

## Cases and Controversies in Glaucoma

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## Disclosures

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    - Aerie, Allergan, Bausch + Lomb, Carl Zeiss Meditec, Heidelberg Engineering, Topcon inc.

## Cases and Controversies in Glaucoma

- Questions to be addressed
  - What region is the most important to image in order to detect glaucomatous damage?
    - Optic Nerve, Retinal Nerve Fiber Layer, Macula (GCC)
  - What is the most important piece of the OCT printout?
    - Colored probability symbols or the TNSIT graph or something else (B-scans)
  - Do we need to do fundus photography if we have done an OCT?
  - Do we need to perform perimetry if we do an OCT exam?
  - Do we need to include central visual field testing as part of the diagnostic workup?
  - Is OCT useful to monitor for progression?
  - Should SLT be offered as primary therapy for newly diagnosed patients?
  - Should Vyuzulta become the first-line prostaglandin?
  - Is Rhopressa the preferred second-line agent?
  - Is MIGS the best approach for glaucoma surgery?
  - Is the future of glaucoma therapy in drug delivery devices?

## Cases and Controversies in Glaucoma

- What region of the eye should we image?
  - Optic Nerve, Retinal Nerve Fiber Layer, Macula (GCC)
- Historically the RNFL was the primary region imaged and evaluated
  - initial devices such as GDx and Stratus OCT only imaged RNFL
- In past 10 years, data has shown that the macula is damaged early in the glaucoma process
  - Host of experts have recommended that GCC testing is important
  - Some cases may show macula loss with full RNFL
- Optic disc measurements such as C/D ratio, Minimum Rim Width (MRW), cup volume, rim area are available
  - How important are these areas for detecting glaucoma damage?
  - There is evidence that the optic disc is damaged early

## OCT: Evaluating the Results

- OCT has become an important adjunct in the evaluation of the optic nerve/RNFL for glaucoma
- OCT can image optic nerve, macula, area surrounding optic nerve, angle
- Future versions will even allow choroidal evaluation
- Printouts are most common method used to evaluate the results
- Printouts must be evaluated carefully or erroneous diagnosis possible
- OCT printout similar to visual field in that unreliable images are possible

## Macula Testing in Glaucoma

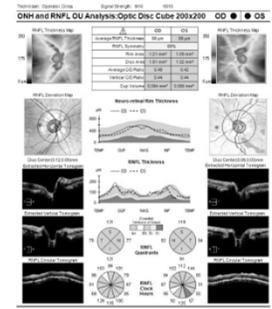
- Imaging allows measurement of features that are not possible otherwise
- Imaging to detect glaucoma damage has concentrated around RNFL and optic nerve evaluation
- Complicating the assessment of the optic nerve when evaluating for glaucoma damage is:
  - High variability of the ONH size and shape
    - Even among healthy individuals
  - Wide range of optic cup shapes and sizes
  - Variable size and configuration of blood vessels
  - Variable angle of penetration into the eyeball of the optic nerve (tilted disc)
  - Parapapillary changes such as atrophy

### Macula Testing in Glaucoma

- Imaging can detect changes in the macular region
  - The eye has about 1 million retinal ganglion cells, and their numbers are densest in the macula
    - about six cells deep
  - About 50% of ganglion cells are in the central 4.5 mm of the retina
    - an area that represents only 7% of the total retinal area
  - This area is not well covered in most visual field testing
- Compared to the optic nerve, the macula is a relatively simple structure
    - Devoid of large vessels
    - Has multiple cellular and plexiform layers with central depression (fovea) devoid of retinal ganglion cells
    - The RGC layer (shape) within the macula is generally less variable in healthy individuals than RNFL or ONH
      - Perhaps reduction may offer better sensitivity in recognizing glaucoma damage

### What is the most important piece of the OCT printout?

- RNFL Thickness map
- RNFL Deviation Map
- Parameters
- TSNIT Curve (RNFL)
- Neuro-retinal rim Curve
- B-Scans
- Quadrant maps
- Clock-hour maps



### Do we need to do fundus photography if we have done OCT?

**PREFERRED PRACTICE PATTERN®**

**Ophthalmic Evaluation**  
 In completing the elements in the comprehensive adult medical eye evaluation,<sup>1)</sup> the ophthalmic evaluation specifically focuses on the following elements:

- History<sup>2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65,66,67,68,69,70,71,72,73,74,75,76,77,78,79,80,81,82,83,84,85,86,87,88,89,90,91,92,93,94,95,96,97,98,99,100,101,102,103,104,105,106,107,108,109,110,111,112,113,114,115,116,117,118,119,120,121,122,123,124,125,126,127,128,129,130,131,132,133,134,135,136,137,138,139,140,141,142,143,144,145,146,147,148,149,150,151,152,153,154,155,156,157,158,159,160,161,162,163,164,165,166,167,168,169,170,171,172,173,174,175,176,177,178,179,180,181,182,183,184,185,186,187,188,189,190,191,192,193,194,195,196,197,198,199,200,201,202,203,204,205,206,207,208,209,210,211,212,213,214,215,216,217,218,219,220,221,222,223,224,225,226,227,228,229,230,231,232,233,234,235,236,237,238,239,240,241,242,243,244,245,246,247,248,249,250,251,252,253,254,255,256,257,258,259,260,261,262,263,264,265,266,267,268,269,270,271,272,273,274,275,276,277,278,279,280,281,282,283,284,285,286,287,288,289,290,291,292,293,294,295,296,297,298,299,300,301,302,303,304,305,306,307,308,309,310,311,312,313,314,315,316,317,318,319,320,321,322,323,324,325,326,327,328,329,330,331,332,333,334,335,336,337,338,339,340,341,342,343,344,345,346,347,348,349,350,351,352,353,354,355,356,357,358,359,360,361,362,363,364,365,366,367,368,369,370,371,372,373,374,375,376,377,378,379,380,381,382,383,384,385,386,387,388,389,390,391,392,393,394,395,396,397,398,399,400,401,402,403,404,405,406,407,408,409,410,411,412,413,414,415,416,417,418,419,420,421,422,423,424,425,426,427,428,429,430,431,432,433,434,435,436,437,438,439,440,441,442,443,444,445,446,447,448,449,450,451,452,453,454,455,456,457,458,459,460,461,462,463,464,465,466,467,468,469,470,471,472,473,474,475,476,477,478,479,480,481,482,483,484,485,486,487,488,489,490,491,492,493,494,495,496,497,498,499,500,501,502,503,504,505,506,507,508,509,510,511,512,513,514,515,516,517,518,519,520,521,522,523,524,525,526,527,528,529,530,531,532,533,534,535,536,537,538,539,540,541,542,543,544,545,546,547,548,549,550,551,552,553,554,555,556,557,558,559,560,561,562,563,564,565,566,567,568,569,570,571,572,573,574,575,576,577,578,579,580,581,582,583,584,585,586,587,588,589,590,591,592,593,594,595,596,597,598,599,600,601,602,603,604,605,606,607,608,609,610,611,612,613,614,615,616,617,618,619,620,621,622,623,624,625,626,627,628,629,630,631,632,633,634,635,636,637,638,639,640,641,642,643,644,645,646,647,648,649,650,651,652,653,654,655,656,657,658,659,660,661,662,663,664,665,666,667,668,669,670,671,672,673,674,675,676,677,678,679,680,681,682,683,684,685,686,687,688,689,690,691,692,693,694,695,696,697,698,699,700,701,702,703,704,705,706,707,708,709,710,711,712,713,714,715,716,717,718,719,720,721,722,723,724,725,726,727,728,729,730,731,732,733,734,735,736,737,738,739,740,741,742,743,744,745,746,747,748,749,750,751,752,753,754,755,756,757,758,759,760,761,762,763,764,765,766,767,768,769,770,771,772,773,774,775,776,777,778,779,780,781,782,783,784,785,786,787,788,789,790,791,792,793,794,795,796,797,798,799,800,801,802,803,804,805,806,807,808,809,810,811,812,813,814,815,816,817,818,819,820,821,822,823,824,825,826,827,828,829,830,831,832,833,834,835,836,837,838,839,840,841,842,843,844,845,846,847,848,849,850,851,852,853,854,855,856,857,858,859,860,861,862,863,864,865,866,867,868,869,870,871,872,873,874,875,876,877,878,879,880,881,882,883,884,885,886,887,888,889,890,891,892,893,894,895,896,897,898,899,900,901,902,903,904,905,906,907,908,909,910,911,912,913,914,915,916,917,918,919,920,921,922,923,924,925,926,927,928,929,930,931,932,933,934,935,936,937,938,939,940,941,942,943,944,945,946,947,948,949,950,951,952,953,954,955,956,957,958,959,960,961,962,963,964,965,966,967,968,969,970,971,972,973,974,975,976,977,978,979,980,981,982,983,984,985,986,987,988,989,990,991,992,993,994,995,996,997,998,999,1000</sup>
- Pupillary examination<sup>1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65,66,67,68,69,70,71,72,73,74,75,76,77,78,79,80,81,82,83,84,85,86,87,88,89,90,91,92,93,94,95,96,97,98,99,100,101,102,103,104,105,106,107,108,109,110,111,112,113,114,115,116,117,118,119,120,121,122,123,124,125,126,127,128,129,130,131,132,133,134,135,136,137,138,139,140,141,142,143,144,145,146,147,148,149,150,151,152,153,154,155,156,157,158,159,160,161,162,163,164,165,166,167,168,169,170,171,172,173,174,175,176,177,178,179,180,181,182,183,184,185,186,187,188,189,190,191,192,193,194,195,196,197,198,199,200,201,202,203,204,205,206,207,208,209,210,211,212,213,214,215,216,217,218,219,220,221,222,223,224,225,226,227,228,229,230,231,232,233,234,235,236,237,238,239,240,241,242,243,244,245,246,247,248,249,250,251,252,253,254,255,256,257,258,259,260,261,262,263,264,265,266,267,268,269,270,271,272,273,274,275,276,277,278,279,280,281,282,283,284,285,286,287,288,289,290,291,292,293,294,295,296,297,298,299,300,301,302,303,304,305,306,307,308,309,310,311,312,313,314,315,316,317,318,319,320,321,322,323,324,325,326,327,328,329,330,331,332,333,334,335,336,337,338,339,340,341,342,343,344,345,346,347,348,349,350,351,352,353,354,355,356,357,358,359,360,361,362,363,364,365,366,367,368,369,370,371,372,373,374,375,376,377,378,379,380,381,382,383,384,385,386,387,388,389,390,391,392,393,394,395,396,397,398,399,400,401,402,403,404,405,406,407,408,409,410,411,412,413,414,415,416,417,418,419,420,421,422,423,424,425,426,427,428,429,430,431,432,433,434,435,436,437,438,439,440,441,442,443,444,445,446,447,448,449,450,451,452,453,454,455,456,457,458,459,460,461,462,463,464,465,466,467,468,469,470,471,472,473,474,475,476,477,478,479,480,481,482,483,484,485,486,487,488,489,490,491,492,493,494,495,496,497,498,499,500,501,502,503