UNIVERSIDADE DE SÃO PAULO
FACULDADE DE MEDICINA DE RIBEIRÃO PRETO

BRUNA MELCHIOR SILVA

Frequência de testes complementares para detecção de progressão no glaucoma

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Versão corrigida

Tese apresentada à Faculdade de Medicina de Ribeirão Preto da Universidade de São Paulo para obtenção do Título de Doutor em Ciências.

Área de Concentração: Mecanismos Fisiopatológicos dos Sistemas Visual e Áudio-Vestibular.

Orientador: Prof. Dr. Jayter Silva de Paula

Coorientador: Prof. Dr. Carlos Gustavo Vasconcelos de Moraes

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FOLHA DE APROVAÇÃO

Aluno: Bruna Melchior Silva

Título: Frequência de testes complementares para detecção de progressão no glaucoma

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Dedicatória

Dedico todo meu trabalho aos meus pais, por estarem incansavelmente ao meu lado em todos os momentos da minha vida, celebrando minhas vitórias e minhas alegrias, aliviando minhas dores, me apoiando nas minhas dificuldades e sempre iluminando e facilitando meu caminho. Não sei o que seria de mim sem vocês e não tenho palavras para agradecer tanto amor, carinho e cuidado. Sou a pessoa mais abençoada do mundo pela sorte de serem vocês os meus pais. Vocês são minha força, minha luz e meu coração.

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Epígrafe

Se queremos dar a todo gênero feminino - e não apenas a poucas pessoas específicas - lugar nas estruturas de poder, precisamos pensar com mais afinco como e por que pensamos como pensamos."

Mary Beard, historiadora

Resumo

Silva BM. **Frequência de testes complementares para detecção de progressão no glaucoma.** Tese (Doutorado) - Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo. Ribeirão Preto. 2023.

Objetivos: Investigar a frequência de testes para otimização da detecção da progressão glaucomatosa nos exames de tomografia de coerência óptica de domínio espectral (SD-OCT) e Perimetria Acromática Padrão (SAP). **Métodos**: Dois bancos de dados de estudos clínicos multicêntricos prospectivos, o ADAGES (*African Descent and Glaucoma Evaluation Study*) e OHTS (*Ocular Hypertension Treatment Study*) e um *big data* multicêntrico retrospectivo (*Glaucoma Network Research*) foram utilizados nos estudos. Simulações computacionais foram realizadas para estimar o poder de detecção de glaucoma e a frequência ideal de testes em diversos cenários. As variáveis dependentes do estudo foram a *Mean Deviation* da SAP *e* a medida global de camada de fibras nervosas da retina peripapilar (pp-CFNR) da SD-OCT. Foram utilizadas as perimetrias com estratégias 10-2, 24-2 e 30-2, a depender do objetivo de cada estudo. A variabilidade dos exames da amostra real foi medida a partir do desvio padrão dos resíduos dessas variáveis. A população de estudo foi ampliada em diversos cenários a partir da distribuição normal dos resíduos, com simulação de 10.000 olhos em cada cenário. Foi, então, calculado o tempo para detectar progressão estatisticamente significativa ($p<0,05$), em cenários com poder de detecção do teste de 80% e 90%. **Resultados**: As SD-OCTs mais frequentes resultaram em menor tempo para detectar a progressão. Embora houvesse clara desvantagem para testes em intervalos de 24 *versus* 12 meses (22,4% de tempo [25 meses] de aumento no tempo para detecção de progressão) e ao testar 12 *versu*s seis meses (22,1% de tempo [20 meses] de aumento), a melhora do tempo para detectar a progressão foi menos pronunciada ao comparar seis v*ersus* quatro meses (11,5% de redução do tempo [10 meses]). Considerando o tempo para detectar a progressão em hipertensos oculares com poder de 80%, observou-se benefício maior para SAP a cada seis *versus* 12 meses e 12 *versus* 24 meses (aproximadamente 18% de redução do tempo em ambos) em comparação com quatro *versus* seis meses (aproximadamente 11,5% de redução de tempo), considerando a progressão de -0,42 dB/ano. Entre os diferentes padrões de SAP analisados, o tempo para detectar progressão significativa com poder de 80% foi menor com a SAP 10-2, com diminuição de 14,6% a 18,5% quando comparada à SAP 24-2 e redução de 22,9% a 26,5% quando comparada aos pontos centrais da SAP 24-2. A variabilidade da SAP 10-2 foi menor em relação ao 24-2 e aos pontos centrais do 24-2. **Conclusões**: Há vantagem no uso semestral da SD-OCT, porém pacientes de alto risco podem se beneficiar com intervalos de quatro meses (aqueles com glaucoma inicial e maior variabilidade na SD-OCT). Olhos com hipertensão ocular de alto e médio risco de conversão para glaucoma podem ser seguidos a cada seis meses, enquanto os de baixo risco podem ser acompanhados a cada 12 meses. Na comparação entre os padrões de SAP, o padrão 10-2 apresentou menor variabilidade quando comparado ao 24-2 e aos 12 pontos centrais do 24-2 e, por isso, apresentou melhor desempenho e menor tempo para detecção de progressão no glaucoma. Os achados deste estudo podem servir de base para orientação de seguimento na prática clínica do glaucoma, considerando características particulares dos paciente e as limitações do sistema de saúde.

Palavras-chave: Glaucoma. Variabilidade. Frequência. Campo visual. Tomografia de coerência óptica. Progressão.

Abstract

Silva BM. **Frequency of ancillary tests to detect progression in glaucoma.** Tese (Doutorado) – Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo. Ribeirão Preto. 2023.

Purpose: To investigate the frequency of tests to optimize the detection of glaucomatous progression in Spectral Domain Optical Coherence Tomography (SD-OCT) and standard automated perimetry (SAP). **Methods:** Two databases of prospective multicenter clinical studies, ADAGES (African Descent and Glaucoma Evaluation Study) and OHTS (Ocular Hypertension Treatment Study) and a retrospective multicenter big database (Glaucoma Network Research) were used in the studies. Computer simulations were performed to estimate glaucoma detection power and optimal frequency of testing in various scenarios. The dependent variables of the study were the Mean Deviation from the SAP and the global measure of the peripapillary retinal nerve fiber layer (pp-RNFL) from the SD-OCT. Perimetries with 10-2, 24-2 and 30-2 patterns were used, depending on the objective of each study. The variability of the tests in the real sample was measured from the standard deviation of the variable residuals. The study population was expanded in several scenarios based on the normal distribution of residuals, with a simulation of 10,000 eyes in each scenario. The time for detection of statistically significant progression ($P < 0.05$) was then calculated, in scenarios with test detection power of 80% and 90%. **Results:** More frequent SD-OCTs resulted in a shorter time to detect progression. Although there was clear evidence for tests at 24 versus 12 month intervals (22.4% time [25 months] increase in time to detection of progression) and when testing 12 versus 6 months (22.1% time [20 months] increase), the improvement in time to detect progression was less pronounced when comparing 6 versus 4 months (11.5% reduction in time [10 months]). Considering the time to prevent progression in ocular hypertensives with an 80% power, we observed a greater benefit for SAP at every 6 versus 12 months and 12 versus 24 months (approximately 18% time reduction in both) compared to 4 versus 6 months (approximately 11.5% time reduction) considering a progression of -0.42dB/year. Among the different SAP patterns analyzed, the time to detect significant progression with a power of 80% was shorter with SAP 10-2, with a decrease from 14.6% to 18.5% when discovered at SAP 24-2 and a drop from 22.9% to 26.5% when detected at SAP 24-2 midpoints. SAP 10-2 variability was lower in relation to 24-2 and the central points of 24-2. **Conclusions:** There is an advantage in the biannual use of SD-OCT; however, high-risk patients may benefit from 4-month intervals (those with early glaucoma and greater variability in SD-OCT). Eyes with ocular hypertension at high and medium risk of converting to glaucoma can be followed every 6 months, while low-risk eyes can be followed every 12 months. When comparing the SAP patterns, the 10-2 pattern showed less variability when compared to 24-2 and the 12 central points of 24-2 and, therefore, showed better performance and shorter time to detect progression in glaucoma. The findings of this study can serve as a basis for follow-up guidance in the clinical practice of glaucoma, considering both patient features and limitations of the health system.

Keywords: Visual field. Optical coherence tomography. Glaucoma. Progression. Frequency.

Lista de Símbolos e Abreviaturas

ADAGES- Estudo de Avaliação de Glaucoma em Afrodescendentes (sigla do inglês *African Descent and Glaucoma Evaluation Study*)

CFNR- Camada de Fibras Nervosas da Retina

CNO- Cabeça do Nervo Óptico

dB- Decibel

GHT- Do inglês *Glaucoma Hemifield Test*

GPA- Do inglês *Guided Progression Analysis*

MD- Desvio Médio (sigla do inglês, *Mean Deviation*)

OCT- Tomografia de Coerência Óptica (sigla do inglês *Optical Coherence Tomography*)

OHTS- Estudo do Tratamento da Hipertensão Ocular (sigla do inglês *Ocular Hypertension Treatment Study*)

PIO- Pressão intraocular

pp-CFNR- Camada de Fibras Nervosas da Retina Peripapilar

PSD- Do inglês *Pattern Standard Deviation*

SAP- Perimetria Acromática Padrão (sigla do inglês *Standard Achromatic Perimetry*)

SD-OCT- Sigla do inglês *Spectral Domain Optical Coherence Tomography*

SITA- Algoritmo de Limiar Interativo Sueco (sigla do inglês, *Swedish Interactive Threshold Algorithm*)

Vs- Versus

<- Menor que

>- Maior que

=- Igual

%- Percentagem

+- Mais

***-** vezes

SUMÁRIO

1- Introdução

1.1. Aspectos clínicos e epidemiológicos do glaucoma

O glaucoma é uma neuropatia óptica caracterizada pela perda lenta e progressiva de células ganglionares da retina e seus axônios, resultando em afinamento da camada de fibras nervosas da retina (CFNR), aspecto distinto da cabeça do nervo óptico (CNO) e perda de campo visual com padrão característico.[1-3] O glaucoma primário de ângulo aberto (GPAA) é o tipo mais comum e tem a sua classificação baseada no aspecto do ângulo irido-corneano à gonioscopia, onde ocorre a drenagem do humor aquoso. As bases biológicas da doença ainda não são completamente compreendidas, mas a pressão intraocular (PIO) é o único fator de risco tratável, diretamente relacionado à piora da doença.[4-7]

Pacientes com PIO estatisticamente elevadas (> 21 mmHg) e sem sinais de glaucoma (disco óptico e campo visual normais) são denominados como hipertensos oculares.[7] A prevalência de PIO maior que 21 mmHg entre diferentes populações, sem considerar presença ou ausência de diagnóstico de glaucoma, varia entre 0,3% e 8,9% em amostras grandes não selecionadas,[8,9] sendo a idade associada a níveis maiores de PIO.[10]

