Chapter 3. The Normative Database

The normative database provides the clinician the necessary tool for fast and effective RNFL evaluation. The normative database establishes the range of normal RNFL thickness across the peripapillary retina. The database characterizes the normal 3-Dimensional RNFL thickness profile in terms of both the absolute thickness and the pattern or shape of the RNFL profile. Sophisticated data analysis compares individual RNFL profiles to the database and reveals RNFL loss due to disease. This analysis also monitors small change over time that occurs with disease progression. RNFL analysis is presented with the Thickness Map, Deviation Map, TNSIT Graph, and output parameters such as a neural network based descriptor, the Nerve Fiber Indicator (NFI). These measures are described in detail in Chapter 4.

The database includes both normals and glaucoma patients. The glaucoma patient data was used to train the machine learning classifier (the NFI) to detect and characterize the pattern of global RNFL loss caused by glaucoma. Glaucoma patient data was used to evaluate the parameters to determine which measures are the best discriminators for distinguishing normal from glaucoma. This data also defines how the RNFL and the parameters change with the severity of the disease.

The database (normals and glaucoma patients) was collected with the commercially available GDx VCC device under a stringent protocol with external Institutional Review Board (IRB) approval. The data was collected from six US sites beginning in September 2001.

The investigators and data collection sites were:

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Robert D. Fechtner, MD	New Jersey Medical School (UMDNJ)
Jerome Sherman, OD	SUNY College of Optometry
Chris Girkin, MD	University of Alabama Birmingham
Neil Choplin, MD	Eye Care of San Diego
Thomas Hixson, OD	La Mesa Vision Care

All individuals in the database (normals and glaucoma patients) had complete ophthalmic exams.

These exams included:

- Medical History Review
- Refraction and Visual Acuity (VA)
- Biomicroscopy
- IOP
- Standard Automated Perimetry (Humphrey 24-2 SITA standard program)
- Ophthalmoscopy
- GDx VCC

Inclusion/Exclusion Criteria

- All eyes had best corrected visual acuity of 20/40 or better.
- Normal eyes had normal appearing optic discs, normal IOP, normal visual fields, no family history of disease, and no optic neuropathy.
- Glaucoma eyes had abnormal appearing optic discs, open angles, and no other optic neuropathy.
- IOP and visual field results were not a consideration.

Definition of Normality

IOP - Under 22 m Hg

Visual Field - Glaucoma Hemifield Test within normal limits and PSD > 5% probability level

Optic Disc - A normal appearing optic disc based on clinical exam including no C/D ratio asymmetry between eyes of > 0.2, no rim thinning, notching, excavation, or observable RNFL defect.

Summary statistics

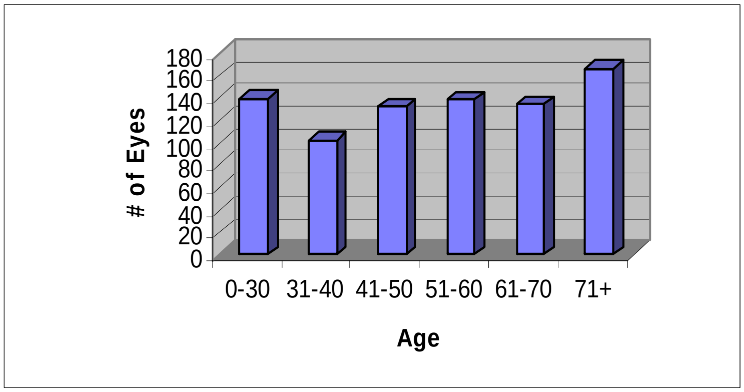
The Table below provides the summary statistics of the database. The number of eyes, age, refraction, and visual field results are provided. These numbers are valid for software version 5.0. Normative data continues to be collected.