,504,505,506,507,508,509,510,511,512,513,514,515,516,517,518,519,520,521,522,523,524,525,526,527,528,529,530,531,532,533,534,535,536,537,538,539,540,541,542,543,544,545,546,547,548,549,550,551,552,553,554,555,556,557,558,559,560,561,562,563,564,565,566,567,568,569,570,571,572,573,574,575,576,577,578,579,580,581,582,583,584,585,586,587,588,589,590,591,592,593,594,595,596,597,598,599,600,601,602,603,604,605,606,607,608,609,610,611,612,613,614,615,616,617,618,619,620,621,622,623,624,625,626,627,628,629,630,631,632,633,634,635,636,637,638,639,640,641,642,643,644,645,646,647,648,649,650,651,652,653,654,655,656,657,658,659,660,661,662,663,664,665,666,667,668,669,670,671,672,673,674,675,676,677,678,679,680,681,682,683,684,685,686,687,688,689,690,691,692,693,694,695,696,697,698,699,700,701,702,703,704,705,706,707,708,709,710,711,712,713,714,715,716,717,718,719,720,721,722,723,724,725,726,727,728,729,730,731,732,733,734,735,736,737,738,739,740,741,742,743,744,745,746,747,748,749,750,751,752,753,754,755,756,757,758,759,760,761,762,763,764,765,766,767,768,769,770,771,772,773,774,775,776,777,778,779,780,781,782,783,784,785,786,787,788,789,790,791,792,793,794,795,796,797,798,799,800,801,802,803,804,805,806,807,808,809,810,811,812,813,814,815,816,817,818,819,820,821,822,823,824,825,826,827,828,829,830,831,832,833,834,835,836,837,838,839,840,841,842,843,844,845,846,847,848,849,850,851,852,853,854,855,856,857,858,859,860,861,862,863,864,865,866,867,868,869,870,871,872,873,874,875,876,877,878,879,880,881,882,883,884,885,886,887,888,889,890,891,892,893,894,895,896,897,898,899,900,901,902,903,904,905,906,907,908,909,910,911,912,913,914,915,916,917,918,919,920,921,922,923,924,925,926,927,928,929,930,931,932,933,934,935,936,937,938,939,940,941,942,943,944,945,946,947,948,949,950,951,952,953,954,955,956,957,958,959,960,961,962,963,964,965,966,967,968,969,970,971,972,973,974,975,976,977,978,979,980,981,982,983,984,985,986,987,988,989,990,991,992,993,994,995,996,997,998,999,1000</sup>
- Anterior segment examination<sup>1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65,66,67,68,69,70,71,72,73,74,75,76,77,78,79,80,81,82,83,84,85,86,87,88,89,90,91,92,93,94,95,96,97,98,99,100,101,102,103,104,105,106,107,108,109,110,111,112,113,114,115,116,117,118,119,120,121,122,123,124,125,126,127,128,129,130,131,132,133,134,135,136,137,138,139,140,141,142,143,144,145,146,147,148,149,150,151,152,153,154,155,156,157,158,159,160,161,162,163,164,165,166,167,168,169,170,171,172,173,174,175,176,177,178,179,180,181,182,183,184,185,186,187,188,189,190,191,192,193,194,195,196,197,198,199,200,201,202,203,204,205,206,207,208,209,210,211,212,213,214,215,216,217,218,219,220,221,222,223,224,225,226,227,228,229,230,231,232,233,234,235,236,237,238,239,240,241,242,243,244,245,246,247,248,249,250,251,252,253,254,255,256,257,258,259,260,261,262,263,264,265,266,267,268,269,270,271,272,273,274,275,276,277,278,279,280,281,282,283,284,285,286,287,288,289,290,291,292,293,294,295,296,297,298,299,300,301,302,303,304,305,306,307,308,309,310,311,312,313,314,315,316,317,318,319,320,321,322,323,324,325,326,327,328,329,330,331,332,333,334,335,336,337,338,339,340,341,342,343,344,345,346,347,348,349,350,351,352,353,354,355,356,357,358,359,360,361,362,363,364,365,366,367,368,369,370,371,372,373,374,375,376,377,378,379,380,381,382,383,384,385,386,387,388,389,390,391,392,393,394,395,396,397,398,399,400,401,402,403,404,405,406,407,408,409,410,411,412,413,414,415,416,417,418,419,420,421,422,423,424,425,426,427,428,429,430,431,432,433,434,435,436,437,438,439,440,441,442,443,444,445,446,447,448,449,450,451,452,453,454,455,456,457,458,459,460,461,462,463,464,465,466,467,468,469,470,471,472,473,474,475,476,477,478,479,480,481,482,483,484,485,486,487,488,489,490,491,492,493,494,495,496,497,498,499,500,501,502,503,504,505,506,507,508,509,510,511,512,513,514,515,516,517,518,519,520,521,522,523,524,525,526,527,528,529,530,531,532,533,534,535,536,537,538,539,540,541,542,543,544,545,546,547,548,549,550,551,552,553,554,555,556,557,558,559,560,561,562,563,564,565,566,567,568,569,570,571,572,573,574,575,576,577,578,579,580,581,582,583,584,585,586,587,588,589,590,591,592,593,594,595,596,597,598,599,600,601,602,603,604,605,606,607,608,609,610,611,612,613,614,615,616,617,618,619,620,621,622,623,624,625,626,627,628,629,630,631,632,633,634,635,636,637,638,639,640,641,642,643,644,645,646,647,648,649,650,651,652,653,654,655,656,657,658,659,660,661,662,663,664,665,666,667,668,669,670,671,672,673,674,675,676,677,678,679,680,681,682,683,684,685,686,687,688,689,690,691,692,693,694,695,696,697,698,699,700,701,702,703,704,705,706,707,708,709,710,711,712,713,714,715,716,717,718,719,720,721,722,723,724,725,726,727,728,729,730,731,732,733,734,735,736,737,738,739,740,741,742,743,744,745,746,747,748,749,750,751,752,753,754,755,756,757,758,759,760,761,762,763,764,765,766,767,768,769,770,771,772,773,774,775,776,777,778,779,780,781,782,783,784,785,786,787,788,789,790,791,792,793,794,795,796,797,798,799,800,801,802,803,804,805,806,807,808,809,810,811,812,813,814,815,816,817,818,819,820,821,822,823,824,825,826,827,828,829,830,831,832,833,834,835,836,837,838,839,840,841,842,843,844,845,846,847,848,849,850,851,852,853,854,855,856,857,858,859,860,861,862,863,864,865,866,867,868,869,870,871,872,873,874,875,876,877,878,879,880,881,882,883,884,885,886,887,888,889,890,891,892,893,894,895,896,897,898,899,900,901,902,903,904,905,906,907,908,909,910,911,912,913,914,915,916,917,918,919,920,921,922,923,924,925,926,927,928,929,930,931,932,933,934,935,936,937,938,939,940,941,942,943,944,945,</sup>

