucoma specialists have increasingly been using macular thickness values, often as a surrogate for ganglion cell complex thickness.

As noted above, each manufacturer undertakes its own studies on which to base its normative database. In many cases the results of these studies are unpublished, proprietary information, so it can be difficult to "see into" the database to understand its contents. Comparisons of retinal thickness measurements across different SD-OCT systems in the same population of patients tend to show differences in measurements from 1 system to another.

For example, in a study of 184 healthy and diseased eyes of 106 patients,³ examined using the Stratus TD-OCT (Carl Zeiss Meditec) and the Cirrus (Carl Zeiss Meditec) and Spectralis (Heidelberg Engineering, Inc.) SD-OCT systems, the difference in foveal thickness between the 2 SD-OCT machines was 24.3 μm . (This study also found that retinal thickness measurements from the SD-OCT models were both greater than those from the TD-OCT device.)

In another study,⁴ measurements with the Stratus TD-OCT and the Cirrus, the RTVue-100 (Optovue Inc.),

For this issue's focus on retinal imaging, *Retina Today* invited all manufacturers of SD-OCT devices of which we are aware to tell us about any recent updates to the normative databases or related software for their devices. Not all manufacturers responded to our requests, but we received the following updates.

SPECTRALIS

The Spectralis platform features a fovea-to-disc alignment technology (FoDi) that helps to improve comparisons of individual patient scans to the normative database. For peripapillary scans, FoDi draws a line from the center of the optic nerve head to the macula, and it uses that line as the start-stop point for every analysis, no matter how the patient's head is oriented. This decreases the amount of noise or error in the database due to patient positioning variations. It also does the same for comparing serial studies to an individual patient's baseline or to the database, decreasing noise and improving the assessment of the patient's status over time.

– Heidelberg Engineering, Inc.
Carlsbad, CA

CIRRUS HD-OCT

The age-matched normative databases for the Cirrus HD-OCT have been cleared by the Food and Drug Administration and include:

- RNFL, including superpixels across the Cirrus 6 x 6 mm cube
- Optic Nerve Head, also adjusted based on disc area
- Macular Thickness
- Ganglion Cell + Inner Plexiform Layer Thickness

Results are color-coded to make interpretation visual, simple and fast. At 1 glance, the operator will know if a patient's measurement falls outside the normal limits (based on the 1st, 5th, 95th and 99th percentiles). Cirrus normative databases are not only age-matched but are also ethnically diverse.

– Carl Zeiss Meditec
Dublin, CA

and the 3D OCT-1000 (Topcon, Inc.) SD-OCT and Fourier-domain OCT units were compared in a group of 40 randomly selected healthy volunteers. The authors found that the SD-OCT instruments varied greatly in scanning protocols, and they warned clinicians to be aware that differences in system calibration, scan protocols, and segmentation algorithms could contribute to disparities in thickness measurements between instruments.

In other words, these differences arise not so much because the study populations differ, but because each model uses a different algorithm to calculate thickness. Therefore it is vital that the normative database must be specific to the SD-OCT machine being used. Measurements cannot be reliably translated from one device to another.

The other potential problem with the use of a normative database is that demographic differences in retinal thickness values may confound one's ability to interpret a patient's thickness relative to the normative database.

Demographic differences in macular thickness have been observed since the days of TD-OCT. In a study using the OCT-1 (Zeiss-Humphrey), black and Asian subjects had thinner central macular thickness compared with white subjects ($-18.4 \mu\text{m}$ and $-3.9 \mu\text{m}$; $P = .003$ and $P = .01$, respectively).⁵ In a study using the TD-OCT Stratus, investigators found that mean foveal thickness was significantly less for black individuals ($181.0 \mu\text{m}$) than for white ($200.2 \mu\text{m}$; $P < .0001$) or Hispanic ($194.7 \mu\text{m}$; $P = .005$) individuals.⁶

The same investigators also observed differences in retinal thickness between the sexes using the TD-OCT Stratus. They found that mean foveal thickness in male subjects ($201.8 \mu\text{m}$) was significantly greater than in female subjects, ($186.9 \mu\text{m}$; $P < .001$).⁶ In a study in a Japanese population using the 3D OCT-1000 model SD-OCT, mean foveal thickness was again significantly greater in men ($226 \mu\text{m}$) than in women ($218 \mu\text{m}$; $P = .002$).⁷

Based on these studies and others, it has become clear that there are statistically significant differences in retinal thickness among subjects of different races and sexes. African-American heritage is a predictor of decreased mean foveal thickness in comparison with white and Hispanic subjects, and male sex is a significant predictor of increased mean foveal thickness regardless of race. It is therefore important that clinicians consider these differences when evaluating an individual on the basis of a normative database.

PRACTICAL USES

Given these caveats, there are practical uses for normative databases in clinical and research settings. When a new patient presents, the normative database can provide a quick snapshot to help determine whether this individual falls within or outside normal parameters—keeping in

mind the sex and race differences outlined above.

In addition, in a research setting, the normative database can help to determine a patient's inclusion in or exclusion from a clinical trial. The designers of clinical trials have to make decisions about how to ensure that patients with a certain pathology are included in a study's population. If they are evaluating, for example, a drug that is meant to decrease retinal thickness, they want to ensure that patients start with an abnormally thick retina in order to be able to measure change. A normative database can be used to determine an average thickness, and a value at some point above that—perhaps 2 standard deviations—can be used as a cutoff point for enrollment.

For everyday management of patients, however, I find normative databases to be of limited value. I am more inclined to take a baseline SD-OCT image and then serially follow each patient compared to him- or herself. This is important, because I am treating an individual patient, not the average patient. So for an example, if I am using retinal thickness as a way of monitoring response to a treatment designed to decrease retinal thickness, I take serial images and follow the patient's own results over time.

In addition, I look at a number of factors on the OCT study, not just thickness. The morphology, in particular, helps me to determine whether there is pathology that would make a given retina abnormal, whatever the thickness is.

For me, the gold standard is the baseline OCT of the individual patient. I use the normative information from large populations keeping in mind the average differences among different demographic groups. Normative databases provide a quick screen, but it is important to evaluate multiple aspects of the OCT, particularly the morphology, and to make sure that the thickness measurements recorded were correct and not artifacts. All of these things are important in the management of patients with retinal disease. ■

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