New Developments in the Structural and Functional Assessment of the Glaucomas

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1. A method for detecting abnormality and also documenting optic nerve structure should be part of routine clinical management of glaucoma.

2. Sensitivity and specificity of imaging instruments for detection of glaucoma are comparable to that of expert interpretation of stereo color photography………….

3. Digital imaging is recommended as a clinical tool to enhance and facilitate the assessment of the optic disc and retinal nerve fibre layer in the management of glaucoma.

4. a. Automated analysis of results using appropriate databases is helpful for identifying abnormalities consistent with glaucoma.

   b. 2007 addition:
   Automated analysis of change using appropriate assessment of variability is helpful for identifying change consistent with glaucoma.

5. Different imaging technologies may be complementary, and detect different abnormal features in the same patients.

What’s New

- Primer
- Acquisition Quality Control
- Alignment Algorithm
- Larger Database
- Ethnic Selectable
- Printout
- Glaucoma Probability Score
- Glaucoma Change Analysis
- Enhanced Progression Analysis
HRT 3 Databases

- Caucasian database – over 700 healthy eyes
- African Descent database – over 200 healthy eyes
- Southeast Indian database – over 100 healthy eyes

- Hispanic and Asian databases coming soon

Effect of Ethnic Appropriate Database: Indian Patient

Disc Size

OHTS Ancillary Results

Baseline Topographic Optic Disc Measurements Are Associated With the Development of Primary Open-Angle Glaucoma

Archives of Ophthalmology, September 2005
Risk Assessment:

--- Risk Factor ---
- IOP (per mm Hg)
- PSD (per 0.2 dB)
- Age (per decade)
- Vertical/GD (per 0.1)
- CCT (per 48 microns)

--- HRT Risk Factor ---
- Cup Depth (per 0.1 mm)
- RNFL Profile Mean Height
- Moorfields Temporal/Superior
- Moorfields Temporal/Inferior
- Moorfields Global Result

OHTS Predictive Factors

Hazard Ratio

Moorfields Global Result
Moorfields Temporal/Superior
Moorfields Temporal/Inferior
Moorfields Global Result

Relative Risk

Glaucoma Predictors: Baseline Predictive Values
UCSD Study 2006

<table>
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<tr>
<th>Predictor</th>
<th>Relative Risk</th>
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<tr>
<td>IOP</td>
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<tr>
<td>PSD</td>
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<td>Stratus OCT</td>
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<tr>
<td>CCT</td>
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<td>Stereo Photos</td>
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Glaucoma Predictors: Baseline Predictive Values
OHTS Ancillary Study 2005

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Hazard Ratio</th>
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<tr>
<td>IOP</td>
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<tr>
<td>PSD</td>
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<tr>
<td>CCT</td>
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<td>HRT (MRA Global)</td>
<td>5.64</td>
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<tr>
<td>HRT (MRA Temp Superior)</td>
<td>8.68</td>
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Glaucoma Probability Score: GPS

- Utilizes the entire 3-D Surface Topography
- Characterizes the image with 5 parameters
  - 3 parameters describe the optic disc
  - 2 parameters describe the RNFL

Swindale et al. IOVS. 2000; 41:1730-1742

Topographic Change Analysis

- New alignment - automatically identifies several hundred local features
- Uses statistical matching of features to align images
- More accurate comparisons

TCA Printout

Baseline Exam
Follow-up Exams

Trend analysis
Structural Assessment in Glaucoma

- The Optic Nerve Head
- The Nerve Fibre Layer

Cluster Analysis
Trend Analysis

Cluster Outline

Area change

Volume change

Area and Volume of change tracked over time

Scanning Laser Polarimetry

SLP Basic Principles

- Nerve fiber layer is form-birefringent
- Light passing through a birefringent medium:
  - Light traveling perpendicular to fibers undergoes a phase shift
  - "Slows down" (retardation)

The amount of retardation from the RNFL is directly proportional to the RNFL thickness.

\[ \text{Retardation} = \frac{\text{thickness of RNFL}}{\text{constant}} \]

ECC versus VCC (50 yr. W, F, IOL)

- ECC method reduces measurement noise in the nasal region in the eye of a patient with IOL implant

Identification of Progression

Identify progressing patients

<table>
<thead>
<tr>
<th>Likely progression</th>
<th>OD</th>
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</thead>
<tbody>
<tr>
<td>TSNI</td>
<td>Progression Grid</td>
</tr>
<tr>
<td>Summary Parameter Charts</td>
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</table>

- Possible Progression
- Likely Progression (design specificity 95%)