## Cases and Controversies in Glaucoma

- OCT and Visual field will manifest change and stop showing change at different time points as glaucoma gets worse
  - OCT will show loss earlier but has a floor effect
    - Around 60um will no longer show change
    - This may vary if macula scans are used
- Visual fields start to show loss when the RNFL is reduced to around 75um
- Will continue to show loss throughout the person's lifetime

## What is the floor effect

- The RNFL layer is composed of glial and other structural tissue
  - 40% of its makeup
- The floor varies with OCT device but is between 50-60 um
- With advancing damage, never goes to 0
- Floor effect
  - Spectralis 49.2um
  - Cirrus – 57 um
  - RTVue– 64.7 um

### Glaucoma

#### Residual and Dynamic Range of Retinal Nerve Fiber Layer Thickness in Glaucoma: Comparison of Three OCT Platforms

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Glaucoma Mwanza J, Kim HY, Budenz DL, et al. Residual and dynamic range of retinal nerve fiber thickness in glaucoma: comparison of three OCT platforms. *J Optom Vis Sci*. 2015;92(11):675. DOI:10.1167/jov.15.17.248

**Purpose:** To estimate visual field (VF) sensitivity at which retinal nerve fiber layer (RNFL) thinning reaches the measurement floor and at which RNFL stops thinning (change points), the dynamic range of RNFL thickness, and the number of steps from normal to RNFL floor among three optical coherence tomography (OCT) devices.

**Methods:** Glaucomatous patients ( $n = 58$ ) and healthy subjects ( $n = 55-60$ ) prospectively underwent VF testing and RNFL thickness measurement with Cirrus, Spectralis, and RTVue. Change points and corresponding RNFL thicknesses were estimated with simple linear regression (SLR) and Bayesian change-point (BCP) analyses. The dynamic range and number of steps to RNFL floor were determined.

**Results:** The average VF change points and corresponding residual thickness at the time RNFL stopped thinning were  $-22.2$  dB and  $57.0$   $\mu\text{m}$  (Cirrus),  $-25.5$  dB and  $49.2$   $\mu\text{m}$  (Spectralis), and  $-21.6$  dB and  $64.7$   $\mu\text{m}$  (RTVue). The RNFL dynamic ranges derived from SLR values were wider on Spectralis (52.9  $\mu\text{m}$ ) than on Cirrus (53.1  $\mu\text{m}$ ) and RTVue (55.8  $\mu\text{m}$ ); the corresponding number of steps to reach the RNFL floor were 9.0 on Cirrus, 10.6 on Spectralis, and 8.1 on RTVue.

**Conclusions:** The relative VF sensitivity at which average RNFL thickness reaches the measurement floor, the residual layer thickness, and RNFL dynamic measurement range differ among the three devices. However, the number of steps from normal to the RNFL thickness floor is comparable.

**Keywords:** glaucoma, optical coherence tomography, retinal nerve fiber layer

## When is the OCT Abnormal?

- The average RNFL thickness at 70yo is 107um at the 95%
- The green range for average RNFL is from 107-75um
  - Flips to yellow at 75um
  - There are from 4-8 steps of detectable change while the RNFL is in the green range
- Visual field loss occurs at 75um thickness for average RNFL
- Flips from yellow to red for average RNFL at 67um
- Floor effect at approximately 55um
  - Will not go any lower
  - Visual field may be present when at floor

## Is Diabetes a Risk Factor For Developing Glaucoma?

#### Increased risk of open-angle glaucoma among patients with diabetes mellitus: a 10-year follow-up nationwide cohort study

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**ABSTRACT.**  
**Purpose:** To evaluate the risk of open-angle glaucoma among patients with diabetes.  
**Methods:** This retrospective propensity score-matched cohort study included patients with diabetes and a matched comparison group from the Korean National Health Insurance Service National Health Screening Cohort, which includes approximately 500 000 adults aged  $\geq 40$  years. Nondiabetes group was matched to diabetes group in a 1:1 ratio using a propensity score based on age, sex, comorbidities, antihypertensive medication use and medical care visits. Each group was followed from January 1, 2004 to either the date of developing open-angle glaucoma or the date of last follow-up in 2013.  
**Results:** Incidence of open-angle glaucoma was 20.0/10 000 person-years in diabetes group ( $n = 58$  358) and 17.0/10 000 person-years in nondiabetes group ( $n = 58$  358). Age- and sex- adjusted hazard ratio (HR) was 1.19 (95% confidence interval [CI], 1.09–1.30). In the subgroup analyses, diabetes was associated with an increased risk of open-angle glaucoma in both younger and older age groups (HR = 1.20 for those aged 40–59 years and HR = 1.18 for those aged 60–79 years) and in both sexes (men, HR = 1.13; women, HR = 1.27).  
**Conclusion:** Patients diagnosed with diabetes were more likely to develop open-angle glaucoma compared with patients without diabetes.

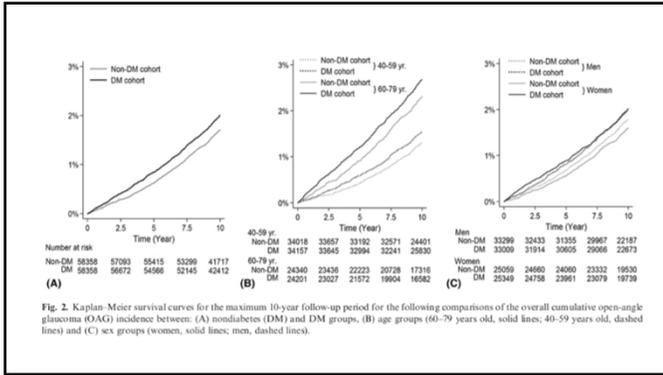


Fig. 2. Kaplan-Meier survival curves for the maximum 10-year follow-up period for the following comparisons of the overall cumulative open-angle glaucoma (OAG) incidence between: (A) nondiabetic (DM) and DM groups, (B) age groups (60-79 years old, solid lines; 40-59 years old, dashed lines) and (C) sex groups (women, solid lines; men, dashed lines).

## Do we need to include central visual field testing as part of the glaucoma diagnostic workup?

Will a Central 10° Field Defect Be Present When the 24-2 is Full?