	Eyes	Age		Sphero-equivalent		MD		PSD	
		mean +/- sd	range	mean +/- sd	range	mean +/- sd	range	mean +/- sd	range
Normal	540	43.9 +/- 16.5	18 - 82	-.92 +/- 2.3	-8 - 5.25	-.69 +/- .95	-2.9 - 1.7	1.5 +/- .5	.07 - 3.9
Glaucoma	271	65.7 +/- 13.1	25 - 89	-.3 +/- 2.5	-8.4 - 5.5	-5.5 +/- 6.0	-31.6 - 2.8	5.0 +/- 4.0	.6 - 16.4

Age Distribution

The distribution by age of the GDx VCC database is shown in Figure 3.1. It includes both normals and glaucoma patients.

Figure 3.1. The distribution of eyes in the database.



Ethnicity Breakdown in the Database

The relative ethnic breakdown of the database is shown in Figure 3.2. The inclusion of a high percentage of Asians and individuals of African descent is important because the prevalence for glaucoma is higher in minorities. The prevalence for people of African descent is as much as 6 times higher than for Caucasians of the same age[10,11].

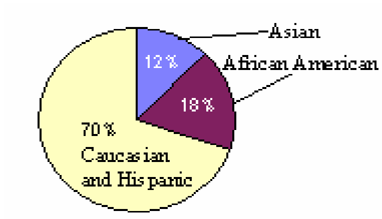


Figure 3.2. The ethnic breakdown by percentage of the normative database.

RNFL changes with Age in Healthy Eyes

The GDx VCC normative database is stratified by age. Patient comparisons to the database are made using appropriate age-matched normals. The normal RNFL loss with age is small, but significant, making age-matched comparisons an important aspect of the analysis. It is estimated that a healthy eye losses roughly 5,000 ganglion cells per year as part of the normal aging process [66-68]. Numerous studies have used scanning laser polarimetry to document RNFL thinning with age [69-73]. In order to accurately differentiate RNFL changes due to the aging process from loss due to disease, the relationship of the RNFL profile with age in the normative database was evaluated. Figure 3.3 shows how several GDx VCC parameters change with age in normal eyes.

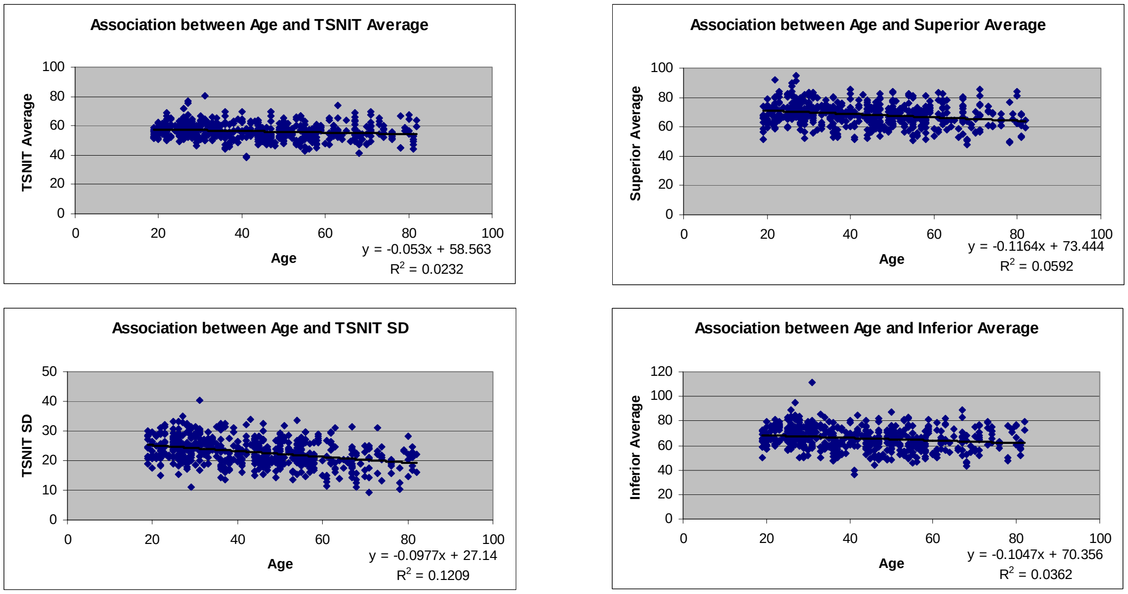


Figure 3.3. The relationship between age and several GDx VCC parameters in healthy eyes. The regression line for each parameter is given along with the regression equation. Although the RNFL changes with age are small, they are significant.