Embora o glaucoma seja frequentemente associado com PIO elevada, uma significativa proporção dos indivíduos apresenta pressões consideradas normais (≤ 21 mmHg) e são classificados como portadores de glaucoma de pressão normal.[11] Abaixar a PIO em pacientes com hipertensão ocular ou glaucoma reduz o risco de perda visual a longo prazo,[12] porém os resultados de longo seguimento do *Ocular Hypertension Treatment Study* (OHTS) demonstraram que apenas um quarto dos pacientes hipertensos oculares desenvolveram alguma perda perimétrica em algum olho durante 20 anos de seguimento.[13] Assim, nem todos os pacientes com PIO limítrofe ou elevada devem ser tratados, sendo que o médico deve avaliar a relação risco/benefício do tratamento em pacientes com moderado ou elevado risco de desenvolver glaucoma.[7]

No momento do diagnóstico de GPAA, os principais fatores de risco para evolução para a cegueira bilateral são PIO aumentada e perda avançada de campo visual, assim como longa expectativa de vida,[14] sendo que a média de idade em que se desenvolve cegueira bilateral devido a GPAA é de aproximadamente 86 anos.[15] A

não aderência ao tratamento também é fator de risco para cegueira,[16] porém idade, sexo e número de medicações não foram associadas à cegueira.[17]

O glaucoma é a principal causa de cegueira irreversível no mundo. Dentre as 33,6 milhões de pessoas cegas acima de 50 anos em 2020, 3,6 milhões foram devido ao glaucoma.[18,19] Entretanto, a doença é sub-diagnosticada. No Brasil, em estudo amostral, 90% dos pacientes com glaucoma avaliados não haviam recebido diagnóstico da doença antes do estudo.[20]

A perda de visão geralmente não é percebida até que a doença esteja bastante avançada.[4] Como a perda visual é insidiosa e mesmo em perdas avançadas ainda pode haver ilhas de visão, o paciente muitas vezes consegue atingir níveis de acuidade visual normais ou pouco alterados, principalmente nas fases iniciais da doença. Entretanto, a perda visual provocada pelo glaucoma vai além daquela medida pela acuidade visual, causando perda de contraste, de campo visual e da qualidade de vida, com prejuízos socioeconômicos, sendo assim um problema de saúde pública.[21-24] Por exemplo, adultos mais velhos com restrição de campo visual são mais propensos a terem colisões em acidentes de carro do que indivíduos não afetados pela doença.[25] Portadores de glaucoma também apresentam velocidade diminuída de leitura quando comparados a indivíduos saudáveis,[26] devido à influência na percepção de contraste. Esta limitação pode alterar a qualidade de vida e a função do paciente, já que a leitura é um hábito diário na atualidade. Mesmo pacientes com perdas leves de campo visual referem autopercepção de qualidade de vida reduzida, como sensação de dependência e dificuldades para dirigir e realizar outras atividades diárias que dependam da visão periférica.[27] Entre os pacientes com glaucoma, o medo de ficar cego aumenta de acordo com as dificuldades diárias, mais do que com as perdas de acuidade visual e de campo visual detectadas.[28]

Assim, o glaucoma transcorre com importante impacto econômico e social nas populações; necessitando, cada vez mais, de estratégias de saúde efetivas para rastreamento, diagnóstico precoce e tratamento adequado, visando a prevenção de perda visual e a diminuição dos danos causados pela doença.

Nos últimos anos, estudos têm mostrado avanços diagnósticos e terapêuticos que ajudaram a diminuir a incidência de cegueira após dez anos de diagnóstico de

glaucoma.[29] Entretanto, uma porcentagem considerável de portadores de glaucoma ainda apresenta cegueira: 25% unilateral e 10% bilateralmente.[30]

O diagnóstico e o acompanhamento do glaucoma são feitos com avaliação clínica (anamnese, biomicroscopia de câmara anterior, gonioscopia, fundoscopia e medida da PIO) e exames complementares, por meio de testes estruturais (como paquimetria, retinografia e tomografia de coerência óptica [OCT, da sigla em inglês para *Optical Coherence Tomography*]) e funcionais (como a Perimetria Acromática Padrão [SAP, da sigla em inglês *Standard Achromatic Perimetry*]). Exames complementares são essenciais para avaliação e seguimento do glaucoma, uma vez que a avaliação clínica de alterações da CNO é bastante subjetiva e apresenta pouca concordância interobservador. Alhadeff et al.[31] mostraram que sinais focais e difusos, observados nas retinografias (estereofotografias), corresponderam a sinais encontrados nas SAPs e OCTs, porém o contrário não se mostrou verdadeiro, uma vez que danos apresentados nas SAPs e OCTs frequentemente passaram despercebidos nas retinografias.

Uma vez que o glaucoma é diagnosticado, o principal objetivo é detectar precocemente a progressão da doença, com o intuito de prevenir ou retardar a perda visual por meio de tratamento adequado. Porém, o tratamento dispensado ao glaucoma depende do estágio da doença e da sua taxa de progressão, por isso a detecção de progressão depende substancialmente dos exames complementares.[32] Ademais, o tratamento do glaucoma não é isento de efeitos colaterais.[33] As mais variadas classes de medicamentos utilizadas causam efeitos indesejados, tanto localmente (hiperemia conjuntival, escurecimento da pele palpebral, crescimento dos cílios, alteração da coloração da íris, conjuntivite alérgica, ceratopatia epitelial etc) quanto sistemicamente (boca seca, cefaleia, sonolência, fadiga, arritmia, impotência sexual, broncoespasmo, etc...).[34] As cirurgias filtrantes aumentam o risco de infecções oculares, como blebite e endoftalmite; com prognóstico, muitas vezes, pouco favoráveis. Os procedimentos ciclodestrutivos também podem levar à diminuição da acuidade visual e *phtisis bulbi*. Assim, torna-se imperativa a avaliação criteriosa do paciente ao longo do tempo para a melhor conduta terapêutica[35] e, nesse sentido, os exames complementares exercem papel ainda mais fundamental no acompanhamento do glaucoma.

1.2 Métodos diagnósticos e avaliação da progressão do glaucoma

A avaliação da CNO e da retina é essencial para o diagnóstico e seguimento do glaucoma. Características importantes a serem avaliadas incluem relação escavação/CNO, rima neurorretiniana, coloração da CNO e a aparência da CFNR, dentre outras.[36] As alterações na CNO consistem no afilamento difuso ou focal da sua rima, especialmente nos polos inferior e superior. O exame da camada de fibras nervosas da retina adjacente ao nervo óptico fornece informações úteis em relação ao glaucoma. Em olhos saudáveis, observa-se o brilho característico da camada de fibras nervosas, que é relativamente espessa. Já no glaucoma, a refletividade da luz nessas regiões é reduzida, podendo ser ausente.[4] A avaliação clínica da CNO é melhor realizada na lâmpada de fenda por meio do uso de uma lente para visualização indireta. O oftalmolmoscópio direto é menos apropriado para tal exame devido a ausência de binocularidade e, consequentemente, ausência de esteroscopia.[4]

A documentação fotográfica da CNO e da camada de fibras nervosas pode ser realizada por meio de retinografia ou de estereofotografia. Entretanto, a análise dos exames apresenta muita variabilidade entre os examinadores, mesmo quando avaliado entre especialistas em glaucoma.[37] Além disso, fotografias não conseguem quantificar adequadamente e com detalhes suficientes a possível progressão glaucomatosa.[38] Assim, outros métodos tornam-se necessários para melhor seguimento da doença.

1.2.1 A Tomografia de coerência óptica (OCT)

A tecnologia da OCT revolucionou o diagnóstico e acompanhamento do glaucoma ao permitir uma avaliação objetiva das estruturas neurais por meio de aquisição de imagens de alta resolução e de forma não invasiva *in vivo*.[39-41] A OCT usa interferometria de baixa coerência para produzir imagem bidimensional de dispersão óptica de microestruturas tissulares internas de forma análoga ao eco do ultrassom, porém usando luz ao invés de som, com resolução axial muito alta (3 a 15 μm).[42] A tecnologia original de OCT com domínio de tempo atualmente vem sendo substituída pelas tecnologias de domínio espectral (SD-OCT, da sigla em inglês

Spectral Domain OCT) e por fonte de varredura (*swept source OCT*), que melhoraram a velocidade de aquisição e a resolução de imagem das estruturas oculares.[43]

A OCT supera algumas limitações das fotografias da CNO e pode ser usada para medidas da camada de fibras nervosas da retina peripapilar (pp-CFNR), da CNO e da mácula, sendo útil para diagnóstico e avaliação da progressão do glaucoma. A SD-OCT classifica o olho como normal, anormal ou limítrofe, comparando os valores advindos da varredura com o banco de dados de cada aparelho. A medida estrutural normal pode variar bastante entre os indivíduos, tornando possível uma perda neural significativa antes do paciente ser de fato considerado fora dos limites normais. Assim, estabelecer uma medida de base e observar mudanças ao longo do tempo ajuda a estabelecer melhor o diagnóstico e acompanhar a progressão, principalmente em suspeitos de glaucoma.[44]

1.2.2 A Perimetria Acromática Padrão (SAP)

A perda funcional no glaucoma é avaliada por meio da avaliação de perdas no campo visual por meio da perimetria. O campo visual é a região do espaço visível quando se fixa o olhar em determinado ponto, estendendo-se por 60º superiormente e nasalmente, 75º inferiormente e 100º temporalmente. O termo “perimetria” se deve ao fato de se avaliar o campo visual numa superfície curva, mantendo o ângulo visual constante. O objetivo da perimetria é determinar o limiar visual de cada ponto do campo visual, definido como o estímulo mais fraco visível em determinado local na condição do exame. A SAP "branco-no-branco" utiliza-se de estímulos luminosos estáticos, brancos e de tamanho constante sob fundo branco e continua a ser o teste mais comumente realizado para avaliar o campo visual, sendo as estratégias *full-threshold* (alteração de luminância em passos de 4-2 dB) atualmente amplamente substituídas pelo *Swedish Interactive Threshold Algorithm* (SITA - que utiliza funções ajustadas a cada resposta positiva ou negativa aos estímulos luminosos).[45]

Na SAP, é medida a sensibilidade a vários estímulos luminosos de intensidades variadas em cada ponto de teste do campo visual. É, então, elaborado um gráfico com os valores numéricos da sensibilidade de cada ponto e outro em

tons de cinza correspondente, para visualização mais direta e intuitiva do campo visual e de seus pontos de perda de sensibilidade. O valor limite calculado para cada ponto é, então, comparado a um banco de dados de indivíduos com visão normal e idade semelhante, sendo construído um novo gráfico, conhecido como "*Total Deviation*", em que valores negativos indicam valores abaixo do esperado. A média desses valores é referida como a variável MD (do inglês *Mean Deviation*).

Um quarto gráfico, o "*Pattern Deviation*", é, então, construído com o propósito de anular o efeito da redução geral de sensibilidade (devido à opacidade de meios, por exemplo), evidenciando defeitos localizados. Assim, o aparelho utiliza o 7º ponto menos negativo do gráfico *Total Deviation* e o transforma em zero, para comparar os outros pontos a este, ajustando assim a ilha de visão. Há mais dois gráficos que representam a probabilidade das alterações encontradas nos gráficos *Total Deviation* e *Pattern Deviation* serem estatisticamente significativas, fornecendo por meio de uma escala de cinzas as probabilidades de 0,5%, 1%, 2% e 5% das alterações estarem presentes na população normal.