## Central Field in Glaucoma

- Improvements in imaging (OCT) allow us to recognize involvement of macula in earlier stages of glaucoma
- OCT allows us to better evaluate the layers of the retina and understand where damage is occurring
- Understanding if there is central visual field loss (within 10° of fixation) is important for the patient
  - Decreased reading speed and errors
  - Altered driving ability – reading signs
  - Increased risk of falls
- Peripheral visual field loss
  - Asymptomatic (unless bilateral and severe)
  - Does not impact function as significantly

## Central Visual Fields and Glaucoma

- Recent papers have suggested that the 24-2 test pattern has limited ability to detect central field defects
  - 50% of retinal ganglion cells are found within 4.5mm of fovea
  - Macula region comprises only 10% of overall visual field area though it is responsible for 60% of area of visual cortex
  - Damage to central 10° associated with diminished contrast sensitivity, reduced reading ability

### Spatial Pattern of Glaucomatous Visual Field Loss Obtained with Regionally Condensed Stimulus Arrangements

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**Abstract**

Visual field (VF) loss is a common feature of glaucoma. The spatial pattern of VF loss is characterized by a central island of preserved vision surrounded by a ring of peripheral loss. This pattern is thought to be due to the higher density of retinal ganglion cells (RGCs) in the central retina. However, the spatial pattern of VF loss in glaucoma is not fully understood. We investigated the spatial pattern of VF loss in glaucoma using regionally condensed stimulus arrangements. We compared the spatial pattern of VF loss in glaucoma to the spatial pattern of VF loss in normal vision. We found that the spatial pattern of VF loss in glaucoma is similar to the spatial pattern of VF loss in normal vision. This suggests that the spatial pattern of VF loss in glaucoma is determined by the spatial pattern of RGC density in the retina.

**Introduction**

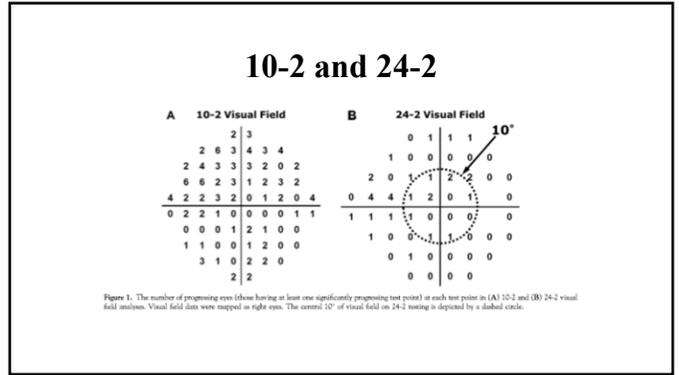
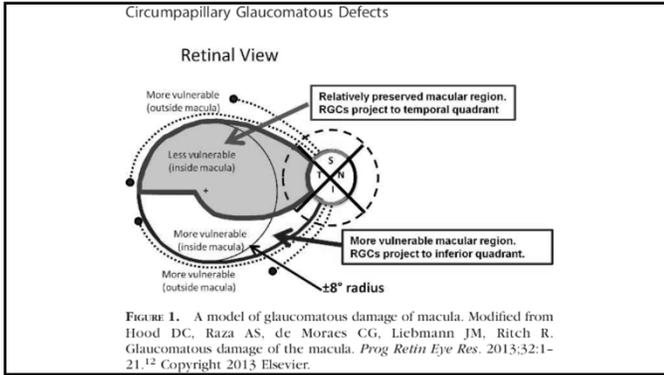
Visual field (VF) loss is a common feature of glaucoma. The spatial pattern of VF loss is characterized by a central island of preserved vision surrounded by a ring of peripheral loss. This pattern is thought to be due to the higher density of retinal ganglion cells (RGCs) in the central retina. However, the spatial pattern of VF loss in glaucoma is not fully understood. We investigated the spatial pattern of VF loss in glaucoma using regionally condensed stimulus arrangements. We compared the spatial pattern of VF loss in glaucoma to the spatial pattern of VF loss in normal vision. We found that the spatial pattern of VF loss in glaucoma is similar to the spatial pattern of VF loss in normal vision. This suggests that the spatial pattern of VF loss in glaucoma is determined by the spatial pattern of RGC density in the retina.

### Glaucomatous damage of the macula

Donald C. Hood<sup>1,2,3</sup>, Ali S. Raza<sup>4,5</sup>, Carlos Gustavo V. de Moraes<sup>6,7</sup>, Jeffrey M. Liebmann<sup>8,9,1</sup>, Robert Ritch<sup>5,11</sup>

**Abstract**

There is a growing body of evidence that early glaucomatous damage involves the macula. The anatomical basis of this damage can be studied using frequency domain optical coherence tomography (FD-OCT) by which the total thickness of the central macular region (total macular thickness [TMT]) and central macular thickness (CMT) can be measured. In this study, we compared the spatial pattern of TMT and CMT loss in glaucoma to the spatial pattern of TMT and CMT loss in normal vision. We found that the spatial pattern of TMT and CMT loss in glaucoma is similar to the spatial pattern of TMT and CMT loss in normal vision. This suggests that the spatial pattern of TMT and CMT loss in glaucoma is determined by the spatial pattern of RGC density in the retina.



### The Central Field in Glaucoma

- Does the 24-2 detect functional vision loss in the central 10° in all cases?
  - Points in test grid are 6° apart in a grid pattern
- Is there a role for a complementary test such as the 10-2 in which 55 points are placed in a 10° area that are 2° apart?
  - Will this detect small scotomas that fall between the cracks?
- Is glaucoma a disease that involves the macula region early in the condition?

### Reasons to Perform 10-2 Test

- Better resolution
  - 24-2 tests 54 points 6° apart
    - Only 12 points in central 10°
    - This area accounts for 50% of ganglion cells in retina
  - 10-2 tests 54 points 2° apart
  - Paracentral scotomas may be missed on 24-2 test pattern

## Is OCT useful to monitor for progression?

### Glaucoma Progression

- For patients diagnosed with glaucoma or are glaucoma suspects due to large cupping or unusual optic discs (myopic, tilted), detecting change is important
- This is a difficult task requiring periodic tests to be performed over time watching for change
- Change can occur at any time
  - 10% of newly diagnosed glaucomas are rapid progressors
  - Glaucoma patients can go years before change develops
- Change does not occur at the same rate over the lifetime of the patient
- Due to test variability, just because a test is different from the previous one does not mean the person got worse
- Ability to discriminate true change, over and beyond measurement variability, is a requirement for any progression technique
  - Perimetry or Imaging

## Glaucoma Progression

- Progression may be measured by structural changes at the
  - optic nerve head
  - retinal nerve fiber layer
  - macula region
- Not clear which region provides best sensitivity and probably depends in part on the individual and stage of the disease
  - Evidence that change is first seen on optic disc but that does not mean that present clinical tools recognize this loss
- Change may also be seen by enlargement of parapapillary atrophy
  - Not usually on clinician's radar

Which test is most sensitive to detect change – OCT vs VF

What Changes First – The RNFL or The Macula Area or the Optic Disc?