The effect of age on the normal range of the TSNIT graph is shown in Figure 3.4. Notice how the entire shaded region shifts to lower RNFL values as age increases.

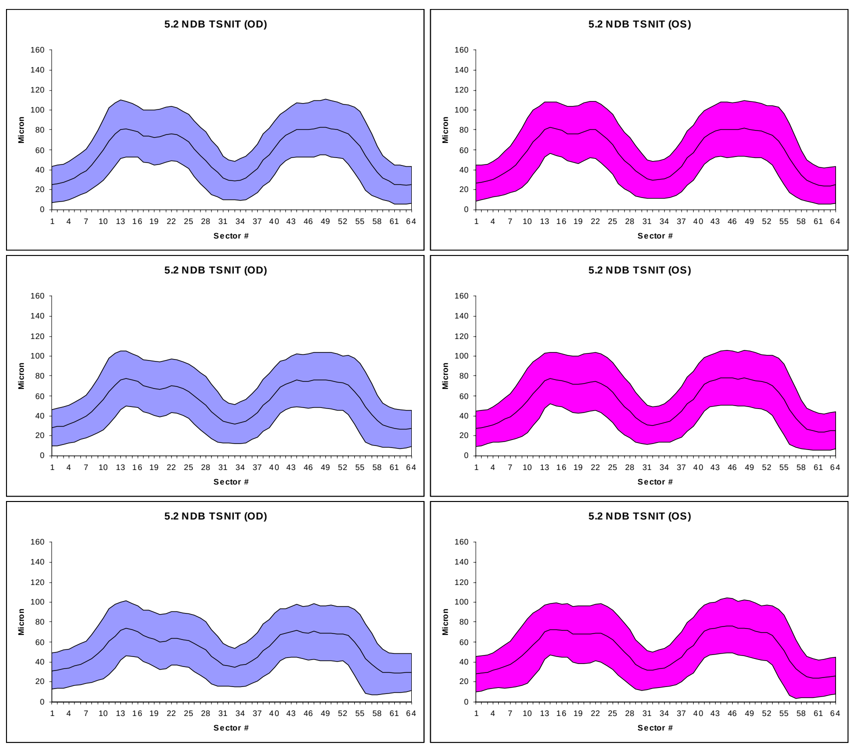


Figure 3.4. The mean and 95% normal range of the TSNIT graph for normals is shown for 30 year olds (top), 60 year olds (middle), and 90 year olds (bottom).

Discrimination with the Parameters

The GDx VCC calculates output parameters that are compared to the normative database to determine statistical significance based on age-matched comparisons. The discriminating power of these parameters was evaluated using Receiver Operating Characteristic (ROC) curves. ROC curves and sensitivity and specificity is discussed in detail in Appendix A. Below are 2 tables that show the area under the ROC curve, and the sensitivity and specificity at fixed specificity values of 80% and 90%. The table on the top compares the normals from the database to all glaucoma patients in the database, the table on the bottom compares all the normals to only the patients with visual field defects (n = 179). A visual field defect is defined as a Glaucoma Hemifield Test result "Outside Normal Limits" or a PSD value with a probability value of p < 5%.