Cada um dos seis gráficos da perimetria são divididos em quatro quadrantes por dois meridianos, que se cruzam no ponto central correspondente anatomicamente à fóvea. A "mancha cega" do gráfico, localizada temporalmente ao ponto central, corresponde à CNO. O meridiano horizontal corresponde à constituição histológica da rafe mediana da retina temporal.

Há vários programas de análise perimétrica. O padrão 30-2 mede os 30 graus temporais, nasais, superiores e inferiores à fóvea, testando 76 pontos separados à distância de seis graus. Já o padrão 24-2 mede 30 graus nasais e 24 graus temporais, superiores e inferiores à fóvea, testando 54 pontos separados também à distância de seis graus. O padrão 10-2 mede os 10 graus temporais, nasais, superiores e inferiores à fóvea, testando 68 pontos separados à distância de dois graus entre si.

Apesar de a perda visual glaucomatosa se iniciar tipicamente na periferia do campo visual e progredir de forma centrípeta, pode haver perda central, tanto como extensão da perda periférica quanto nos estágios iniciais do glaucoma.[46-48] O campo visual central, particularmente seus 10º centrais, tem relevante importância na função visual e está estreitamente relacionado à qualidade de vida.[49-51] Entretanto, o

programa de SAP 24-2, mais utilizado para o seguimento de glaucoma, tem capacidade limitada para detectar alterações centrais do campo visual. Os programas 30-2 e 24-2 avaliam somente 12 pontos nos 10º centrais da perimetria, enquanto o programa 10-2 avalia 68 pontos. Por isso, parte dos olhos com SAP 24-2 normal apresenta SAP 10-2 alterado[52], assim como a SAP 10-2 ajuda a confirmar casos suspeitos de glaucoma nos casos em que a SAP 24-2 perde essa detecção.[53]

Como a SAP é um exame subjetivo, há índices que permitem avaliar a confiabilidade do exame: taxa de perda de fixação (resposta a estímulo na mancha cega), taxa de falsos positivos (resposta positiva a estímulos não apresentados) e taxa de falsos negativos (resposta negativa a estímulo 9 dB mais forte que outro com resposta positiva prévia).

Vários critérios foram criados para se identificar um defeito provavelmente glaucomatoso na SAP. Dentre os mais utilizados estão os critérios de Anderson, a saber:[54]

- agrupamento de três ou mais pontos não periféricos no gráfico de probabilidades *pattern deviation* com p<5%, sendo um desses pontos com p<1%;
- valor do *pattern standard deviation* (PSD) ocorrendo em menos que 5% de campos visuais confiáveis normais presentes na "database" do aparelho (p<5%); ou
- *glaucoma hemifield test* (GHT) fora dos limites normais.

A partir da avaliação da SAP, pode-se analisar a gravidade do defeito a partir dos critérios de Anderson, Hodapp e Parrish:[55]

- defeito leve: MD >-6 dB, menos que 25% dos pontos no gráfico de probabilidades *pattern deviation* (gpPD) com p<5%, menos que 15% dos pontos do gpPD com p<1% e nenhum ponto dentro dos cinco graus da fixação com sensibilidade <15 dB no gráfico numérico;
- defeito moderado: MD >-12 dB e <-6dB, menos que 50% dos pontos do gpPD com p<5% e menos que 25% dos pontos do gpPD com p<1%, nenhum ponto dentro dos cinco graus com sensibilidade 0 dB no gráfico numérico, ou somente um hemicampo contendo um ponto com

sensibilidade <15 dB no gráfico numérico, dentro dos cinco graus da fixação;

- defeito avançado: MD <-12 dB, mais que 50% dos pontos com p<5% e mais que 25% dos pontos com p<1% no gpPD, qualquer ponto com sensibilidade <0 dB no gráfico numérico dentro dos cinco graus da fixação, ou ambos os hemisférios com um ponto ou mais pontos com sensibilidade <15 dB no gráfico numérico, dentro dos cinco graus da fixação.

A análise da progressão do glaucoma, verificável por meio de comparação da SAP, normalmente realizado na prática clínica, inclui geralmente três critérios:[56]

1) julgamento clínico: baseado na experiência do médico. Entretanto, esta análise pode variar muito entre os observadores.[57,58]
2) análise baseada em eventos: baseia-se no seguimento de exames a partir de um teste inicial (de base). A análise mais usada é a "Guided Progression Analysis" (GPA; Carl Zeiss Meditec, Inc), protocolo derivado do "Early Manifest Glaucoma Trial".[59] Quando a progressão em um ponto a partir do PSD é confirmada em dois exames, uma possível progressão é definida pelo GPA. Quando a progressão é observada em três ou mais exames, uma provável progressão é definida pelo GPA. O GPA oferece um método automatizado para detecção de progressão do campo visual que leva em consideração a variabilidade esperada para cada ponto. Além disso, a análise a partir do PSD dá mais ênfase a defeitos focais, que interessa mais ao glaucoma do que a defeitos difusos dos meios ópticos, que podem ser consequentes a catarata, superfície ocular ou opacidades em outros tecidos no eixo óptico.
3) análise baseada em tendência: envolve a análise sequencial de medidas globais do campo visual usando modelos de regressão linear. As medidas globais utilizadas podem incluir o MD, PSD ou *Visual Field Index* (VFI). A análise por tendência pode ser facilmente interpretada pelos pacientes, facilitando a participação na tomada de decisões

terapêuticas. Uma limitação dessa análise é a baixa sensibilidade em detectar progressão nos estágios iniciais da doença.

A habilidade em detectar progressão na SAP, em comparação com a da OCT, é influenciada significativamente pelo estágio da doença. Assim, olhos com doenças mais leves são melhores acompanhados com OCT, e olhos com doenças mais avançadas, com SAP.[60] Isso se deve ao fato mostrado em alguns estudos de que ao menos metade das células ganglionares da retina e seus axônios podem ser perdidos antes de surgirem alterações na SAP.[61,62] Assim, o dano precoce é visto mais frequentemente pela OCT, já que muita perda estrutural nessa fase geralmente corresponde a pouca ou nenhuma perda funcional. Já no glaucoma avançado, pequena perda estrutural representa importante perda funcional. Além disso, no glaucoma muito avançado, há o efeito *floor* da OCT: a camada de células nervosas não é composta somente por axônios das células ganglionares da retina, mas também por vasos sanguíneos e matriz extracelular. Desta maneira, com a perda total das fibras das células nervosas, a OCT também detecta o volume dessas outras células ainda presentes. Isso se deve ao fato de que a OCT não diferencia as células específicas das camadas da retina, mas somente a espessura das camadas. Dessa forma, o valor mínimo da medida da OCT nunca será zero, diferentemente da SAP. Destarte, em glaucomas avançados, a SAP tem grande importância no seguimento clínico.

1.3 Intervalo ideal de testes para detectar progressão glaucomatosa

A frequência ideal em que exames complementares devem ser feitos para detectar progressão no glaucoma ainda não é bem estabelecida na maioria dos cenários.

Para as perimetrias, Chauhan et al.[63] sugeriram que fossem realizadas seis SAPs nos primeiros dois anos de seguimento da doença, sendo os dois primeiros de base, com o objetivo de se obter boa documentação inicial e para conseguir detectar os progressores rápidos (que progridem com taxa maior que -2 dB/ano). Entretanto, Wu et al.[64] observaram pouco ganho adicional no tempo para detectar com 80% de poder a progressão de -2 dB/ano quando se realizavam testes duas vezes por ano

(2,4 anos) e três vezes ao ano (2,1 anos), além de terem percebido que o aumento da frequência de testes também aumenta a taxa de falsos positivos, além da evidente sobrecarga ao sistema de saúde. Por isso, concluíram que obter dois testes de base com seguimento posterior semianual, com teste adicional para confirmação de progressão e análise dos fatores de risco para possíveis ajustes, é uma boa estratégia nos primeiros anos de seguimento do paciente com glaucoma.

A avaliação dos pontos centrais se torna importante não só em perdas avançadas em que o paciente apresenta escotomas difusos com apenas ilhas de visão, mas também em estágios iniciais, dada a gravidade e o impacto na qualidade de vida que representa a perda de visão central. Não há, entretanto, dados suficientes sobre o poder e o tempo de detecção de progressão de diferentes padrões de SAP, especialmente 24-2 *versus* 10-2, tampouco comparações com o poder de detecção dos pontos centrais do próprio 24-2.

Da mesma forma, a frequência com que a OCT deve ser realizada no seguimento do glaucoma permanece incerta. Sociedades de Oftalmologia, como a *American Academy of Ophthalmology* (AAO) e a *European Ophthalmology Society* (EGS), recomendam, de maneira genérica, que pacientes com glaucoma que apresentam estabilidade devem ser seguidos clinicamente e com exames complementares a cada 6 - 12 meses, enquanto aqueles com sinais de progressão requerem acompanhamento mais frequente.[65,66] Entretanto, até este momento, há poucos dados que suportem essas recomendações. E apesar de alguns estudos prévios que avaliaram frequência de SAP recomendável em pacientes com glaucoma,[64] não há nenhuma investigação sobre qual seria a frequência de testes adequada para hipertensos oculares. O OHTS foi desenvolvido para estudar olhos com hipertensão ocular e sua associação com o glaucoma. Neste estudo, demonstrou-se que a diminuição da PIO reduziu a incidência de GPAA em 50%,[7] porém apenas 25% dos hipertensos desenvolveram glaucoma em 20 anos de seguimento, o que torna injustificável o tratamento de todos os pacientes com hipertensão ocular. Assim, como para aqueles já com diagnóstico de glaucoma, a detecção de progressão de hipertensão ocular para glaucoma exige monitoramento frequente para que se possa observar mudanças funcionais e estruturais a tempo de se intervir para prevenir perda visual.

2. Objetivos

2.1 Objetivo geral

Avaliar a frequência ideal de teste para otimizar a detecção de progressão glaucomatosa nos exames de SD-OCT e SAP, assim como avaliar como a variabilidade presente nesses exames poderia influenciar na determinação dessa frequência.

2.2 Objetivos específicos

- Investigar o tempo necessário para se detectar progressão significativa no GPAA com SD-OCT em olhos de pacientes em diferentes estágios da doença e diferentes taxas de progressão, usando como variável a medida global da pp-CFNR.

- Investigar o efeito de diferentes intervalos para realização de testes para se detectar progressão na SAP 30-2 em olhos com hipertensão ocular, usando como variável a MD.

- Comparar a variabilidade e o tempo de detecção de progressão na SAP 24-2, SAP 10-2 e nos 12 pontos centrais da SAP 24-2 em olhos com glaucoma, usando como variável a MD.

3. Casuística e Métodos

3.1 Bancos de dados do projeto

No presente estudo foram utilizados três bancos de dados:

- The African Descent and Glaucoma Evaluation Study (ADAGES) - registrado no site clinicaltrials.gov sob o número de inscrição NCT00221923 (Anexo A).
- The Ocular Hypertension Treatment Study (OHTS) - registrado no site clinicaltrials.gov sob o número de inscrição NCT00000125 (Anexo A).
- Glaucoma Research Network (GRN) (Anexo A).

