The Clinical Utility of the Normative Database

Constructing normative databases for retinal diseases poses unique challenges.

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A normative database calculates the average anatomic values, such as retinal thickness, of theoretically normal patients by averaging the measurements of a large number of patients. This measurement can be used as a baseline to track a patient's response to an intervention with pharmaceutical or other treatments. It is important to note, however, that a normative database is only of value if it is developed from a representative population; for instance, what may be considered "normal" in patients with diabetes would be vastly different from "normal" in patients without diabetes. Taking this thought a step further, and using the example of a diabetic retinopathy treatment trial, a normative database for the average thickness of the retina may not accurately reflect normal for a diabetic patient because the normal retinal thickness in a diabetic patient is actually thicker than in a patient without diabetes.

BUILDING THE IDEAL NORMATIVE DATABASE

Unlike for glaucoma, where normative databases composed of aggregated patient data are successfully used to track changes in nerve fiber layer thickness over time, for retinal thickness, it is more relevant to compare values against an individual patient's baseline. Ideally, patients should be followed over time to compare their current visit with the previous visit instead of comparing it against a normative database. In this way, physicians can track changes between 2 visits and determine the impact of interventions during that time frame. During a clinical trial involving a pharmaceutical and a placebo, reading centers monitor whether or how a patient's retinal thickness transformed between 2 visits.

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Normative databases for retinal applications continue to evolve, as they are constructed using diverse demographic populations, a wide range of age criteria, and larger numbers of patients. Normative databases must be much more precise for clinical trials than for clinical practices in order to determine if a treatment is or is not effective. Data analysis on the effect of change in response to an intervention is more precise and accurate when there is a clear understanding of what a baseline normal retinal thickness is in patients with different pathologic conditions.

There are still challenges that must be overcome to develop normative databases sufficient for use in clinical trials. The ideal normative database would include a wide variety of patients and diseases and incorporate the retinal thicknesses of the same patients from many devices. Different devices measure differently, and current normative databases are being produced by multiple companies using different instruments. There is no standardized approach for comparing measurements across devices in a clinical study. Also, an individual's retinal thickness changes over the course of a day, and so it would be ideal

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to measure the same patients multiple times during the day for inclusion in a normative database. It would also be beneficial to image multiple patients on different devices on the same day to get an understanding of the differences between the devices. However, comparing between devices is difficult and would require the use of a universal reading software so that patients were analyzed with 1 formula no matter the device.

THE REGULATORY PATHWAY

Ora Inc. has recently begun an effort to create a normative database with a wide variety of parameters from a diverse range of patients and disease states. Creating a statistically significant sample size of all potential subgroups will take a very large number of patients. Ultimately, we would also like to include age parameters to further build these datasets.

One approach to building a more representative dataset would involve a well-controlled prospective study that covers multiple groups. However, we believe there could be another way to develop a normative database of retinal thickness. As studies are performed on pharmaceutical agents being targeted at degenerative diseases, advanced imaging allows a better understanding of the inclusion and exclusion for patients that may show changes from the baseline. Such prescreening tools are critical—and for more reasons than may be obvious. Using an integrated regulatory approach to collect data from these clinical trials could help to build a normative database without as much cost and time to the device manufacturer. ■

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