For All Normals and all glaucoma patients (including pre-perimetric)				
Tables			Specificity at 80%	Specificity at 90%
	Area	SEM	Sensitivity	Sensitivity
NFI	0.89	0.013	81	77
Norm. Sup. Area	0.83	0.016	74	61
Superior Average	0.83	0.016	72	61
Inter-Eye Symmetry	0.83	0.022	71	59
TSNIT SD	0.81	0.016	68	56
Norm. Inf. Area	0.80	0.017	70	57
TSNIT Average	0.80	0.018	70	60
Inferior Average	0.79	0.018	66	54
Superior Maximum	0.77	0.019	64	55
Superior Ratio	0.75	0.019	63	48
Inferior Ratio	0.75	0.019	59	45
Inferior Maximum	0.73	0.020	56	46
Maximum Modulation	0.72	0.019	52	37
Ellipse Modulation	0.72	0.019	51	35
Modulation	0.72	0.019	51	35
Superior Nasal	0.64	0.020	41	28
Inferior Nasal	0.61	0.020	29	19
Symmetry	0.57	0.022	36	22

For All Normals and Glaucoma Patients with visual field defects				
Tables			Specificity at 80%	Specificity at 90%
	Area	SEM	Sensitivity	Sensitivity
NFI	0.95	0.011	93	91
Norm. Sup. Area	0.90	0.015	85	74
Superior Average	0.90	0.016	82	76
TSNIT SD	0.88	0.016	79	67
Norm. Inf. Area	0.87	0.017	81	68
TSNIT Average	0.86	0.020	79	72
Inferior Average	0.86	0.018	77	65
Superior Maximum	0.84	0.021	78	67
Superior Ratio	0.81	0.021	73	58
Inferior Ratio	0.80	0.021	69	55
Inferior Maximum	0.78	0.023	63	54
Maximum Modulation	0.77	0.022	59	42
Ellipse Modulation	0.76	0.022	59	40
Modulation	0.76	0.022	59	40
Superior Nasal	0.69	0.024	47	35
Inferior Nasal	0.64	0.023	32	21
Symmetry	0.61	0.029	42	26

From this analysis, six parameters were chosen for the standard analysis printout, and many of the remaining parameters are displayed on the second page of the analysis. The six parameters chosen were TSNIT average, Superior Average, Inferior Average, TSNIT SD, Inter-Eye Symmetry, and the NFI. These six had the highest sensitivity and specificity values that represent unique RNFL information that is easily interpreted. All except the NFI are calculated from the calculation circle (described in Chapter 4). The TSNIT Average, Superior Average, and Inferior Average represent the average RNFL thickness over the entire calculation circle, the superior region, and the inferior region of the calculation circle respectively. TSNIT SD captures the amount of modulation of the RNFL in the calculation circle, and the Inter-Eye Symmetry captures the degree of similarity of the RNFL profiles between eyes. This approach provides the clinician with the best parameters that can be clearly understood. Other parameters did perform as well, however their information is redundant with the six parameters and they are more difficult to interpret. For example, Normalized Superior Area performed the same as Superior Average in the ROC analysis (ROC area = 0.9 for both), however these parameters were redundant, and the normalized Superior Area is more difficult to interpret, therefore Superior Average was chosen to be included on page 1 of the printout and Normalized Superior Area was included on page 2.

The ROC curves for five parameters are shown in Figure 3.5 (see Appendix A for more