In summary, in glaucoma eyes the overall rate of circumpapillary RNFL loss is 1.3 times faster compared to macular GCIPL loss. In healthy eyes, the rate of circumpapillary RNFL loss also tended to be faster than macular GCIPL loss, but the difference did not reach statistical significance. These results suggest that the establishment of longitudinal reference databases of healthy eyes can help improve the clinician's ability to differentiate between macular GCIPL and circumpapillary RNFL age-related loss and disease progression. Moreover, as significant change in macular GCIPL was detectable in severe glaucoma eyes, imaging may provide important information on whether a patient is progressing at all stages of glaucoma, including advanced disease.

While the RNFL changed quicker, due to the floor effect reducing RNFL use through the entire life of glaucoma, the GCIPL was able to monitor from mild to advanced glaucoma

Should SLT Be Offered as Primary Therapy for Newly Diagnosed Individuals?

## Selective Laser Trabeculoplasty (SLT)

- Q-switched, frequency doubled Nd:Yag 532 nm laser
  - Selecta 7000- Lumenis
- Targets pigmented cells in trabecular meshwork
  - little damage to non-pigmented cells
  - less destructive procedure
- Advantage
  - Little destruction to TM supports biologic theory
    - No coagulation effects
  - reduced incidence of IOP spikes and complications
- Relies on selective photothermolysis
  - targets melanin granules within cell
    - cell death occurs
  - Less need for pigmented tissue
- Patient type
  - Effective as adjunctive or replacement tx
  - Also may be used as primary therapy
  - Being used early in stepped medical therapy
    - Do not wait until patient exhausted all medical options
- Contraindications
  - Secondary glaucomas
    - Traumatic angle recession
    - Inflammatory
    - Neovascular

Should Vyzulta or Rocklatan be offered as Primary Therapy for Newly Diagnosed Individuals?

## New Drugs – Will they replace the ones we are presenting using

- Latanoprost bunod
  - Approved November 2017
  - Nitric oxide donating Prostaglandin F<sub>2α</sub>
  - Vyzulta Bausch & Lomb
- Rho Kinase Inhibitors
  - Approved December 2017
  - Netarsudil 0.02%
  - Rhopressa
  - Aerie
- Rho Kinase Inhibitors and latanoprost
  - Roclatan
  - Aerie
  - 1<sup>st</sup> quarter 2019

## Latanoprostone bunod (Vyzulta)

- 0.024% used once daily to reduced IOP
  - Bausch & Lomb
  - Approved Nov. 2017
- Metabolized to latanoprost acid plus butanediol mononitrate
- Butanediol mononitrate is a nitric-oxide donating moiety NO molecule attached to latanoprost backbone provide dual action
- Works over 24 hour period with >35% IOP reduction
- One molecule leads to IOP reduction via the uveoscleral and trabecular meshwork pathways
- NO is a signaling molecule that regulates outflow facility via the TM
- Can dilate blood vessels
- Modulates TM contractility, cell adhesion and the cytoskeleton leading to reduced IOP
- Medication acts on both the
  - Uveoscleral outflow pathway by altering the extracellular matrix in the ciliary muscle and the sclera
  - Trabecular meshwork outflow by inhibiting actomyosin contractility in trabecular meshwork cells thereby relaxing the meshwork

## Is Rhopressa the Preferred Second-Line Agent?

Second line Options- Beta blockers, Topical CAls, Alpha Agonists, Fixed Combination Agents such as generic timolol-dorzolamide, Simbrinza, Combigan, SLT

## New Medication Rho Kinase Inhibitors

- Rho kinase inhibitors
  - Rhopressa (Aerie pharmaceuticals)
- Reduce cellular stiffness in trabecular meshwork
  - Target trabecular meshwork cells to enhance outflow
  - May offer neuroprotective as well as anti inflammatory effects
  - Aerie

## New Glaucoma Medications

- Aerie Pharmaceuticals
  - Two compounds
    - AR-13324 lowers IOP by enhance outflow through TM (ROCK) and inhibit aqueous production (NET)
    - Also believed to reduce episcleral venous pressure which may allow it to better reduce IOP when it is below 21 mm Hg
  - Triple action ROCK + NET + latanoprost (Roclatan)
    - PG324 fixed combination of AR-13324 and latanoprost
      - Additional IOP reduction through uveoscleral outflow
- Both agents are once per day dosage
- Hyperemia is most common side effect found in studies to date

### *Purpose*

To evaluate the efficacy and ocular and systemic safety of netarsudil 0.02% ophthalmic solution, a rho-kinase inhibitor and norepinephrine transporter inhibitor, in patients with open-angle glaucoma and ocular hypertension.

### *Design*

Double-masked, randomized non-inferiority clinical trials.

### *Methods*

After a washout of all pre-study ocular hypotensive medications, eligible patients were randomized to receive netarsudil 0.02%, q.d., timolol 0.5% b.i.d., and (ROCKET-2 only), netarsudil 0.02%, b.i.d. Data through 3 months from both studies are provided in this report.

### *Results*

Enrolled into the two studies were 1,167 patients. Treatment with netarsudil q.d. produced clinically and statistically significant reductions from baseline intraocular pressure ( $p < 0.001$ ), and was non-inferior to timolol in the per-protocol population with maximum baseline IOP  $< 25$  mmHg in both studies (ROCKET-2, primary outcome measure and population, ROCKET-1, post hoc outcome measure). Netarsudil b.i.d. was also non-inferior to timolol (ROCKET-2). The most frequent adverse event was conjunctival hyperemia; the incidence of which ranged from 50% (126/251, ROCKET-2) to 53% (108/203, ROCKET-1) for netarsudil q.d., 59% (149/253, ROCKET-2) for netarsudil b.i.d., and 8% (17/208, ROCKET-1) to 11% (27/251, ROCKET-2) for timolol ( $p < 0.0001$  for netarsudil vs. timolol).