Summary of Progression.
Identification of Retinal Layers

- NFL: Nerve Fiber Layer
- ILM: Inner Limiting Membrane
- GCL: Ganglion Cell Layer
- IS/OS: Junction of inner and outer photoreceptor segments
- RPE/CC: Retinal Pigment Epithelium/Choriocapillaris
- IPL: Inner Plexiform Layer
- OPL: Outer Plexiform Layer

Cross-sectional image of live tissue; a virtual biopsy

Stratus OCT in Glaucoma

- RNFL Analysis: Three 1.73mm radius circle scans
- Optic Nerve Head Analysis: Six 4mm radial line scans
- Macular Analysis: Six 6mm radial line scans

Early Glaucoma

Physiological Cupping
Stratus GPA Serial Analysis

- TSNIT overlays
- Average thickness plots
- OU analysis

Old OCT Does Not Account for Eye Movement

- While Time Domain OCT scans, the eye keeps moving
- The black line is the camera’s perspective
- The white line is the actual scan path

Scan location and eye movements affect results

Properly centered
Inferior RNFL “Loss”
Superior RNFL “Loss”

Time Domain OCT

Broadband Light Source
SLD

Scanner creates A-scan 1 pixel at a time

Reference mirror moves back and forth
Distance determines depth in A-scan

Data Acquisition
Processing
Final A-scan

Process repeated many times to create B-scan

Fourier Domain OCT

Broadband Light Source
SLD

Grating splits signal by wavelength

Interferometer combines light from reference with reflected light from retina

Reference mirror stationary

Spectral interferogram
Fourier transform converts signal to typical A-scan

Spectral: Fourier transform converts signal to typical A-scan

Comparison of OCT Images

OCT 1 (Time Domain)
Stratus OCT (Time Domain)
RTVue (Fourier Domain)
Cirrus™ HD-OCT
Spectral Domain OCT for ocular imaging.
Developed in collaboration with Univ. Vienna, Univ. Miami, & Univ. Pittsburgh.
27,000 A-Scans per second, 5 micron axial resolution.

Stratus OCT
Time domain OCT for ocular imaging.
Developed in collaboration with and licensed from Massachusetts Institute of Technology.
400 A-Scans per second, 10 micron axial resolution.

Glaucoma – RNFL Thickness Analysis
An OU analysis example.

OCT from Carl Zeiss Meditec

Time Domain and Spectral Domain

Stratus OCT high-resolution line scan and the Cirrus HD-OCT scan reveal details of retinal structure.

OCT from Opto-Vue

Glaucoma Analysis with the RTVue

The Ganglion Cell Complex (ILM – IPL)

Inner retinal layers provide complete Ganglion cell assessment:
- Nerve fiber layer (g-cell axons)
- Ganglion cell layer (g-cell body)
- Inner plexiform layer (g-cell dendrites)
Normal vs Glaucoma

- NHM4
- Cup
- Rim
- RNFL
- GCC
  - Normal
  - Glaucoma

Ganglion cell assessment with inner retinal layer map

Early Glaucoma

- Borderline Sector results in Superior-temporal region
- Abnormal parameters
- TSNIT dips below normal
- TSNIT shows significant Asymmetry

Anterior Chamber Module

- Cornea Adapter Lens (CAL)

High Resolution Cross Scan

3-D Angle assessment

Pachymetry Maps
Visante™ OCT

OCT from Topcon

OCT from Heidelberg Engineering

High Resolution Cross Section

SL-OCT Anterior chamber (15-7 mm)

Normal Eye

Circle OCT Image

HRA-OCT Spectralis

40,000 scans per second
Spectralis Tracks Change Over Time

- Real-time alignment
- Accurate measurement of change

Heidelberg Image Filtering Technology

Heidelberg Image Filtering produces higher quality images, compared to “higher” resolution images without IF

Optic Nerve Head – Detail

Functional Assessment of the Glaucomas

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“Purpose of routine visual field examination is
  – the early and efficient detection,
  – the assessment and
  – the follow-up
of functional loss in the visual system”

Greve 1973
Standard Automated Perimetry

- Clinical Gold Standard
- Oldest, most documented test of visual function
- >3000 refs since 1980 (VF and glaucoma)
- Standardized testing parameters
- Comparison with normal data
- Assumed relationship between loss of visual function and retinal ganglion cell loss

Perimetry and the Detection of Progression

Detection of progression limited by:

- Physiologic fluctuation
  - Short term fluctuations
    - Test-retest measurement error
  - Long term fluctuations
    - Drift in biologic system
  - Learning effect

Progression in Glaucoma

- Earliest diagnosis
- Disease management
- Forecasting
  - Rate of progression
  - Quality of vision

Identifying Progression in Visual Fields

- Progression defined as repeatable change
- Contributors to variability:
  - Deviation from normal
  - Eccentricity
  - Patient ability
  - Test strategy
- Glaucoma database defines expected variability
- GPA flags progression at points exceeding expected patient variability

Glaucoma Progression Analysis

Multiple Exams

Baseline

Follow-up

Rate of Progression Plot

Inter-individual variability of progression rates (treated EMGT cohort)
Progression Analysis

Baseline exams.
• Establishes initial visual field status.