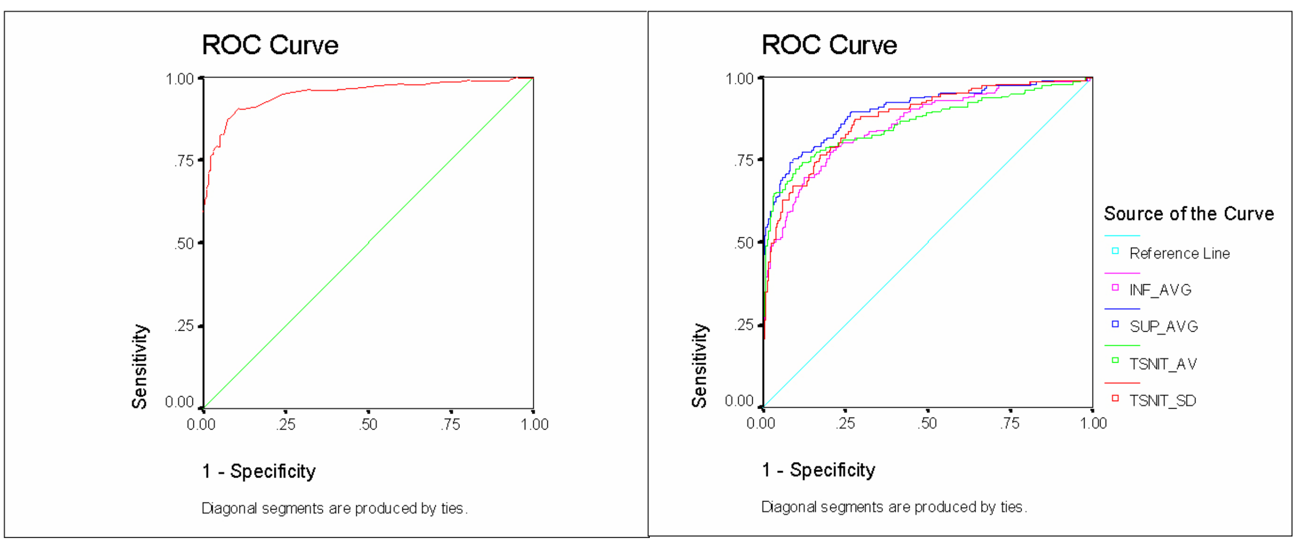


Figure 3.5. The ROC curves for the NFI (left) and four parameters displayed on page 1 of the standard printout (right).

detail on ROC curves). The closer the curve gets to the upper left-hand portion of the graph, the higher the sensitivity and specificity. If the curve were to touch the top left-hand corner, it would represent perfect discrimination with 100% sensitivity and 100% specificity with an area under the ROC curve of 1.0. Sensitivity is plotted on the y-axis and 1-specificity is plotted on the x-axis. The NFI had the largest area under the ROC curve for all parameters, indicating that in general, it is the most accurate parameter for detecting glaucoma.

The NFI is based on an advanced form of neural network analysis, trained to optimally differentiate normal from glaucoma. It analyzes the entire RNFL profile and provides a single number representing the integrity of the entire RNFL (see Chapter 4 for more details on the NFI). The diagnostic classification of the output of the NFI was determined from the normal distribution of the NFI from the database (see Figure 3.6). The 95th percentile was used as the cut-off for classifying the RNFL either 'Within Normal Limits' (0-30), or 'Borderline' (31-50). The 99th percentile was used as the cut-off for 'Outside Normal Limits' (51-100). The NFI distribution for glaucoma patients with visual field loss is shown in Figure 3.7. Figure 3.8 shows the NFI distribution for pre-perimetric patients. These patients have abnormal optic discs, however their visual fields are still normal (GHT was 'within normal range' and PSD and MD had p values > 5%).