3.1.1 The African Descent and Glaucoma Evaluation Study (ADAGES)

O ADAGES é um estudo prospectivo, observacional e multicêntrico, que inclui a University of California-San Diego, a Columbia University e a University of Alabama-Birmingham, todas dos Estados Unidos da América. Todos os participantes assinaram Termo de Consentimento Livre e Esclarecido e os Comitês de Ética em Pesquisa de cada instituição aprovaram a metodologia, que adere à Declaração de Helsinki. O recrutamento de pacientes começou em janeiro de 2003 e o acompanhamento durou até 2017 para este estudo.

Esse estudo foi desenhado com a finalidade de identificar fatores responsáveis pelas diferenças da apresentação e progressão do glaucoma entre indivíduos negros e brancos. O tratamento dos pacientes não seguiu protocolo específico, sendo indicado a critério médico. O desenho metodológico do ADAGES está devidamente descrito em artigo publicado pelo grupo.[67] Resumidamente, os participantes foram submetidos a exame oftalmológico completo, incluindo avaliação anual da história médica, acuidade visual corrigida, exame na lâmpada de fenda, medida da PIO com tonômetro de Goldmann, fundoscopia sob dilatação pupilar, paquimetria e estereofotografia da CNO. Houve também avaliação semestral de SAP Humphrey 24-2 usando SITA (Carl Zeiss Meditec, Inc., Dublin, CA, USA) e da estrutura da CNO e da pp-CFNR com SD-OCT (Cirrus HD-OCT software; Carl Zeiss Meditec, Inc., Dublin, CA, USA).

Para esse estudo, todos os participantes tinham mais de 18 anos, ângulo aberto, melhor acuidade visual corrigida ≥ 20/40, erro refrativo < 5,0 dioptrias esféricas e < 3,0 dioptrias cilíndricas. Ao menos uma estereofotografia e uma SAP confiável de base foram necessárias. Os dois olhos foram incluídos, exceto nos casos em que somente um olho atendia aos critérios do estudo. Pacientes diabéticos sem retinopatia também foram incluídos. Foram excluídos pacientes com história de cirurgia intraocular (exceto cirurgias de catarata e glaucoma não complicadas), causas secundárias de glaucoma, doenças oculares ou sistêmicas capazes de alterar o campo visual, comprometimento cognitivo importante, história de acidente vascular cerebral, doença de Alzheimer ou demência, problemas outros que afetassem a visão e cores ou inabilidade de realizar a SAP de forma confiável. Também foram excluídos pacientes com menos que cinco visitas e menos de dois anos de acompanhamento. Somente SD-OCT com força de sinal ≥6 e considerada de boa qualidade pelo *Imaging Data Evaluation and Analysis (IDEA) Reading Center* foram incluídos.

3.1.2 The Ocular Hypertension Treatment Study (OHTS)

O OHTS é um estudo multicêntrico prospectivo e randomizado, conduzido em 22 centros clínicos. É o estudo com o maior tempo de seguimento de hipertensos oculares.[13] Todos os participantes assinaram Termo de Consentimento Livre e Esclarecido e os Comitês de Ética em Pesquisa de cada instituição aprovaram a metodologia, que adere à Declaração de Helsinki (Anexo A). Esse estudo foi desenhado para avaliar a eficácia e a segurança de colírios hipotensivos na prevenção ou no retardo do aparecimento de perdas perimétricas e/ou da CNO em participantes com hipertensão ocular com risco moderado de desenvolver GPAA. O objetivo secundário foi identificar os fatores de risco que levavam a tais desfechos. O desenho metodológico do OHTS está devidamente descrito em artigo publicado pelo grupo[68] e no artigo desta tese. Resumidamente, os participantes foram randomizados nos grupos observacional e medicamentoso. O grupo medicamentoso iniciou tratamento para reduzir os níveis da PIO. Visitas de acompanhamento, SAP e

retinografias foram realizadas semestralmente, por um período mínimo de cinco anos.

O desfecho primário do estudo foi a detecção de uma alteração reprodutível na SAP ou o aumento da escavação da CNO atribuídos ao GPAA por um comitê. A confirmação de um defeito na SAP foi determinada como mudanças no *Glaucoma Hemifield Test* (GHT de dentro dos limites normais para fora dos limites normais, p<0,01), ou do *Corrected Pattern Standard Deviation* (CPSD com p<0,05) em originalmente duas, mas posteriormente três consecutivas SAPs confiáveis.[68] A progressão da CNO foi definida como afilamento generalizado ou localizado da sua rima comparada com a inicial, determinado por uma ou mais das seguintes características: desenvolvimento de *notch*, fosseta adquirida, palidez, mudança na posição dos vasos ou afilamento da rima.[68] O tratamento para esse grupo foi feito a critério médico.

Como já descrito, no presente estudo foram excluídos pacientes com menos que cinco visitas e menos de dois anos de acompanhamento. Também foram excluídas as SAPs que não alcançaram os critérios de confiança para os algoritmos *Full Threshold*: falso positivo, falso negativo e perda de fixação, todos < 33%; para SITA: falso positivo < 15%, falso negativo e perda de fixação < 33%.

Para as simulações, utilizou-se taxa de progressão de -0,42 dB/ano, que foi a taxa encontrada para hipertensos oculares que desenvolveram defeitos, tanto na SAP quanto na CNO ao longo do seguimento do OHTS,[69] em três níveis de risco de conversão para glaucoma: baixo, moderado e alto. Essa estratificação de risco foi feita de acordo com o seu risco inicial de desenvolver glaucoma em cinco anos, mensurado pela calculadora de risco do OHTS/*European Glaucoma Prevention Study* (EGPS):[70] abaixo de 6% (baixo risco), entre 6 e 13% (médio risco) e acima de 13%(alto risco). Para determinar um desfecho de progressão clinicamente significativa, estabeleceu-se a perda de -3dB no MD da SAP, valor selecionado a partir de relatos de perda de qualidade de vida a partir de tal perda, mensurados com o NEI-VFQ.[27,71] Em outras palavras, para cada grupo de risco (baixo, moderado e alto), foi calculado o tempo necessário para atingir uma perda clinicamente significativa (-3dB), assumindo taxa de progressão a -0,42 dB/ano.

3.1.3 Glaucoma Research Network (GRN)

O banco de dados do GRN compreende todas as SAPs realizadas em vários intervalos de tempo nas seis instituições participantes: Wilmer Eye Institute (Johns Hopkins University), Wills Eye Hospital (Thomas Jefferson University), Bascom Palmer Eye Institute (University of Miami), Massachusetts Eye and Ear (Harvard University), New York Eye and Ear Infirmary (Icahn School of Medicine at Mount Sinai) e Edward S. Harkness Eye Institute (Columbia University). Esse consórcio coletou grande quantidade de dados, de forma retrospectiva, de pacientes seguidos em cada serviço, sem que houvesse nenhum elemento identificador ou características clínicas/diagnósticas de qualquer participante, sendo considerado um "*big data*". A assinatura de Termo de Consentimento Livre e Esclarecido foi dispensada devido à natureza do estudo.

Para o presente estudo, foram selecionadas as SAPs 24-2 e 10-2 usando o algoritmo SITA (*Standard* e *Fast*), sendo excluídas as que não alcançaram os critérios de confiança: falso positivo < 15% e perda de fixação < 20%. Os falsos positivos não foram incluídos nos critérios de confiança pois poderiam excluir glaucomas avançados. Também foram excluídos pacientes com menos de cinco visitas e menos de dois anos de acompanhamento. Como esse banco de dados de SAPs não identifica os pacientes quanto a diagnósticos, foram considerados como olhos com glaucoma aqueles que apresentavam GHT fora dos limites normais e PSD < 0,05 em pelo menos três SAPs iniciais.

3.2 Coleta de dados

Os exames selecionados para estudo foram SAP e SD-OCT, para avaliar a progressão funcional e estrutural, respectivamente.

3.2.1 Perimetria Acromática Padrão (SAP)

Os exames de SAP foram realizados com o *Humphrey Field* (Carl Zeiss Meditec, Inc., Dublin, CA, Estados Unidos da América) utilizando os programas 10-2,

24-2 e 30-2 com a estratégia SITA-standard ou SITA-fast. As perimetrias foram utilizadas nas análises dos bancos de dados do OHTS e GRN. Em ambos os artigos em que foi avaliada a SAP acromática, a variável analisada foi a MD e, a partir dela, foram acessadas a severidade e a taxa de progressão do glaucoma.

3.2.2 Tomografia de coerência óptica (OCT)

Os exames de OCT foram realizados em um aparelho de domínio espectral (Cirrus HD-OCT software; Carl Zeiss Meditec, Inc., Dublin, CA, USA) para medir a espessura global da pp-CFNR, em microns, que é a medida de 360 graus da CFNR ao redor da CNO. No artigo em que foi estudada a SD-OCT, foram acessadas a severidade e a taxa de progressão do glaucoma a partir da variável pp-CFNR.

3.2.3 Outras variáveis

Nos bancos de dados do OHTS e do ADAGES, para avaliação demográfica, também foram colhidas outras informações como sexo, raça e idade, além do tempo de acompanhamento e quantidade de visitas.

3.3 Análise Estatística

As análises estatísticas para estimar a frequência ideal de testes foram realizadas por meio de simulações de computador a partir de dados da população real de cada banco de dados, de forma similar a estudos prévios.[72,73] Os detalhes específicos de cada estudo estão descritos com detalhes em cada artigo, de acordo com os objetivos de cada um e do banco de dados disponível, porém as simulações de computador foram feitas de forma semelhante em todos os casos e serão aqui detalhadas.

Para simular diferentes cenários e amplificar a amostra real, foram criados bancos de dados virtuais por meio de simulação de computador a partir de dados reais da população. Para criar esse banco de exames a partir da variável em estudo

(MD das SAPs ou medida global da pp-CFNR das SD-OCTs), procedeu-se da seguinte forma:

- Definiu-se, a partir do objetivo de cada estudo, o valor de base da variável dos pacientes de cada subgrupo a ser analisado da amostra;
- Definiu-se, para cada cenário e para cada objetivo, uma taxa de progressão da variável;
- Para simular os valores das variáveis próximas à população real, foi adicionado o valor da variabilidade real da população em cada teste simulado.

A variabilidade foi calculada a partir dos resíduos da variável em estudo. Para tanto, as taxas de progressão da população real foram calculadas por regressão linear da variável sobre o tempo, aplicando o teste do mínimo quadrado ordinário. Considerou-se como resíduo a diferença entre o valor estimado da regressão linear (valor da variável = variável de base + [taxa de progressão * tempo]) e o valor real individual de cada teste (da população real). Foi, então, calculado o desvio padrão desses resíduos para cada subgrupo de interesse em cada estudo.

Para amplificar substancialmente a amostra e criar diversos cenários que cumprissem os objetivos dos estudos, foram obtidas sequências de exames de 10.000 olhos virtuais para cada cenário, em que foram pré-definidos o valor de base da variável e sua taxa de progressão. O valor final da variável sobre o tempo foi calculado após adicionar os resíduos a partir da distribuição normal do seu desvio padrão com média zero. Assim, foi possível obter uma amostra grande com vários valores de base e várias taxas de progressão, simulando uma amostra real a partir dos seus resíduos, ou seja, sua variabilidade.

