Detecting Functional and Structural Progression in Glaucoma
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Glaucoma
• A chronic, progressive disease of retinal ganglion cells that results in characteristic optic nerve and retinal nerve fiber layer changes and corresponding visual field loss

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Glaucoma Progression
“Once the diagnosis of glaucoma has been made, the MOST IMPORTANT remaining question is whether the disease is stable and the therapy/compliance are sufficient, or whether the disease is progressive and the therapy in relation to the life expectancy has to be intensified.”

Progression of Glaucoma
“Although most glaucoma patients will show some evidence of progression if followed long enough, the rate of deterioration can be highly variable among them. While most patients progress slowly, others have aggressive disease with fast deterioration which can eventually result in blindness or substantial impairment unless appropriate interventions take place.”
WGA Consensus Statements on Structure & Function

• Both ON structure and function should be evaluated for detection of progression
• Currently, no specific test can be regarded as the perfect standard for determination of progression
• Progression detected by functional means will not always be corroborated using structural tests, and vice-versa

WGA Consensus Statements

• The use of standard automated perimetry as the sole method for detection of change may result in failure to detect or underestimation of progression in eyes with early glaucoma damage.
• Progressive structural changes are often but not always predictive of future development of or progression of functional deficits in glaucoma.

Trends in Use of Ancillary Glaucoma Tests for Patients with Open-Angle Glaucoma from 2001 to 2009

• A statistically significant change in structure and/or function is not always clinically relevant.
• Life expectancy should be considered when evaluating the clinical relevance of a structural and/or functional change in glaucoma.
• Structural and/or functional testing should be conducted throughout the duration of the disease.
  – Detection of progression is more difficult in eyes with advanced disease
When Should We Suspect Progression?

• Rates of blindness in POAG are low
  – @ 20 years
  • 27% blind in one eye
  • 9% bilaterally blind

Risk Factors for Progression

• Clinical risk factor assessment in glaucoma serves two roles:
  1. Prognostic information
  2. A basis for disease management
• Risk factor assessment should take into account
  1. The strength of the risk factor
  2. The practicality & potential harm of reducing that risk factor

Detection & Measurement of Change (Structure & Function)

• Event Analysis (EA): change that exceeds a certain predefined threshold compared to the baseline value; generally determined by measurement reproducibility
• Trend Analysis (TA): change over a designated time period using regression analysis. Generally takes more exams to obtain a reliable slope

Risk Factors for Progression

• Higher mean IOP
  – Higher IOP fluctuations
• Thinner CCT in patients with higher baseline IOP
• Presence of pseudoexfoliation
• Presence of disc hemorrhage
• Older age
• Lower ocular perfusion pressure
• Advanced visual field at presentation
• Family history of glaucoma (1st degree relative)

Structural Progression: WGA Consensus

• Serial optic disc photography and RNFL photography are valuable and enduring methods for monitoring structural progression
  – Subjective estimate of C/D is insufficient
• Color fundus imaging is the preferred modality to identify disc hemorrhage & change in PPA
• Critically evaluate for:
  – Narrowing of NRR/notching
  – Enlargement of cupping
  – Disc hemorrhage
Structural Changes - WGA

- The most important QUALITATIVE parameter indicating structural progression may be an optic disc hemorrhage.
- The most important QUANTITATIVE parameters indicating structural progression are:
  - Loss of NRR
  - Change in thickness of RNFL
  - Change in contour of ONH
  - Enlargement of PPA
  - Potentially macular thickness

Structural Changes

- Several imaging instruments provide reproducible measurements & quantitative assessment of ONH and RNFL changes:
  - Image quality is crucial**
  - Multiple baseline exams facilitate progression analysis.

Structural Changes - WGA

- The agreement for progression among ONH, RNFL, and macular parameters is poor.
- The rates of change vary considering within and between glaucoma patients.
- Differences in technologies and scan protocols could influence the detection of progression.
Cirrus RNFL and ONH

Report shows RNFL and ONH for both eyes, using the Optic Disc Cube 200x200 scan.

Cirrus GPA™ Analysis

Using the Cirrus HD-OCT, we can identify progression in RNFL loss through event analysis and trend analysis.

Event analysis assesses changes that are beyond an expected variability at certain points compared to normative data. If a patient falls outside this area, it is identified as progression.

Trend analysis looks at the rate of change over time, using linear regression to determine whether or not the trend is outside the expected rate of RNFL loss.

Cirrus GPA™ Analysis

RNFL Thickness Change Maps demonstrate change in RNFL between exams. Up to 6 progression maps are compared to baseline. Areas of statistically significant change are color-coded yellow when first noted and then red when the change is sustained over consecutive visits.