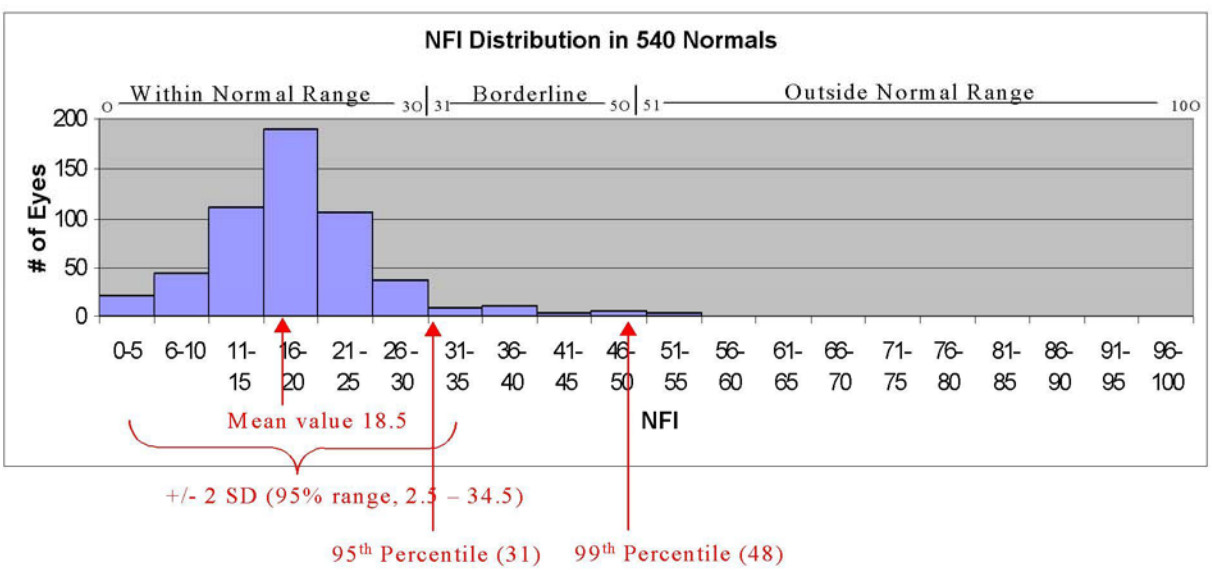


Figure 3.6. The distribution of the NFI values from the normative database. The mean value for healthy eyes is 18.5, the 95th percentile of the distribution is 31, and the 99th percentile is 48.

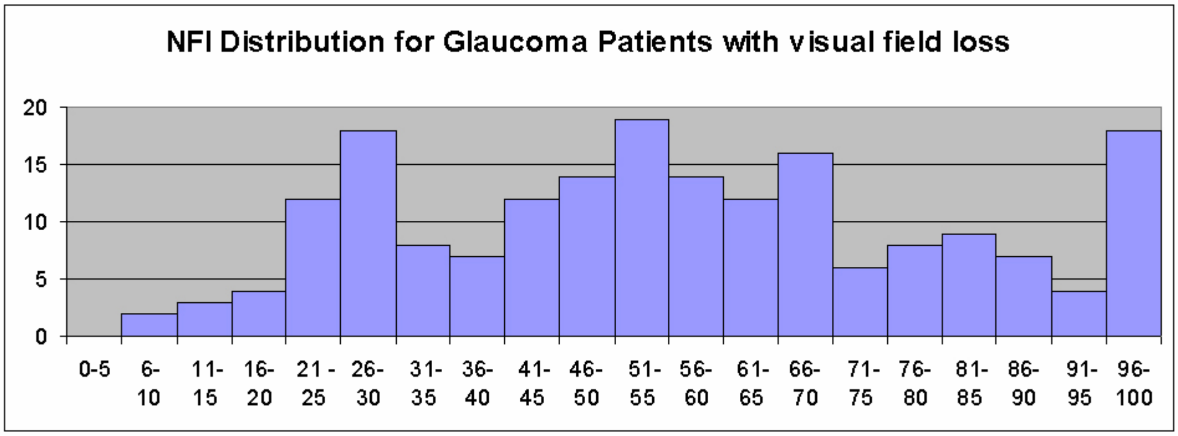


Figure 3.7. The distribution of the NFI values for glaucoma patients with visual field loss.