Para os estudos, a progressão foi definida quando um coeficiente negativo de progressão estatisticamente significativo ($p<0,05$) da variável estudada (MD da SAP e pp-CFNR da SD-OCT) foi detectado em duas visitas consecutivas. O tempo usado para detecção de progressão foi aquele em que se atingia 80 ou 90% de poder de detecção.

Para as SAPs, dadas as diferenças de sensibilidade entre os algoritmos SITA e *Full Threshold*, uma correção de +1,0 dB foi adicionada aos exames que usaram o

algoritmo *Full Threshold* para que fossem comparáveis, como realizado em estudos prévios.[74-76]

Os detalhes dos cenários das simulações de cada estudo, que variam conforme os objetivos de cada um, estão descritos nos respectivos artigos.

Todas as construções de simulações e a análise estatística foram realizadas utilizando o programa Stata 16 (StataCorp LP, College Station, TX, USA).

4. Resultados

Abaixo, encontram-se anexados os artigos relacionados a esta tese, na ordem que segue, com a devida autorização das respectivas editoras (Anexo B).

4.1 Frequency of optical coherence tomography testing to detect progression in glaucoma

Artigo publicado no *Journal of Glaucoma* em novembro de 2022 (Melchior B, De Moraes CG, Paula JS, Cioffi GA, Girkin CA, Fazio MA, Weinreb RN, Zangwill LM, Liebmann JM. Frequency of Optical Coherence Tomography Testing to Detect Progression in Glaucoma. J Glaucoma. 2022 Nov 1;31(11):854-859. doi: 10.1097/IJG.0000000000002101. Epub 2022 Aug 11. PMID: 35980865; PMCID: PMC9633358).

4.2 What is the optimal frequency of visual field testing to detect rapid progression among hypertensive eyes?

Artigo publicado no *Journal of Glaucoma* em novembro junho de 2023 (Melchior B, De Moraes CG, Paula JS, Cioffi GA, Gordon MO, Kass MA, Liebmann JM. What is the Optimal Frequency of Visual Field Testing to Detect Rapid Progression Among Hypertensive Eyes? J Glaucoma. 2023 Sep 1;32(9):721-724. doi: 10.1097/IJG.0000000000002260. Epub 2023 Jun 21. PMID: 37343189)

4.3 Variability and power to detect progression of different visual field patterns

Artigo publicado na *Ophthalmology Glaucoma* em novembro/dezembro de 2021 (Susanna FN, Melchior B, Paula JS, Boland MV, Myers JS, Wellik SR, Elze T, Pasquale LR, Shen LQ, Ritch R, Susanna R, Hood DC, Liebmann JM, De Moraes CG. Variability and Power to Detect Progression of Different Visual Field Patterns. Ophthalmol Glaucoma. 2021 Nov-Dec;4(6):617-623. doi: 10.1016/j.ogla.2021.04.004. Epub 2021 Apr 20. PMID: 33848653).

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Frequency of Optical Coherence Tomography Testing to Detect Progression in Glaucoma

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Synopsis/Precis: With high specificity and less variability than perimetry, more frequent testing resulted in shorter time to detect progression, though a 6-month testing interval

provides a reasonable trade-off for following glaucoma patients using optical coherence tomography.

ABSTRACT

Purpose: To investigate the time to detect progression in glaucomatous eyes using different optical coherence tomography (OCT) test intervals.

Methods: Participants with manifest glaucoma from the African Descent and Glaucoma Evaluation Study (ADAGES), a multicenter, prospective, observational cohort study, were included. A total of 2,699 OCT tests from 171 glaucomatous and 149 normal eyes of 182 participants, with at least 5 tests and 2 years of follow-up, were analyzed. Computer simulations (n = 10,000 eyes) were performed to estimate time to detect progression of global circumpapillary retinal nerve fiber layer thickness (cpRNFL) measured with OCT tests. Simulations were based on different testing paradigms (every 4, 6, 12 and 24 months) and different rates of change (μm/year). Time to detect significant progression ($P < 0.05$) at 80% and 90% power were calculated for each paradigm and rate of cpRNFL change.

Results: As expected, more frequent testing resulted in shorter time to detect progression. While there was clear disadvantage for testing at intervals of 24 vs 12 months (~22.4% time [25 months] increase in time to progression detection) and when testing 12 vs 6 months (~22.1% time [20 months] increase), the improved time to detect progression was less pronounced when comparing 6 vs 4 months (~11.5% time [10 months] reduction).

Conclusion: With high specificity and less variability than perimetry, a 6-month testing interval provides a reasonable trade-off for following glaucoma patients using OCT.

Keywords: optical coherence tomography, glaucoma, progression

INTRODUCTION

Glaucoma is an acquired optic neuropathy characterized by the death of retinal ganglion cells (RGC) and their axons and associated anatomical changes to the optic nerve head (ONH) and retinal nerve fiber layer (RNFL),[1–3] that results in irreversible vision loss. Once glaucoma is diagnosed, treatment decisions depend upon the rate of progression and aim to halt or slow further irreversible vision loss. Progression monitoring is often based upon clinical findings and ancillary testing, including functional (visual fields, VF) and structural (optical coherence tomography, OCT) tests.

Enabling non-invasive, high-resolution cross-sectional imaging of the retina in vivo, OCT has revolutionized the management and diagnosis of glaucoma, allowing objective evaluation of neural structures affected by the disease.[4–6] However, the optimal intervals at which the test should be administered to most effectively detect disease progression remains unknown. There are broad recommendations from the American Academy of Ophthalmology (AAO) and European Glaucoma Society (EGS) on how frequently patients should be followed with clinical and ancillary examination: in general, patients who have shown long-term stability can be followed every 6 to 12 months, depending on disease severity, whereas patients with evidence of progression may require more frequent follow-up.[7,8] However, to date there is scant data in the literature to support these positions and no consensus on the recommended frequency of OCT testing. This information is important and timely, especially during the SARS-CoV-2 (COVID-19) era, when the use of automated perimetry can be limited because of the risk of viral exposure.[9,10]

The purpose of this study is to investigate the statistical power and minimum time to detect statistically significant progression with OCT in eyes with established glaucoma at different levels of disease severity and rates of retinal nerve fiver layer (RNFL) change.

MATERIALS AND METHODS

Participants

The multicenter African Descent and Glaucoma Evaluation Study (ADAGES) collaboration (clinicaltrials.gov Identifier: NCT00221923) includes the Hamilton Glaucoma Center at the Department of Ophthalmology, University of California-San Diego (UCSD) (data coordinating center), Edward S. Harkness Eye Institute at Columbia University Irving Medical Center and the Department of Ophthalmology at University of Alabama-Birmingham (UAB). The institutional review boards at all sites approved the study methodology, which adheres to the tenets of the Declaration of Helsinki and to the Health Insurance Portability and Accountability Act. All participants gave written informed consent. ADAGES enrollment began in January 2003 and ended in July 2006, and follow-up continued into 2017 for this study.

ADAGES is an observational, prospective cohort study that aimed to identify factors accounting for differences in glaucoma onset and rate of progression between individuals of African (AD) and European (ED) descent with or suspected glaucoma. Treatment was applied at each physician's discretion.

The ocular testing performed in ADAGES has been described elsewhere.[11] In brief, participants underwent a comprehensive ophthalmic examination, including annual review of medical history, best-corrected visual acuity, slit-lamp biomicroscopy, intraocular pressure measurement (Goldmann tonometry), dilated funduscopic examination, pachymetry, simultaneous stereoscopic optic disc photography, and semiannual standard automated perimetry (SAP) Humphrey 24-2 field test using the Swedish interactive threshold algorithm (SITA) (Carl Zeiss Meditec, Inc., Dublin, CA, USA). The structure of the optic disc and RNFL was semiannually

measured with a variety of OCT scans, including spectral-domain OCT Optic Disc Cube Scans (Cirrus HD-OCT software; Carl Zeiss Meditec, Inc., Dublin, CA, USA).

Inclusion criteria

All participants had open angles, a best-corrected visual acuity ≥ 20/40, and a refractive error < 5.0 diopters sphere and < 3.0 diopters cylinder at study entry. At least one high-quality stereophotograph and one reliable SAP Humphrey 24-2 field test result at baseline were required. Both eyes were included, except in cases where only one eye met the study criteria. All participants were older than 18 years. Diabetic participants without evidence of retinopathy were included.

Exclusion criteria

Participants were excluded if they had a history of intraocular surgery (except for uncomplicated cataract surgery or uncomplicated glaucoma surgery), secondary causes of glaucoma (e.g., iridocyclitis, trauma), other systemic or ocular diseases known to affect the VF (e.g., pituitary lesions, demyelinating diseases, etc.), significant cognitive impairment, history of stroke, Alzheimer disease, or dementia, problems other than glaucoma affecting color vision, an inability to perform VF examinations reliably, or a life-threatening disease that precluded retention in the study.

In this study, patients with less than 5 visits and less than 2 years of follow-up were excluded. Only Cirrus Optic Disc Cube OCT scans with signal strength ≥ 6 and deemed of good quality by the Imaging Data Evaluation and Analysis (IDEA) Reading Center were included in this study.

Glaucoma Definition

Glaucomatous optic neuropathy was defined as excavation, neuroretinal rim thinning or notching, localized or diffuse retinal nerve fiber layer defect, or vertical cup-disc ratio asymmetry > 0.2 between eyes (not explained by differences in disc size) based on masked grading of stereophotographs by two graders using standardized protocols from the IDEA Reading Center. Only photographs of adequate quality were used for evaluation. Disagreements were resolved by consensus or adjudication by a third experienced grader. An abnormal 24-2 VF was defined if the pattern standard deviation was $P < 0.05$ or the Glaucoma Hemifield Test result was "outside normal limits." An abnormality had to be confirmed with an additional VF test.[11]

Simulations and statistical analyses

The methods employed for the simulation and definition of progression have been described elsewhere.[12–16] In brief, instead of VF data, rates of OCT progression for each eye were calculated after performing linear regression of global circumpapillary (cp) RNFL thickness (microns) over time (years) using ordinary least squares estimation. The residuals of the regression, defined as the difference between the best fitted value and the observed measurement of the cpRNFL average thickness were obtained for each data point of each eye. The standard deviation (SD) of these residuals were calculated for each 10 µm bin of the best cpRNFL thickness value (< 65 µm, 65 – 75 µm, 75 – 85 µm and > 85 µm). Because a previous study showed that residuals derived from VF testing (and, therefore, test variability) were different between individuals of African (AD) and European (ED) descent,[17] we also compared the variability of OCT RNFL thickness measurements between racial groups.