Cirrus GPA™ Analysis

• TSNIT values from baseline and current exams are plotted.
• Areas of statistically significant change are color-coded yellow when first noted and then red when the change is sustained over consecutive visits.
Cirrus GPA™ Analysis

• Average RNFL Thickness values are plotted for each exam.
• Yellow marker denotes change from both baseline exams.
• Red marker denotes change sustained over consecutive visits.
• Rate and significance of change are shown in text.

RNFL Summary

• Legend summarizes GPA analyses and indicates with a check mark if there is possible or likely loss of RNFL:
  - RNFL Thickness Map Progression (best for focal change)
  - RNFL Thickness Profiles Progression (best for broader focal change)
  - Average RNFL Thickness Progression (best for diffuse change)
Baseline Scan
First Follow-Up
Second Follow-Up
Guided Progression Analysis™ for GDx
Help Address Key Clinical Needs
- Identify progression
- Determine rate of progression
- Assess treatment effectiveness

GDx Strengths:
- Highly reproducible
- Operator independent
- Able to precisely align images
- No patient learning effects
- Fast—Follow-up exams take as little as 1 minute

Why GPA Analysis for GDx

Identify Progressing Patients

with clear, concise summary of Progression.

Structural Changes - WGA

If structural progression is detected, it needs to be VERIFIED as to whether it is true vs artifact, AND whether it is typical for glaucoma (progressive rim thinning, notch, RNFL defects, disc hemorrhage)

Example 1
Let’s VERIFY…

Example 2

FUNCTION

- Previously believed that only advanced glaucoma impacts patient’s ability to function. More recent studies have demonstrated that early glaucomatous VF loss has an impact on the patient’s ability to function
  - Activity limitation
  - General health, lifestyle, emotion
IDENTIFYING PROGRESSION

- Much more difficult than detecting loss
- Background of dynamic “noise”
- No algorithm uniformly agreed upon for detecting change
- Three main changes:
  - Deepening of defect
  - Enlargement of defect
  - New defect

IDENTIFYING PROGRESSION

- Long-term fluctuation
  - The single biggest problem in determining progression
  - Deeper defects: more long term fluctuation
  - More advanced glaucoma: more long term fluctuation, more fatigue

Progression of VF

Functional Progression - WGA

- Standard white-on-white automated perimetry (SAP) covering at least 24° is preferred
- Decisions on progression should NOT be made by comparing only the most recent VF with the one before.
- Suspected progression should be confirmed with repeat testing.
### Frequency of VF Exams

**Baseline Data — first 2 years**
- At least 2 reliable VF within the first 6 months
  - 3 within first 6 months when there is a high likelihood of visual disability
- At least 2 further VF within the next 18 months
- VF testing should be repeated sooner than scheduled if possible progression is identified
- SIX VF within the first 2 years allows the clinician to identify rapid progression (Chauhan, et al)

**Follow-up data (after first 2 years)**
- Frequency of testing should be based on the risk of clinically significant progression (based on extent of damage, life expectancy)
- In low- and moderate- risk patients, VF should be at least once per year
  - Sooner if possible progression seen on VF — OR — on other clinically relevant observations
- In high risk patients, subsequent VF should be at least 2 per year

### VF Progression: EA vs TA

**Event analysis (EA):** change from baseline greater than a predefined threshold based on test-retest variability according to the level of damage

**Trend analysis (TA):** rate of change over time; significance is determined by both the magnitude of change and the variability of the measurement

### Event Analysis

- **Not Progressing:**
  - Not exceeding predefined/expected LTF
- **Progressing:**
  - Exceeding predefined/expected LTF

![Figure 1: Test-dated: Variability in Progression](image)

### VF Progression: EA vs TA

- In general, **event analysis** is used for follow-up when fewer VF are available
  - When suspected progression is identified, at least TWO further tests should confirm that
- In general, **trend analysis** (rate) is used later in the follow up (later than 2 years)

### Functional Progression - WGA

“Use available software support. Subjective judgment of VF printouts is unreliable and agreement among clinicians is poor.”
GUIDED PROGRESSION ANALYSIS (GPA)

- Humphrey Field Analyzer
  - Based on results of GLAUCOMA patients from mild to advanced disease
  - Patients took 12 different visual field tests within a 4 week period
  - Developed a model for what is “expected” test-test variation for patients with glaucoma

GPA

- Uses 2 baseline exams (any strategy)
  - Follow up tests must be SITA-Standard or SITA-Fast (all same strategy)
- Symbols used on Follow Up Tests
  - Open Triangles
  - Half Triangles
- Messages
  - Possible Progression
  - Likely Progression
- Rate of Progression

Elements of GPA 1-Page Summary Report

- Baseline Tests
- VFI (Trend Analysis)
- Today’s VF (Event Analysis)