### *Conclusions*

In two large, randomized, double-masked trials reported here, once-daily dosing of netarsudil 0.02% was found to be effective and well tolerated for the treatment of patients with ocular hypertension and open-angle glaucoma. The novel pharmacology and aqueous humor dynamic effects of this molecule suggest it may be a useful addition to the armamentarium of ocular hypotensive medications.

## Is MIGS the Best Approach for Glaucoma Surgery?

### NEW MIGS GLAUCOMA SURGICAL DEVICES

Table 1. New glaucoma procedures

Procedure	Anatomical target	Description	Approach	US FDA approval
Trabectome	TM and SC	Ablation of TM and inner wall of SC is performed using plasma-mediated ionization and disintegration	Ab interno	Yes
iStent	TM and SC	1 mm snorkel-shaped stent composed of heparin-coated titanium is inserted into SC	Ab interno	Yes
Hydus Microstent	TM and SC	8 mm nitinol scaffold is inserted into SC	Ab interno	No
Gonioscopy-assisted transilluminal trabeculotomy (GATT)	TM and SC	Illuminated microcatheter or suture is passed through a goniotomy to cannulate SC and create a 360° trabeculotomy	Ab interno	Yes
Canaloplasty	TM and SC	Illuminated microcatheter is used to cannulate SC after which a tensioning suture is placed through SC	Ab externo	Yes
CyPass Micro-Stent	Suprachoroidal space	6.35 mm fenestrated polyimide stent is inserted between scleral spur and ciliary body to create controlled cyclodialysis	Ab interno	Yes
XEN Gel Stent	Subconjunctival space	6 mm gelatinous tube is inserted transcorneally through a scleral tunnel	Ab interno	No
InnFocus MicroShunt	Subconjunctival space	8.5 mm poly(styrene-block-isobutylene-block-styrene) tube is inserted transilluminally through a scleral tunnel	Ab externo	No

SC, Schlemm's canal; TM, trabecular meshwork; US FDA, United States Food and Drug Administration.

### Cases and Controversies in Glaucoma

- MIGS (Minimally Invasive Glaucoma Surgery)
  - Group of operations in which microscopic equipment and tiny incisions often using devices
  - Objective is for reduced complications compared to trabeculectomy with nearly similar IOP reduction
  - New MIGS type devices in development
    - IStent inject and iStent Supra (Glaukos), Ivantis (Hydus), CyPass Micro-stent (Transend Medical), AqueSys (Allergan)
  - Increasing from \$13 Million in 2013 to \$70 million in 2015

### Minimally Invasive Glaucoma Surgery - MIGS

- Glaukos Trabecular Micro-bypass stent (iStent)
  - June 2012 FDA approval
  - Designed to create a permanent opening from the anterior chamber to Schlemm's canal
  - Designed to fit and remain in Schlemm's canal
  - Titanium device 1 mm in length consisting of inlet or snorkel end connected at right angle to implantation portion, which has a pointed end to facilitate entry into canal
  - Theoretic advantages
    - Open a pathway into Schlemm's canal
- Tiny titanium devices that drains aqueous fluid from the anterior chamber
- Minimally traumatic, conjunctiva sparing *ab-interno* procedure
  - performed through a clear corneal micro-incision under 2.0mm
- The objective is to achieve IOP in the mid-teens and reduce medication use
  - leaving the door open for more invasive surgical alternatives if required in the future
- It is approved for use during cataract surgery in the 20% of cataract patients that are treated with medications to reduce intraocular pressure (IOP)

### CyPass - Alcon

- Approved by the FDA August 2016
- MIGS device using Suprachoroidal space
- Approved to be done with cataract surgery
- Mild-moderate glaucoma

### Xen Gel Stent

- IOP lowering device FDA approved - Allergan
- A soft, permanent, minimally invasive ocular shunt (MIGS or micro-invasive glaucoma surgery device) that is implanted in the anterior chamber of the eye to facilitate the continuous flow of aqueous humor into the subconjunctival space
- The ocular shunt is manufactured from gelatin (45 µm internal diameter)
- The implant is 6mm in length and nearly as thin as a strand of human hair.

## Xen Gel Stent

- Implanted through a small 27-gauge needle, single use, pre-loaded proprietary injector using an ab interno (from inside the eye) approach
- The surgeon first advances the needle through the peripheral cornea and across the anterior chamber towards the target area. The needle is then advanced through the trabecular meshwork and sclera and is visualized as it enters the subconjunctival space. The implant is then released and the needle is removed from the eye.
- When implanted, it creates a better outflow of aqueous fluid from the anterior chamber of the eye into the non-dissected tissue of the subconjunctival space
- This procedure is minimally invasive
- The gelatin material is non-inflammatory with minimal stress on the surrounding tissue and doesn't migrate once placed
- The surgery leaves all other options open for future use if needed, and it can be repeated

## Is the Future of Glaucoma Therapy in Drug Delivery Devices?

## Drug Delivery

- Problem – poor adherence in patients taking their medications as directed
  - Common with chronic disease such as glaucoma
  - Estimated 40% or higher of medicines not taken
- Plan - develop therapeutic methods that are independent of patient and delivered by doctor
- Modalities include devices that reside on ocular surface, slow-release depots that are injected into the eye, and punctal plugs that deliver drugs directly into tear film

## New Methods for Drug Delivery

- Eyedrops have drawbacks
  - Relatively inefficient in that large volume is placed in small space
  - Relies on patient's ability to comply and administer drops correctly
- Objectives of new drug delivery methods
  - Ensure drug delivered to the site of action in the eye
  - Reduce side effects of topical medications
  - Improve compliance
  - Improve clinical outcomes
  - Methods may be
    - patient centered and noninvasive or doctor centered and invasive

