Glaucoma Diagnosis & Tracking with Optical Coherence Tomography

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Financial Interests:
Optovue, Inc.: stock options, patent royalty, travel, grant
Carl Zeiss Meditec, Inc.: patent royalty

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The Rationale for Quantitative Imaging in Glaucoma Diagnosis

Visual field has poor repeatability

Confirmation of Visual Field Abnormalities in the Ocular Hypertension Treatment Study

OHTS: 85.9% of abnormal and “reliable” fields were not confirmed on retest!
3 consecutive fields are required to reliably confirm glaucoma!

“The proportion of VF test results that were normal subsequent to a VF POAG end point in eyes whose abnormality was confirmed by 2 consecutive, abnormal, reliable test results was significantly higher (73 [66%] of 110) compared with eyes whose abnormality was confirmed by 3 consecutive, abnormal, reliable test results. (46 [12%] of 381) (P=.01).”


Structural loss precedes functional loss

OHTS results show that without optic disc assessment you may be missing up to 55% of glaucoma patients.

Disc change precedes VF loss in most cases
Quantitative Imaging may detect glaucoma at an earlier stage

Why use OCT? (rather than other imaging modalities)
Let’s compare diagnostic accuracy

David Huang, MD, PhD
www.COOLLab.net

Stratus OCT had significantly better diagnostic accuracy (best combination of continuous variables)

<table>
<thead>
<tr>
<th>Continuous scale</th>
<th>AROC</th>
<th>P. v. OCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stratus: overall, Inferior or superior quadrant RNFL</td>
<td>0.92</td>
<td></td>
</tr>
<tr>
<td>GDx-ECC NFI</td>
<td>0.87</td>
<td>0.006</td>
</tr>
<tr>
<td>HRT2 C/D area ratio</td>
<td>0.83</td>
<td>0.0008</td>
</tr>
</tbody>
</table>

### Previous literature comparisons

<table>
<thead>
<tr>
<th>Paper</th>
<th>AROC</th>
<th># Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Stratus</td>
<td>GDx-VCC</td>
</tr>
<tr>
<td>Pueyo et al. J. Glaucoma 2007</td>
<td>Overall RNFL 0.91</td>
<td>NFI 0.88*</td>
</tr>
<tr>
<td>Pueyo et al. ARCH SOC ESP OFTALMOL 2006</td>
<td>Overall RNFL 0.93</td>
<td>NFI 0.88</td>
</tr>
<tr>
<td>Medeiros et al. Arch Ophthalmol. 2004</td>
<td>Inferior RNFL 0.92</td>
<td>NFI 0.91</td>
</tr>
<tr>
<td>Zangwill et al. Arch Ophthalmol. 2001</td>
<td>5 o’clock RNLF 0.87</td>
<td>LDF 0.84</td>
</tr>
</tbody>
</table>

NFI = nerve fiber index; MRA = Moorefields regression analysis; LDF = linear discriminant function; MHC = mean height contour, N/I = nasal/inferior

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**More accurate NFL mapping with FD-OCT**

David Huang, MD, PhD [www.COOLLab.net](http://www.COOLLab.net)
TD-OCT susceptible to eye movements

• 768 pixels (A-scans) captured in 1.92 seconds is slower than eye movements

• Stabilizing the retina reveals true scan path (white circles)

Scan location and eye movements affect results

Properly centered
Poorly centered: too inferior
Poorly centered: too superior

Normal Double Hump

Inferior RNFL “Loss”

Superior RNFL “Loss”

FD-OCT can scan more points in less time – sampling greater area with less motion error

RTVue
FD-OCT

Optic Nerve Head Map
(ONH)

9510 a-scans
0.39 sec

New advances from the Advanced Imaging for Glaucoma Study: Mapping the Ganglion Cell Complex to Further Improve Glaucoma Diagnosis and Tracking

David Huang, MD, PhD www.COOLLab.net
Glaucoma affects 3 areas in the posterior segment of the eye:

- Cupping
- Nerve fiber thinning
- Ganglion cell loss

Glaucoma preferentially thins the **Ganglion Cell Complex (GCC)** which includes the axons, cell bodies, and dendrites of retinal ganglion cells.