Computer simulations were used to estimate the time to detect progression with OCT with different testing paradigms (every 4, 6, 12 and 24 months). Using different rates of average cpRNFL

thickness change, we simulated different slopes for non-progressors (0 µm/year), approximated age-related loss (-0.5 µm/year),[15,16] "significant" glaucoma progressors (-1 µm/year)[16] and "rapid" glaucoma progressors (greater than the 95th percentile of slopes of glaucomatous eyes, (-2.5 µm/year). This was achieved by generating 10,000 sequences of OCT tests (or 10,000 simulated eyes for each scenario) where the "true" cpRNFL average thickness values were determined in 3 steps. First, the baseline values were stablished for each severity group:[18] early (90.5 µm), moderate (79.5 µm) and severe (65.9 µm) glaucoma. Second, the variability values were generated by the normal distribution of the residuals of our sample, divided for every 10 µm bin of best-fitted cpRNFL global thickness values (< 65 µm, 65 – 75 µm, 75 – 85 µm and > 85 µm). Third, different rates of change over time (0, -0.5, -1.0 and -2.5 µm/year) were simulated. The OCT testing paradigms required 2 tests at baseline followed by single tests performed at 4, 6, 12 or 24- month intervals. Progression was defined when a statistically significant ($P < 0.05$) negative cpRNFL average thickness slope was detected on 2 consecutive visits. The time to detect significant progression at 80% and 90% power was calculated for each baseline severity, rate of change, and testing paradigm. The simulations were done for the sufficient time to get 100% of progression detection. This time varies (from 5 to 20 years) according to cpRNFL average thickness slope, test intervals and glaucoma severity.

All statistical analyses and computer simulations were performed using Stata Version 16 (StataCorp LP, College Station, TX, USA).

RESULTS

A total of 2,699 OCT tests from 171 glaucomatous and 149 normal eyes of 182 participants were included. Mean ± SD age of the participants at baseline was 67.3 ± 10.4 years and the follow-

up time was 4.1 ± 1.1 years (range: 2.0 – 7.8 years) over 8.3 ± 3.3 visits (range: 5 – 19 visits). The median and interquartile range (IQR) of average baseline cpRNFL thickness were 76 µm (IQR: 66 to 84.5 µm). The demographic and baseline characteristics are summarized in Table 1.

The SD of cpRNFL thickness residuals for each 10 µm bin of their best fitted value are shown in Figure 1. The variability of cpRNFL thickness measurements were compared between AD and ED and there was no statistically significant difference between residuals in the overall sample ($p = 0.067$) and in eyes without glaucoma ($p = 0.913$), but we found significantly larger SD of residuals in AD compared to ED in eyes with glaucoma ($p = 0.021$). The ED patients had similar variability when comparing eyes with or without glaucoma ($p=0.112$), while AD patients had higher variability when they had glaucoma ($p=0.036$). The variability tended to be higher when average cpRNFL thickness was also higher, except in AD eyes with glaucoma in which the variability did not vary with RNFL thickness. There was no difference between signal strength of the OCT tests between AD and ED patients overall ($p = 0.116$) and when stratified by those with and without glaucoma ($p = 0.218$)

We analyzed the time and power to detect progression by severity group (early, moderate and severe glaucoma). The time to detect statistically significant progression (negative slope at $P < 0.05$) at 80% and 90% power for testing paradigms of 4, 6, 12 and 24-month intervals for each group, at different rates of cpRNFL change (-0.5, -1.0 and -2.5 µm/year), are shown in Table 2. Note that eyes with severe and moderate glaucoma (thinner cpRNFL at baseline) had similar time to detect progression across the different rates of change, whereas eyes with early glaucoma (thicker cpRNFL at baseline) required more time to detect progression.

As expected, more frequent testing resulted in shorter time to detect progression. Nonetheless, while there was clear disadvantage for testing every 24 vs 12 months (~22.4% time [25 months]

increase) and when testing 12 vs 6 months (~22.1% time [20 months] increase), the improved time to detect progression was less pronounced when comparing 6 vs 4 months (~11.5% time [10 months] reduction). The power to detect progression was comparatively higher in ED patients in moderate and severe glaucoma than early glaucoma, while AD patients did not demonstrate differences in the power to detect progression across the severity stages. Considering -6.0 µm as an estimate of clinically relevant global cpRNFL thinning,[19–21] testing at 6 or 4 month intervals appeared similarly effective in detecting early OCT changes in terms of statistical power of detection for different glaucoma severity stages.

When stable eyes were simulated (slope of average RNFL thickness = 0 µm/year), which estimates the false-positive rates for each group, the power to detect progression did not change among early, moderate and severe glaucoma. This false positive rate ranged between 1.01 and 2.04%, depending on testing intervals (Figure 2).

DISCUSSION

Based upon actual measurements of OCT variability from a large prospective cohort, we simulated different progression rates of OCT global cpRNFL thinning for different baseline levels of severity and various testing frequency paradigms. Our findings demonstrate, as expected, that more frequent testing increases the statistical power to detect progression of global cpRNFL thickness in patients with manifest glaucoma. Simulations also showed that more frequent testing (at intervals of 4 and 6 months) resulted in earlier detection of OCT changes among progressing eyes, particularly in those with less rapid slopes, with acceptable specificity (i.e., low false positive rates at slopes = 0 µm/year). Although Yu et al.[22] evaluated test frequency in their test-retest variability models, we

investigated time to detection OCT changes considering both different test intervals and stages of glaucoma severity, which are advantageous in routine settings.

Different rates of glaucoma progression are often observed in clinical practice among patients treated for long periods of follow-up, which can complicate early detection across the disease spectrum.[14,23,24] Because VF measures are subjective and have inherent short- and long-term variability at both central and peripheral regions,[14,24,25] OCT serve as a more objective biomarker for the follow-up of glaucomatous patients, as it correlates significantly with VF decay.[26,27]

The optimal frequency of VF testing was previously studied using computer simulations aiming to identify test intervals with greater power to detect statistically significant glaucoma progression.[14] Various models have been proposed to define clinically acceptable frequencies of testing, considering both time and power, based on global VF metrics (mean deviation, MD) trend slopes. Studies have found that 80% of fast progressors (eyes with MD slope of -2.0 dB/year) will be detected after 2-3 years, if tested at 6 month intervals.[14] Using comparable paradigms, we observed that 80% of eyes categorized as "rapid" progressors (cpRNFL thickness slopes of -2.5 μm/year) will be detected at 2.8, 2.5, and 2.5 years if tested at 4 month intervals, and at 3.1, 2.9, and 2.7 years if tested at 6 month intervals, for the early, moderate and severe OCT damage groups, respectively. Although the specificity to detect progressive changes differed little among the different testing frequencies (Figure 2), how "similar" two or more specificities seem is largely dependent upon their effect on sensitivity. Therefore, the results regarding the power and time to detect progression (Table 2) should be interpreted in light of these differences.

An "optimal" interval of testing should take into account the cost and benefits of prevention of visual impairment, quality of life, and life expectancy. Such parameters were not included in our analysis and warrant further evaluation. Nevertheless, assuming the time to detect more than - 3dB

loss in the VF MD as an estimate of significant vision impairment,[25,28] the approximate corresponding global cpRNFL thinning based upon reported structure-function graphs using Spectral Domain-OCT (SD-OCT),[19–21] is -6 to -8 µm in early of disease stages. Then, considering -6 µm as a significant threshold of global structural loss, both the 6 and 4 months-intervals testing showed a reasonable trade-off for detecting early OCT changes. Given the modest difference in effect when the 6- and 4-months are compared, we believe that the 6-month paradigm with SD-OCT provides a reasonable balance between statistical power, burden to patients and the needs of healthcare systems. Notwithstanding the above, specific groups of high-risk patients may benefit from shorter intervals of SD-OCT examination, such as 4 months, particularly those with early glaucoma. Interestingly, these conclusions are consistent with the frequencies observed for the VF testing.[14] The ease, speed, and reproducibility and patient preference of OCT strongly favor the use of OCT to detect rapid progression in clinical practice as compared to perimetry, which has a longer testing duration, is less reproducible, and is more burdensome to patients and technical staff.

Of note, we found greater variability among AD vs ED in glaucoma subjects, which is consistent with what has been reported with perimetry.[29] The clinical implication, similar to was reported with perimetry, is that progression detection may be delayed among AD patients. For that reason, clinicians may consider more frequent OCT testing among patients of AD. In addition, we found little effect of RNFL variability on severity in AD subjects, suggesting its greater robustness across disease severity stages compared to perimetry. Our findings are based upon the assumption of a normal distribution of residuals at the different severity bins, as previously done in studies using similar methodology. Future work on the effect of resampling residuals from non-normal distributions on the power and time to detect progression are warranted. Nonetheless, one should be

reminded that OCT summary statistics (e.g., global cpRNFL) appears less useful in later stages of the disease due to a floor effect.[30–33]

Our work has some limitations. The relatively small sample sizes limits the characterization of the differences between AD and ED. The lack of a gold-standard for glaucoma progression also affects the estimate of specificity. As reported in studies looking at VF progression, simulations of stable eyes over time have been used to estimate specificity. Moreover, test variability may be higher for the long- compared to short-term periods,[29] which can potentially impact the estimates of specificity in our study. Lastly, our results apply only to global cpRNFL measurements, and might be improved by an SD-OCT parameter that reflects the often localized nature of glaucoma progression.

In summary, these results provide guidance in optimizing the frequency of OCT testing to improve the power to detect statistically significant progression in glaucomatous eyes with different OCT severity levels and rates of change. These results can be used to develop validated guidelines for testing in clinical settings.

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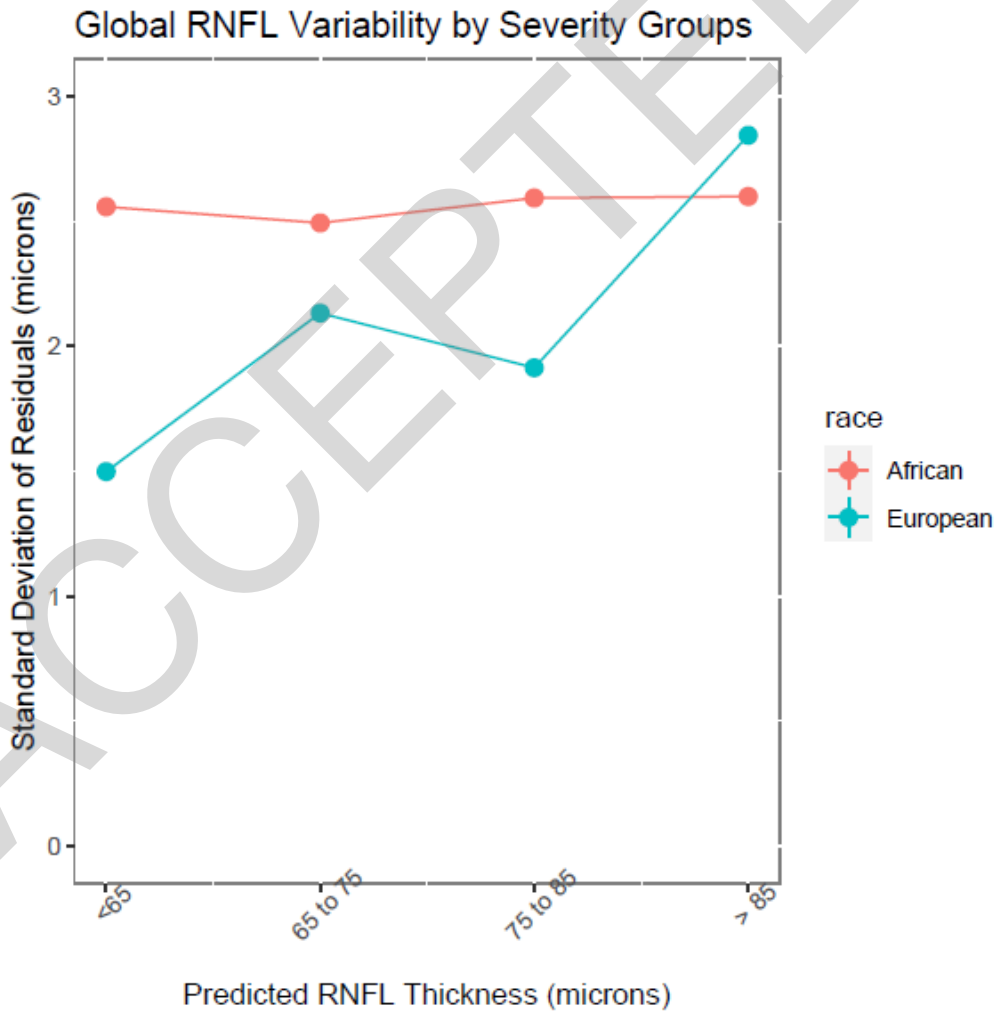
Figure 1. Variability of global circumpapillary retinal nerve fiber layer (cpRNFL) thickness measured with optical coherence tomography (OCT). The variability is described as the standard deviation (µm) of global cpRNFL thickness residuals at 4 levels of RNFL thickness, representing different stages of glaucoma severity. (A) Comparison in eyes with glaucoma by ancestry; (B) comparison in eyes without glaucoma by ancestry.