HFA GPA

VFI Summary - Interpretation at a Glance

- The VFI Regression Plot
  - VFI plotted against age
  - Extrapolates rate of change up to 5 years

Sample: Progression Detected

The VFI Bar
- Historical and projected VFI loss
Sample: High LTF, No progression
Sometimes the messages are contradictory
Functional Progression - WGA
• Do not rely on VF reliability indices
• Stick with the same test throughout the follow-up period
• In advanced glaucoma, there may be a benefit to testing using a 10-2 strategy in a minority of patients.
  — You lose all statistical ability to follow the field

Pearls for VF Progression – Event Analysis
• About 5% chance that a single point will fall outside the expected change on a single test
  — Much less likely that same point will do the same in a subsequent test
  — If point is in same region of VF as existing defect — much more likely to be “real” change
  — Point in central 10 degrees exceeding expected change is much more likely to be “real” change

Pearls for VF Progression - Trend Analysis
• Need a minimum of 6-8 tests for valuable slope
• Cut-off value of 1dB/yr is probably a reasonable, clinically relevant cutoff value
• Greatly influenced by outliers – WATCH FOR OUTLIERS
• Trend analysis might not be good for patients with small isolated scotomas

GPA
• Disadvantages:
  — Cannot be used in advanced glaucoma
  — Trend analysis may not be able to detect progression in patients with smaller paracentral scotomas (often limited to a single point)
  — Additional software needed
  — All tests must be stored on same unit or purchase data management software
• Advantages
  — High level of correlation with clinical assessment of VF by expert observers
  — Much faster than individual analysis of serial VF

Alternatives to GPA
• Non-parametric Analysis (MD, VFI, PSD)
  — 3 baseline VF
  — Suspected progression:
    • 1 field with MD worse than lowest MD of baseline tests
  — Possible progression:
    • 2 consecutive fields with MD worse than lowest MD of baseline tests
  — Likely progression:
    • 3 consecutive fields with MD worse than lowest MD of baseline tests

<table>
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<tr>
<th>GPA</th>
<th>Suspected Progression</th>
<th>Possible Progression</th>
<th>Likely Progression</th>
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<table>
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<tr>
<th>NPA</th>
<th>1 field with MD worse than lowest of 3 baseline VF</th>
<th>2 consecutive fields with MD worse than lowest of 3 baseline VF</th>
<th>3 consecutive fields with MD worse than lowest of 3 baseline VF</th>
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NPA can also be applied to PSD (for MD up to ~-10dB) and/or to VFI

Note: GPA and NPA are compared for their effectiveness in detecting VF progression.
Alternatives to GPA

- Deepening of existing scotoma at 2+ points by 10+dB
- Expansion of 2+ points adjacent to baseline scotoma by 10+dB
- New scotoma
  - 2 or more adjacent points with p<1% on PD probability plot
- Change of 1 point in central 10° of 10+dB in a previously normal location
Excluding non-representative exams

Excluding the poor exam

Before, with poor exam included

After excluding the poor exam
There’s Progression! What Now?

- Think there is progression? VERIFY!
- Know there is progression?
  - Did glaucoma cause the progression?
- Glaucoma caused the progression
  - Consider a change in treatment

Think There’s Progression? Verify!

- Structural tests: Confirm with additional test
- Visual field: Confirm with at least two additional tests
- FAILURE TO CONFIRM PROGRESSION is evidence of stability!

There’s Progression: Is it Glaucoma?

- Structure:
  - Other causes of structural changes? Esp important in polarimetry
- Function:
  - Optical explanation LESS LIKELY
    - Equal damage to total and pattern deviation plots
    - Individual test locations with normal sensitivity
    - Increased PSD
    - Absence of media opacities (Duh!)
  - Optical explanation MORE LIKELY
    - No increase in PSD, in cases where MD is better than -10dB
Glaucoma Caused the Progression: Now What?

• Factors to Consider:
  – Compliance
  – Glaucoma Stage
  – Rate of progression/ time to “event”
  – Location of scotoma
  – Life expectancy of patient
  – Patient preference
  – Potential impact of next therapeutic step

New Baseline!!

• Every time a target IOP is adjusted or there is a significant change in the therapy, the tests need to be re-baselined
  – Last 2 tests that determined/confirmed progression can be the new baseline exams
  – Frequency of testing needs to increase again

Thoughts on Treatment

• ASSESS COMPLIANCE!!!!
  – Poor compliance:
    • Important conversation regarding compliance
    • Emphasize importance of compliance
    • May or may not need to lower target IOP
    • Consider laser trabecuoplasty or surgery
  – Good compliance:
    • Lower target IOP
    • Added medication
    • Laser trabecuoplasty or surgery

Thank you for your attention!

Questions?
Email me:
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