Ishikawa H, et al., IOVS 2005

David Huang, MD, PhD www.COOLLab.net

David Huang, MD, PhD www.AIStudy.net
Glaucoma: Macular Ganglion Cell Mapping

RTVue FD-OCT, 26,000 A-scan per-second 5 micron axial resolution

Ganglion Cell Complex (GCC)
7 mm scan area 14,944 a-scans, 0.58 sec

GCC = Ganglion Cell Complex

mGCC thickness map

Glaucoma: Macular Ganglion Cell Mapping

GCC Deviation Map

% loss = actual scan value – normal value

color coded map

- Percent loss value at each pixel location relative to normal based on age-adjusted normative database of over 300 healthy eyes
  - Blue = thinning 20-30% relative to normal
  - Black = 50% loss or greater

David Huang, MD, PhD www.AIGStudy.net
**GCC Significance Map**

Color coded map shows regions where the change from normal reaches statistical significance:
- **Green** = values within normal range (p-value 5% to 95%)
- **Yellow** = borderline results (p-value < 5%)
- **Red** = outside normal limits (p-value <1%)

David Huang, MD, PhD [www.AIGStudy.net](http://www.AIGStudy.net)

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**FD-OCT GCC mapping provide excellent diagnostic accuracy for glaucoma**

<table>
<thead>
<tr>
<th>OCT system</th>
<th>Thickness Parameter</th>
<th>AROC</th>
</tr>
</thead>
<tbody>
<tr>
<td>RTVue FD-OCT</td>
<td>mGCC-Avg</td>
<td>0.90</td>
</tr>
<tr>
<td></td>
<td>mGCC-GLV</td>
<td>0.92</td>
</tr>
<tr>
<td></td>
<td>mGCC-FLV</td>
<td>0.92</td>
</tr>
<tr>
<td>Stratus TD-OCT</td>
<td>cpNFL-Avg</td>
<td>0.92</td>
</tr>
<tr>
<td></td>
<td>mR-Avg</td>
<td>0.85 (P=0.01)</td>
</tr>
</tbody>
</table>

Combining measurements from all 3 anatomic regions with machine learning classifiers further boosted diagnostic accuracy

<table>
<thead>
<tr>
<th>Diagnostic Parameter</th>
<th>AROC</th>
<th>Sensitivity (at 5 percentile cutoff)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Support Vector Machine (SVM)</td>
<td>0.963</td>
<td>86%</td>
</tr>
<tr>
<td></td>
<td>P &lt; 0.02</td>
<td>P &lt; 0.01</td>
</tr>
<tr>
<td>Best NFL</td>
<td>0.924</td>
<td>67%</td>
</tr>
<tr>
<td>Best GCC</td>
<td>0.920</td>
<td>68%</td>
</tr>
<tr>
<td>Best Disc</td>
<td>0.886</td>
<td>56%</td>
</tr>
</tbody>
</table>

85 normal eyes, 72 perimetric glaucoma eyes

High-speed FD-OCT allows correlation of glaucoma disease patterns – Pre-Perimetric Glaucoma

Peripapillary NFL loss

Macular GCC loss (FLV p<1%)

Focal rim thinning

Visual field “normal”
FD-OCT improved the repeatability of macular ganglion cell complex compared to TD-OCT circumpapillary nerve fiber layer measurements, thus improving the potential to track glaucoma over time

<table>
<thead>
<tr>
<th>OCT system</th>
<th>Thickness Parameter</th>
<th>CV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group</td>
<td>N</td>
<td>PPG</td>
</tr>
<tr>
<td>RTVue FD-OCT</td>
<td>mGCC-avg</td>
<td>1.09</td>
</tr>
<tr>
<td>Stratus TD-OCT</td>
<td>cpNFL-avg</td>
<td>1.72</td>
</tr>
</tbody>
</table>