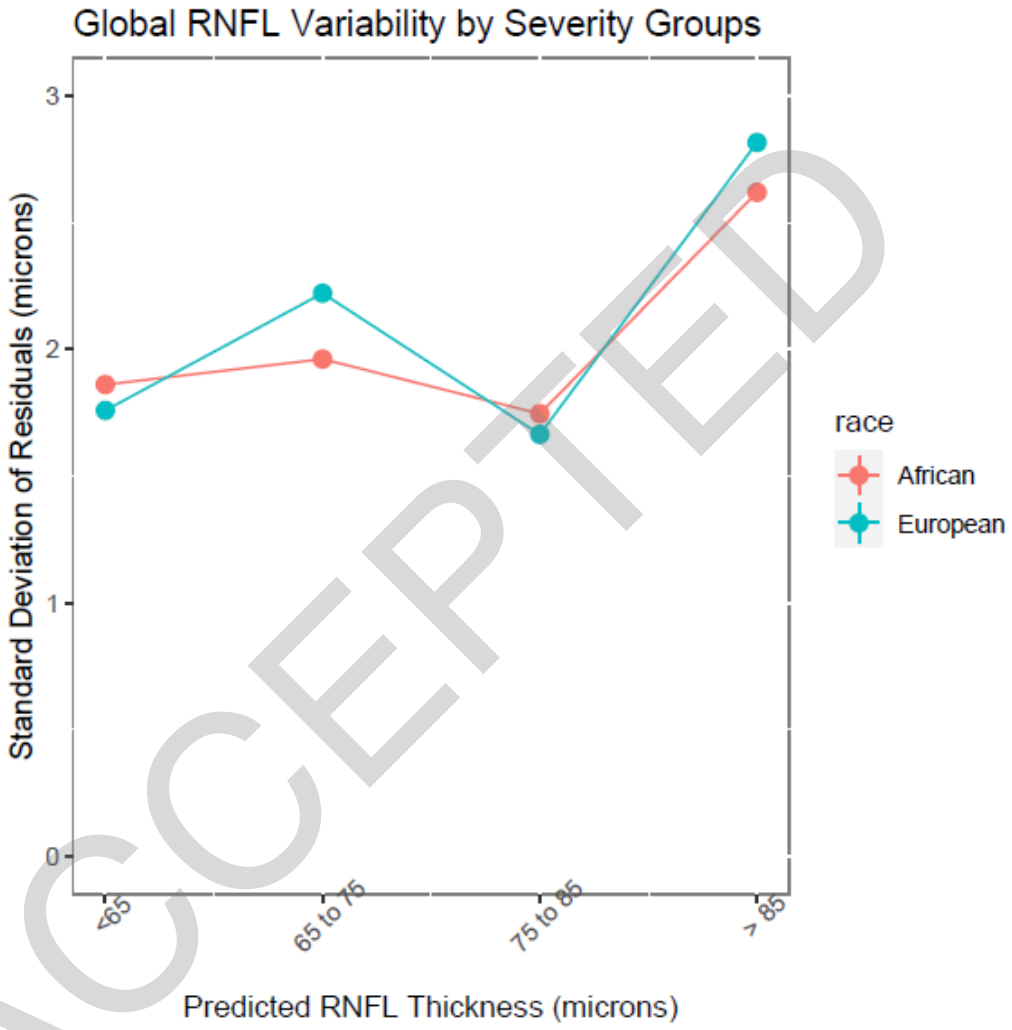


Figure 2. Power to detect progression (%) of retinal nerve fiber layer (RNFL) in stable eyes (slope of average RNFL thickness = 0 µm/year) with optical coherence tomography in different test intervals (4, 6, 12 and 24 months)

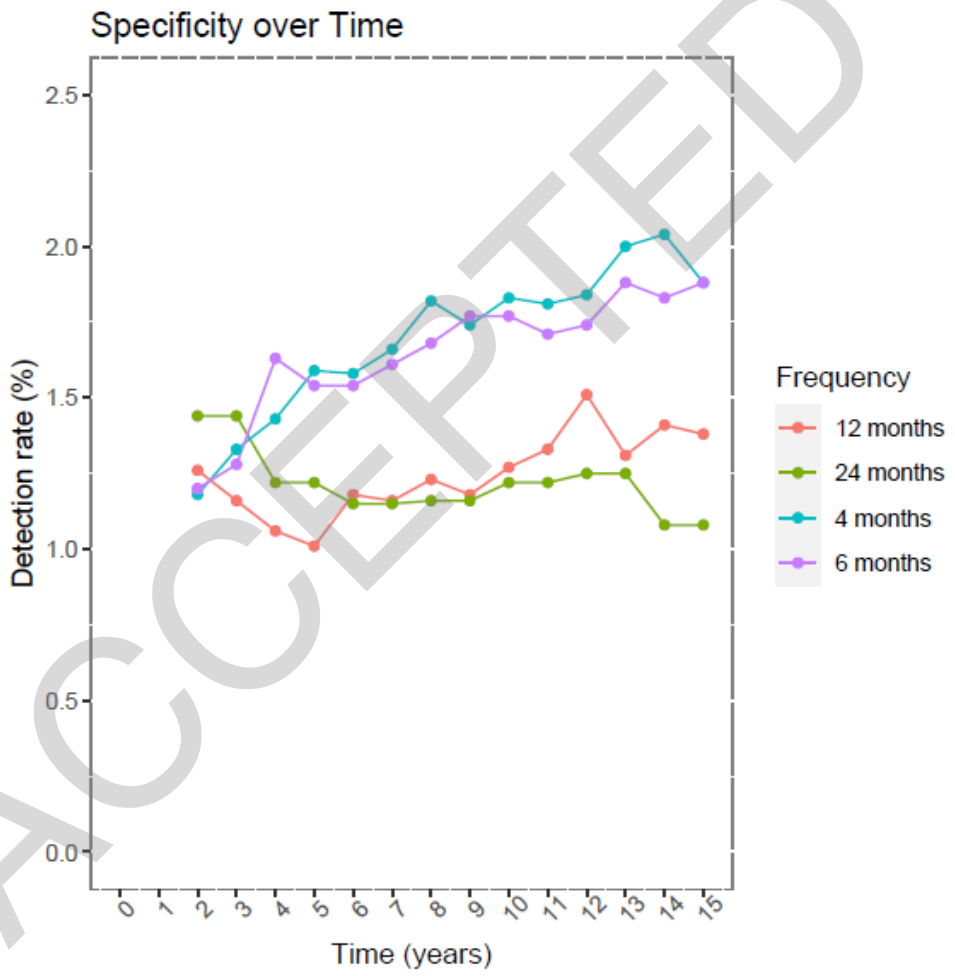


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Table 1. Patients and eyes characteristics

	African Descent	European Descent	Total	P Value
Patients	55 (30.2%)	112 (61.5%)	182 (100%)	-
Age (years)	63.9 (61.3 to 66.5)*	69.5 (67.6 to 71.3)*	67.3 (65.8 to 68.8)*	< 0.01
Gender				0.87
Male	26 (14.3%)	51 (28.0%)	86 (47.2%)	-
Female	29 (15.9%)	61 (33.5%)	96 (52.7%)	-
Eyes	99 (30.9%)	194 (60.6%)	320 (100%)	-
Eyes with Glaucoma	66 (20.6%)	87 (27.2%)	171 (53.4%)	-
Eyes without Glaucoma	33 (10.3%)	107 (33.4%)	149 (46.6%)	-
Follow-up Time (years)	4.0 (3.7 to 4.2)*	4.2 (4.0 to 4.4)*	4.2 (4.0 to 4.3)*	0.14
Total Visits	8.2 (7.5 to 8.8)*	8.4 (7.9 to 8.8)*	8.4 (8.1 to 8.8)*	0.85
Baseline Average cpRNFL (µm)	73.9 (70.9 to 76.8)*	77.2 (75.3 to 79.0)*	75.9 (74.5 to 77.5)*	0.16
Baseline Visual Field MD (dB)	-6.0 (-7.5 to -4.5)*	-3.2 (-4.0 to -2.4)*	-4.2 (-4.9 to -3.5)*	< 0.01
Eyes by Glaucoma Severity (RNFL thickness)				
< 65 µm	28 (8.7%)	31 (9.7%)	65 (20.3%)	
65 -75 µm	30 (9.4%)	53 (16.6%)	92 (28.7%)	
75 to 85 µm	19 (5.9%)	62 (19.4%)	85 (26.6%)	
> 85 µm	22 (6.1%)	48 (15.0%)	78 (24.4%)	

RNFL = Retinal Nerve Fiber Layer
MD = Mean Deviation
* Mean and 95% confidence interval

Table 2. Time (years) to detect progression at different statistical power of global circumpapillary retinal nerve fiber layer thickness with optical coherence tomography using different test paradigms.

	Time to Detect Progression (years) at 80% Power				Time to Detect Progression (years) at 90% Power			
	4-months interval	6-months interval	12-months interval	24-months interval	4-months interval	6-months interval	12-months interval	24-months interval
Slope - 0.5 µm/year								
Early Glaucoma	9.4	10.5	12.6	15.1	10.5	11.8	13.9	16.7
Moderate Glaucoma	7.4	8.5	10.5	13.0	8.3	9.5	11.9	14.7
Severe Glaucoma	7.7	8.7	10.7	13.1	8.5	9.6	11.8	14.5
Slope - 1 µm/year								
Early Glaucoma	5.7	6.3	7.5	9.0	6.4	7.0	8.4	10.1
Moderate Glaucoma	4.6	5.3	6.5	7.9	5.2	6.0	7.3	9.0
Severe Glaucoma	4.7	5.3	6.5	8.0	5.2	5.9	7.2	9.0
Slope - 2.5 µm/year								
Early Glaucoma	2.8	3.1	3.8	4.8	3.1	3.5	4.3	5.6
Moderate Glaucoma	2.5	2.9	3.6	4.4	2.9	3.3	4.1	5.1
Severe Glaucoma	2.5	2.7	3.4	4.3	2.8	3.1	3.8	5.1

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What is the Optimal Frequency of Visual Field Testing to Detect Rapid Progression Among Hypertensive Eyes?