VFI Rate of Progression Analysis.
• Trend Analysis of patients overall visual field history

Today’s Visual Field.
• Complete report of current visual field exam including PD, VFI, progression analysis and GPA Alert.

Function

WGA

1. A method for detecting abnormality and documenting functional status should be part of routine clinical management of glaucoma.
2. It is unlikely that one functional test assesses the whole dynamic range.
3. SAP as usually employed in clinical practice, is not optimal for early detection.

The Global Glaucoma Network

Visual Function Specific Perimetry

• SWAP – SITA
• Matrix - FDP
• HEP - Flicker Defined Form
• Others:
  – Flicker
  – Motion
  – Pulsar
  – High-Pass Resolution Perimetry
  – Rarebit
  – Resolution Perimetry

The Global Glaucoma Network

Human Retinal Ganglion Cells

Human Retinal Ganglion Cells

Updated comment 2007: SAP-SITA has similar sensitivity to detect visual field abnormalities as SWAP-full threshold.

Updated comment 2007: FDT N30 may provide better sensitivity than SAP-SITA or SWAP-full threshold. Evidence concerning the sensitivity of SWAP-SITA and FDT Matrix 24-2 is not yet available.
SWAP: Rationale for the Technique

- **Blue Stimulus**
  - To preferentially stimulate the short wavelength sensitive (SWS) pathway
- **High Luminance Yellow Background**
  - To saturate both the middle and long wavelength sensitive pathways
  - To suppress rod activity

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**Diagnostic Performance**

*Delgado et al, Ophthalmic Technology Assessment: Automated Perimetry. Ophthalmology, December, 2002*

Early glaucoma:
- 88% sensitivity and 92% specificity

SWAP is a lengthy, demanding test, is sensitive to media opacities, and has a greater magnitude of long-term fluctuation.....which makes it difficult to assess progression accurately.”

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# Improvements with SITA SWAP: Speed and Sensitivity

- **Full Threshold**: Test time: 12:50
- **Fastpac**: Test time: 7:50
- **SITA**: Test time: 3:56

Stimuli: V, Blue
Background: Yellow

**Courtesy of Boel Bengtsson Dept of Ophthalmology Malmo University Hospital, Sweden**
Short Wavelength Automated Perimetry (SWAP)

Who should undergo SWAP testing?

- Patients with ocular hypertension
- Glaucoma suspects
- Patients with early glaucoma
- Diabetics
  - non-proliferative retinopathy
  - DME
- Optic neuritis

FDP: Underlying principles

- Preferentially stimulates the magnocellular pathway (M-cells)
- Particularly subset with non-linear contrast response (M-γ-cells)
  - M-γ-cells have large axons
  - M-γ-cells constitute 20% of magnocellular system therefore only 3-5% of nerve fibres
- *FD Illusion is cortically driven*
  
  Whites et al, 2002; Quaid et al, 2003

Diagnostic Performance

*Delgado et al, Ophthalmic Technology Assessment: Automated Perimetry. Ophthalmology, December, 2002*

Early Glaucoma:
85% sensitivity and 90% specificity

Moderate + Severe:
>97% sensitivity and specificity

FDP has “a short testing time and is resistant to blur and pupil size…….may be useful as a screening tool.”

FDT Summary

FDT is as close as we have to a test that meets the requirements of Case-Finding screening
- One Minute Test
- High sensitivity and specificity, for early disease
- Very high for moderate disease
- Level I evidence that predictive of SAP

HFA & Matrix - Glaucoma Patient

The Heidelberg Edge Perimeter
Flicker Defined Form (FDF)

- Originally described 1991\(^1\).
- High temporal frequency stimulus (> 15Hz)
- Counterphase flicker
- Creates a “phantom” contour illusion\(^2,3\)
- Considered a magnocellular-dominated illusion\(^1,2,4\)


Diagnostic Performance

?  
Test-Retest Characteristics

Structure (HRT) and Function (HEP)

Structure (HRT) and Function (HEP)
1. Published literature often lags behind the introduction of new technology. Therefore literature based on previous versions of current technology should be viewed with caution.

2. In different cases, either structural examination or functional testing may provide more definitive evidence of glaucoma, so both are needed for detection and confirmation of the subtle early stages of the disease.