Rule of thumb for progression analysis

- Stratus NFL overall average: 10% loss significant, if confirmed on repeat visit
- RTVue GCC overall average: 5% loss significant, if confirmed on repeat visit
- If IOP more than 2 mm Hg different, the comparison may not be reliable
GCC Progression Analysis (visit every 6 months)

OCT angle imaging is also useful for the glaucoma specialist

Yan Li, PhD

Bing Qin, MD
OCT provides near-histological details of angle structures

Narrow Angle

- Scleral spur
- Schlemm's canal
- Trabecular meshwork
- External limbus
- Schwalbe's line

AOD_SL = 473 µm

Open Angle

- External limbus
- Schwalbe's line
- Schlemm's canal
- Scleral Spur
- Trabecular meshwork

AOD_SL = 473 µm
Neovascular Glaucoma with Synechial Angle Closure

After Trabectome Surgery

Courtesy of Brian Francis, MD; Doheny Eye Institute
FD-OCT provides more information than other advanced imaging technologies

<table>
<thead>
<tr>
<th></th>
<th>FD-OCT</th>
<th>SLT (HRT)</th>
<th>SLP (GDx)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ppNFL thickness</td>
<td>+</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Macular GCC</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disc &amp; Cup</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Total retinal blood flow</td>
<td>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angle</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cornea</td>
<td>+</td>
<td></td>
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</table>

*Under development, not yet released commercially

FD-OCT may have a growing role in glaucoma diagnosis
Glaucoma Diagnosis Case Examples

Subject 005 OS

- 42 year old
- IOP 11
- C/D 0.1
Stratus TD-OCT

Supernasal NFL thinner than normal

Inferotemporal NFL thicker than normal

RTVue
FD-OCT
GCC
Subject 005 OS

- Normal eye
- Stratus TD-OCT NFL abnormal due to superonasal scan decentration
- RTVue FD-OCT within normal for both NFL and GCC

Subject 046 OS

- 62 year old
- IOP 17.5 with medication
- C/D 0.4
Nasal NFL thicker than normal

temporal NFL borderline thin
Subject 046 OS

- Perimetric glaucoma
- NFL by Stratus TD-OCT decentered – probably normal
- NFL normal by RTVue FD-OCT
- Macular GCC is abnormal in agreement with VF: central loss more severe in the superior macula / inferior field

Glaucoma Tracking Case Example
Subject 108 Perimetric Glaucoma OS

Hemorrhage  Rim thinning  Rim thinning  Rim thinning
Baseline 1 year 2 year 3 year

Stratus Advanced Serial Analysis

Rate of change: -1.224 N= 8.899 *P<0.05

* 95% confidence interval

<table>
<thead>
<tr>
<th>OS Date</th>
<th>SSLQ</th>
<th>AVG</th>
<th>SUP</th>
<th>INF</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/23/2000</td>
<td>80</td>
<td>107.63</td>
<td>80.00</td>
<td></td>
</tr>
<tr>
<td>7/25/2000</td>
<td>80</td>
<td>112.63</td>
<td>80.00</td>
<td></td>
</tr>
<tr>
<td>9/27/2000</td>
<td>90</td>
<td>114.63</td>
<td>90.00</td>
<td></td>
</tr>
<tr>
<td>11/4/2000</td>
<td>90</td>
<td>114.63</td>
<td>88.80</td>
<td></td>
</tr>
</tbody>
</table>

Normal Distribution: Percentiles

A: Scan/Date
B: Scan too high
C: Low confidence in analysis
D: Missing data
E: Extra Layer
F: Risk Narrative Data
Humphrey Glaucoma Progression Analysis

Subject 108 OS

- Perimetric glaucoma
- Progression detected by GCC and disc photography
- Progression not detected by NFL or VF
- Drop in IOP on year 2 visit caused artifactual improvement on NFL & GCC