## Drug Delivery

- An ideal sustained release drug delivery system should be able to encapsulate and deliver the necessary drug to the target tissues at a therapeutic level without any detriment to the drug
  - Drug encapsulation should be as high as possible to minimize loss and unless it is specifically desired, the initial burst of drug release should be kept to a minimum
  - By modifying various biomaterials, it is possible to achieve sustained drug delivery to both the anterior and posterior segments of the eye
- Ocular Surface
    - Contact lens
    - Punctal plug
  - Sclera
  - Anterior chamber
  - Intra vitreal
  - Subconjunctival/subchoroidal

## Ocular Drug Delivery Key Points

- Easy to place and easy to remove
- Tolerable
- Consistent efficacy
  - Works close to eye drop with improved compliance
  - Can it work better?
- Cosmetically invisible
- Stays in place
  - At least 90 days
- Use in multiple disease states

## Drug Delivery Systems for Glaucoma

- Lumigan SR (Allergan)
  - Sustained release bimatoprost implant
  - Phase III
- Amorphex Therapeutics
  - A polymer, similar to a contact lens, that contains the drug and sits under the upper eyelid
  - Releases the drug over several months
- Envisia Therapeutics
  - Implantable extended-release device
- pSivida and SKS Ocular
  - Delivery devices
- Kala Pharmaceuticals
  - Drops that can get into the eye more easily
- Ocular Therapeutix (OTX-TP)
  - Sustained release travoprost punctal plugs
- Allergan (Foresight – Helios)
  - Ring
- Mati Therapeutics Inc.
  - Punctal plug device
- Graybug
  - Sustained release

## Platforms delivered outside the eye

- Helios (ForSight Vision 5) - Allergan
  - Bimatoprost-laden polymer-matrix insert embedded in compliant ring
- TODDD (Topical Ophthalmic Drug Delivery Device; Vista Scientific)
  - Nonerosible solid matrix under the eyelid embedded with a drug
  - Similar to contact lens with drug released over several months
  - Amorphex Therapeutics
  - Most of the company's work has focused on timolol and prostaglandins.
- Punctal plugs:
  - Ocular Therapeutix (OTX-TP) is an intracanalicular depot that dissolves over time
  - Mati Therapeutics (L-PPDS) is a latanoprost punctal plug delivery system
  - Kayla Pharmaceuticals
    - Drops that allow medication to get into the eye more effectively.
- Phenylboronic-Acid based polymeric micelles for mucoadhesive anterior segment ocular drug delivery

## Platforms Delivered inside the eye

- Bimatoprost SR
  - Bimatoprost sustained-release implant (Allergan)
  - Currently in Phase 3 clinical trials.
- ENV515 - Envisia Therapeutics
  - Implantable biodegradable polymer drug delivery system using extended-release travoprost using engineered highly-precise microparticles and nanoparticles
- GrayBug microparticle
  - Polymer-based intraocular delivery technologies that would allow customizable sustained release of all therapeutic classes
- pSivida
  - Delivery devices or technology to allow a constant delivery of medication over months or years
- Ohr Pharmaceutical
  - Inject micro- or nanoparticles into the eye that would then release a glaucoma drug/drugs over an extended period of time
- ClearSide Biomedical, Inc.
  - Use of microneedles to inject medication into a specific spot for it to be most effective
- Glaukos - iDose (DoseMedical)
  - Stent with IOP sensor and medication dispenser to regulate IOP

## Sustained Release Devices

- Questions to be considered:
  - Comfortability of device
  - Effectivity
    - Will it replace drops altogether or be replacement of one medication
    - Will OD's be granted rights to insert?
- What is taking so long?
  - Technicalities: Invention, investment, research
  - Modality and barriers within the eye itself
  - Comfortability/Usability for patients

## Drug-Loaded Contact Lenses Simplistic Concept That Has Not Worked

- Soak CL in lens storage solution with drug
  - Hydrophilic matrix of soft CL absorbs drug and then releases it by simple diffusion
  - Limited by drug kinetics which leads to rapid diffusion
  - Diffusion varies drug to drug, often in under one hour
  - Medication with preservatives may cloud CL or effect oxygen permeability
- Issues with both forms
  - Want linear release which is difficult to achieve
- New Codes for 2016
  - 0365T Drug eluting contact lenses

## Punctal Plug Drug Delivery Devices

- Insert slow-release medication depot into the punctum using a punctal plug
  - Plug may dissolved over time, be replenished or replaced
- Advantages
  - Track record of safety in using punctal plugs for dry eye
  - Minimally invasive and low-risk
  - Leverage existing medications used to treat glaucoma

## Punctal Plug Drug Delivery Devices

- Disadvantages
  - Prone to fall out over time which is not acceptable for chronic condition where months occur b/w visits
    - Need to overcome this problem such as improving patient awareness that plug has fallen out
  - Drug delivery is passive depending upon tears to wash into the plug reservoir and transport active drug back into the tear film
    - In cases of severe dry eye or lid anatomy pathologies, plug may not deliver drug in predictable manner
  - Current medications may not be ideal for drug delivery
    - Plug may not hold enough
    - Pulsed dosing as seen with topical use versus constant delivery with depot may lead to different efficacy
      - Prostaglandin not as effective when used in constant manner
- Efficacy varies from slightly less than timolol to close to a PG

## Bimatoprost SR

- Allergan
- Sustained release bioerodible implant that lasts 4-6 months with similar efficacy to eyedrops
- Small disolvable pellet is injected into the anterior chamber
  - Sits in/near the angle that resorbs over time
- Can be performed in the office
- Insert can be visualized in the inferior angle
- Ensures patient compliance
- Phase III trial underway comparing SR to timolol
- Will there ever be a need for removal?
- Could it cause cataracts?

## Bimatoprost SR Study Results

- Baseline IOP 25.2mm Hg
- Mean IOP reduction ranged from 7.2-9.5mm Hg at week 16
- Fellow eye IOP reduction 8.4 mm Hg with topical Bimatoprost eyedrops once daily
- Rescue therapy needed in 8% at week 16
- IOP reduction seen through 6 months
- At 6 months, 71% did not require rescue therapy or a 2<sup>nd</sup> injection