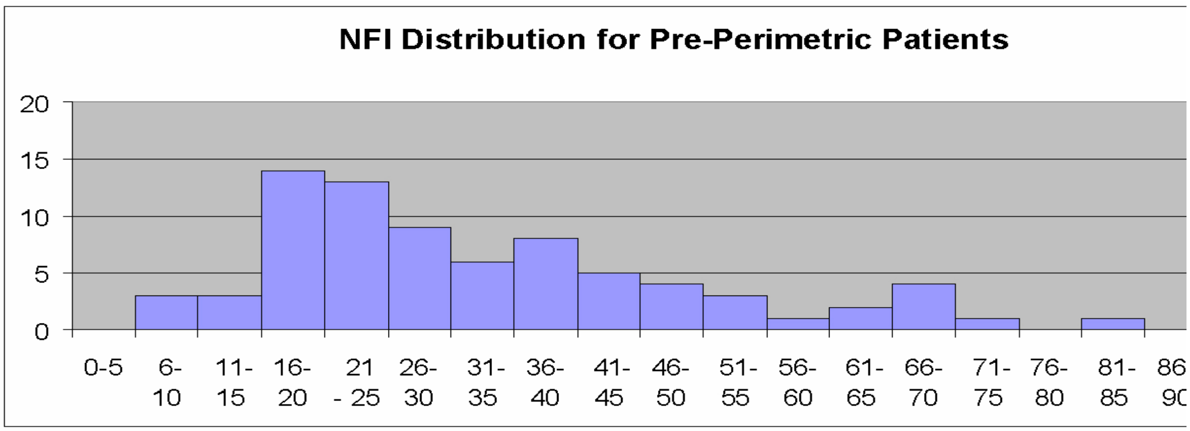


Figure 3.8. The distribution of the NFI values for pre-perimetric patients.

<u>Discrimination with the TSNIT graph</u>

The TSNIT graph is also useful for diagnosing glaucoma. To determine the changes to the TSNIT graph with increasing severity of glaucoma, the TSNIT graph was compared for the normals against the glaucoma patients, which were subdivided into groups based on severity of visual field loss (see Figure 3.9). Glaucoma patients with visual field loss were divided into three groups based on mean deviation (MD), where early glaucoma was defined as an MD > -5 dB, moderate had an MD between –5 and –10, and advanced had MD worse than –10 dB. Another group was considered pre-perimetric due to an abnormal optic disc but normal visual fields. The number of eyes in each group is displayed to the left of the graph in parentheses. A comparison of the TSNIT graph across groups reveals incremental RNFL loss with increasing stages of glaucoma. Furthermore, this graph shows that there are changes in the RNFL in suspicious optic discs, before visual field loss (pre-perimetric RNFL loss). This change can be as much as 15 microns in the superior and inferior regions.

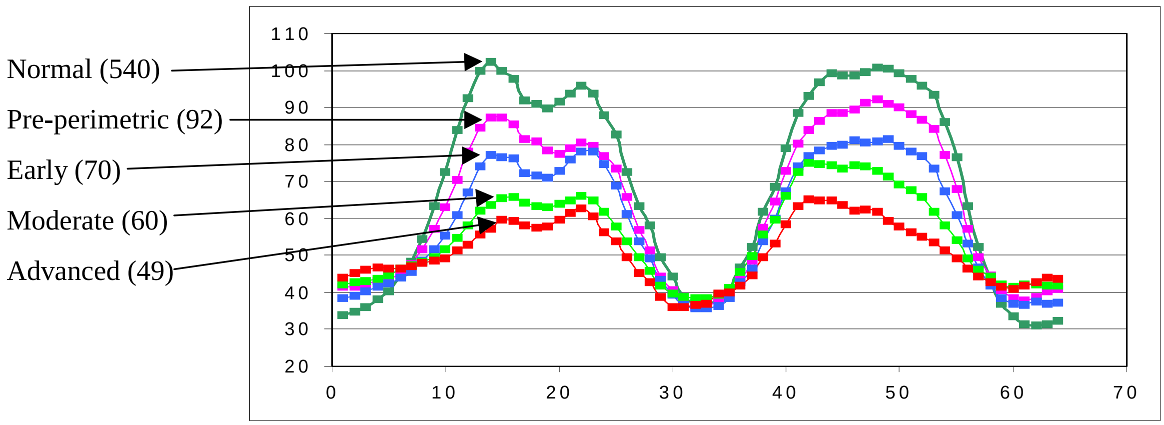


Figure 3.9. The average TSNIT graphs for normals, pre-perimetric, early, moderate, and advanced glaucoma patients.

Summary

A database is critical for any diagnostic tool because it relates a given measure to the normal distribution and from this comparison it can characterize the probability that the measure is within the normal range. However, in order to be valid, the database must be representative of the normal population. This can only be accomplished with large sample sizes that include a proportional representation of key factors such as age and race. The GDx VCC has the largest number of normal eyes of any imaging device and includes a representative proportion of minorities. The RNFL analysis provided through comparisons to the database accurately reveal RNFL loss due to disease.