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Keywords: ocular hypertension; visual field; frequency; progression

Short Title: Visual Field Frequency for Ocular Hypertensives

Abbreviations: intraocular pressure (IOP), primary open-angle glaucoma (POAG), visual field (VF), Ocular Hypertension Treatment Study (OHTS), Swedish Interactive Thresholding Algorithm (SITA), Mean Deviation (MD), central corneal thickness (CCT), clinically meaningful perimetric loss (CMPL), optical coherence tomography (OCT).

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ABSTRACT

Purpose: To investigate the time to detect progression of different visual field (VF) test intervals in eyes with ocular hypertension. To investigate the effect of different testing intervals on time to detect visual field progression in eyes with ocular hypertension.

Methods: A total of 16,351 reliable 30-2 VF tests from 1,575 eyes of the Ocular Hypertension Treatment Study 1 (OHTS-1) observation arm with a mean (95% CI) follow-up of 4.8 (4.7 to 4.8) years were analyzed. Computer simulations (n = 10,000 eyes) based upon MD values and

the residuals of risk groups (according to their baseline 5-year risk of developing POAG: low, medium and high risk) were performed to estimate time to detect progression with testing intervals of 4, 6, 12 and 24 months using linear regression. Time to detect VF progression (P < 5%) at 80% power was calculated based on the mean MD slope of -0.42 dB/year. We assessed time to detect a -3dB loss as an estimate of clinically meaningful perimetric loss (CMPL).

Results: At 80% power, based on progression of -0.42 dB/year, the best trade-off to detect significant rates of VF change to CMPL in high, medium, and low risk patients was 6-, 6-, and 12-month intervals, respectively.

Conclusion: Given the importance of not missing conversion to glaucoma, the frequency of testing employed in OHTS (6 months) was optimal for detection of progression in high-risk patients. Low risk patients could potentially be tested every 12 months to optimize resource utilization.

PRÉCIS:

We evaluated 16,351 visual field tests from OHTS database and showed that more frequent testing resulted in shorter time to detect glaucoma progression, with the best trade-off being the 6-month intervals for high-risk and 12 months for low-risk patients.

INTRODUCTION

Glaucoma is the leading cause of irreversible blindness worldwide, being responsible for 3.6 million cases (95% CI: 2.8–4.4) of blindness in those aged 50 years and older in 2020.[1] Elevated intraocular pressure (IOP) is the main risk factor for the development of primary open-angle glaucoma (POAG) and the only proven modifiable risk factor at present.[2–4] Patients with statistically elevated IOP (> 21 mmHg) and no signs of POAG (normal optic nerve head and normal visual field [VF] tests) are commonly designated as having ocular hypertension.[4] Prevalence of IOP levels greater than 21 mmHg varies across different populations, from 0.3% to 8.9% in non-selected large samples.[5,6] Colton & Ederer[7] showed that the distribution of IOP in the general population displayed a normal distribution curve of pressures up to 21 mmHg with a right skewness. In addition, age has been also consistently associated with higher mean level of IOP.[7]

Both the high prevalence and the relationship of ocular hypertension with POAG, a potentially blinding disease, raised several questions that were investigated in The Ocular Hypertension Treatment Study (OHTS). Initial results from this study demonstrated that lowering IOP decreased the incidence of POAG by 50%.[4,8] However, the low conversion rate from ocular hypertension to POAG may not justify the treatment of all ocular hypertensives, since only 25% of patients with ocular hypertension developed VF defects over 20 years of follow-up.[9] Close monitoring and risk factor assessment are crucial for the decision to treat or not to treat. Notwithstanding, it remains unclear how often untreated ocular hypertensive patients should be examined to determine if they are progressing and when treatment should initiated. Detection of progression from ocular hypertension to POAG relies on accurate observation of changes in either structural (optic nerve head and retinal nerve fiber layer) or functional (VF

tests) over time.[10–12] Although frequency of VF testing has been evaluated in terms of power and time required to identify progression in POAG patients,[13] there is currently no literature to our knowledge on the recommended frequency of VF testing in patients with ocular hypertension.[14] Of note, the recent COVID (there will be future pandemics) pandemic also intensified the debate on how frequently patients – particularly older patients with comorbidities – should come to eye care providers for imaging.[15]

Therefore, this study aims to investigate the ability of different VF test intervals to detect progression to POAG in eyes with ocular hypertension.

METHODS

The Ocular Hypertension Treatment Study (OHTS) is a multi-center randomized controlled clinical trial (clinicaltrials.gov Identifier: NCT00000125) conducted in 22 participating clinical centers. The institutional review boards at all sites approved the study protocol, which adheres to the tenets of the Declaration of Helsinki and to the Health Insurance Portability and Accountability Act. All participants gave written informed consent. OHTS enrollment began in February 1994 and ended in October 1996.

OHTS was designed to evaluate the safety and efficacy of topical ocular hypotensive medication in preventing or delaying the onset of VF loss and/or optic nerve damage in participants with ocular hypertension at moderate risk for developing POAG. The secondary aim of OHTS is to identify risk factors that predict which participants with ocular hypertension are most likely to develop VF loss and/or optic nerve damage due to POAG[8].

The OHTS study protocol has been described elsewhere[8]. In brief, at phase 1 (OHTS-1), eligible participants were randomized at their baseline/randomization visit to either the close

observation group or medication group. Participants randomized to the medication group began a stepped medical regimen to reduce IOP levels. Follow-up visits were at 6-month intervals for a minimum of 5 years or until a closure date determined by the Data and Safety Monitoring Committee. VF testing was performed every 6 months and optic disc photographs were obtained every 12 months.[8]

The primary study endpoint was the development of either a reproducible VF abnormality or reproducible progressive optic disc cupping attributed to POAG by an Endpoint Committee. A confirmation of VF abnormality was determined as changes on originally two, but later three, consecutive reliable VF tests in either the Glaucoma Hemifield Test (from normal limits to outside normal limits, $P < 0.01$) or the Corrected Pattern Standard Deviation (CPSD with $P < 0.05$).[8]

Optic disc progression was defined as generalized or localized thinning of the optic disc rim compared to baseline as determined by one or more of the following characteristics: development of a notch, acquired pit or pallor, change in the vessels' position or thinning of the rim.[8] Participants who developed POAG continued both the same follow-up schedule and examination protocol. The treatment course for this group of participants has been decided at the discretion of the treating clinician.[8]

Criteria for inclusion in this report

Participants in the observation arm of OHTS-1 were included in the present analyses. Patients with fewer than 5 visits or less than 2 years of follow-up were excluded. VFs that did not meet the established reliability criteria (for Full Thresholding testing: false positives, false

negatives and fixation loss, all < 33%; for Swedish Interactive Thresholding Algorithm [SITA]-SAP: false positives < 15%, false negatives and fixation loss <33%) were excluded.

Statistical analyses

Given the differences in sensitivity between SITA and Full Thresholding testing algorithms, a correction of +1.0 dB was added to test points of the full threshold tests, so that data from the transition between algorithms could be comparable, as done in previous studies.[16–18]

Least squares linear regression of MD values (dB) over time (years) was performed on the final, filtered database. The residuals were used to define the variability of each group and simulate different scenarios from real data. They were defined as the difference between the best fitted value and the observed measurement for MD at each time point, were obtained from the dataset and separated into 3 groups according to their baseline 5-year risk of developing POAG (as obtained from the OHTS/European Glaucoma Prevention Study risk calculator[19]: low, medium and high risk). The predictors for the development of POAG identified in this risk calculator were baseline age, IOP, central corneal thickness (CCT), vertical cup-to-disc ratio, and Humphrey VF pattern standard deviation (PSD).

Based upon the work of Demirel et al, [20] we defined -0.42 dB/year as a rapid rate of progression as it corresponded to the MD slope associated with eyes that developed both OHTS-defined visual field and optic nerve endpoints (hence more specific for glaucoma conversion).

Then, computer simulations were used to estimate the time to detect statistically significant VF progression with different testing frequencies (every 4, 6, 12 and 24 months) and a rapid MD rate of progression as defined above. This was achieved by generating 10,000 sequences of VF

tests where the "true" MD values derived from the predictions of each of the aforementioned slopes (MD = Baseline MD + Slope*Time), whereas the residuals were added after sampling from a distribution with mean of zero and standard deviation as calculated above for each of the 3 risk groups. The baseline MD used in each simulation was the mean baseline MD of each risk group. Similar methodology has been described elsewhere.[21,22]

The VF testing simulation paradigm included 2 tests at baseline and following-up with 4, 6, 12 or 24 months interval testing. The simulated' slopes of MD values (dB) over time (years) were re-calculated with least-squares linear regressions for each virtual eye. Progression was defined when a statistically significant ($P < 0.05$) negative MD slope was detected at 2 consecutive visits. The time to detect significant progression at 80% power was also calculated using ordinary least-squares linear regressions.

To assess a clinically meaningful event-based progression endpoint, we also assessed time to detect a 3dB loss in VF MD as an estimate of clinically meaningful perimetric loss (CMPL) for early glaucoma. In other words, for each risk group (low, medium, and high), we calculated how long it would take to reach a CMPL assuming a rapid MD slope (-0.42 dB/year). A 3 dB loss in MD was chosen as such amount of change previously reported to be associated with decrease in quality of life measured with the NEI-VFQ-25. [23,24] The 3 risk groups were estimated with the risk calculator developed by the OHTS and the *European Glaucoma Prevention Study* (EGPS),[25] which estimated the possibility of glaucoma conversion in 5 years: under 6% (low risk), 6-13% (medium risk) and over 13% (high risk).

All statistical analyses and computer simulations were performed using Stata Version 16 (StataCorp LP, College Station, TX).

RESULTS

A total of 16,351 reliable 30-2 VF tests from 1,575 eyes from 788 participants of the OHTS-1 observation arm were analyzed. The mean (95% CI) follow-up time was 4.8 (4.7 to 4.8) years spanning 10.4 (10.3 to 10.5) visits. The VF characteristics are summarized in Table 1.

Compared to low and medium risk groups, eyes at high risk of developing POAG presented higher MD variability based upon MD residuals (95% CI: 0.19-0.84; p = 0.002).

Considering the time to detect progression in ocular hypertensives at 80% power, we observed a greater benefit for testing every 6 versus 12 months and 12 versus 24 months (each yielding approximately 18% reduction of time) compared to 4 versus 6-month (approximately 11.5% reduction of time) across the proposed slope of progression (Table 2).

For the time to detect CMPL, we calculated the time needed to reach a 3 dB loss for each endpoint slope, for each risk group. The maximum interval of testing needed was considered as having the best trade-off. The results for all scenarios are shown in Table 3.

DISCUSSION

This study describes the intervals to detect significant VF worsening in patients from OHTS, the single cohort with the longest follow-up time in ocular hypertension.[9] Using computer simulations and combining conversion-to-glaucoma risk factors with VF MD slopes, we observed that testing intervals could be appropriate from 6 to 24 months depending on the paradigm examined. Based on our findings, clinicians may choose the best interval for repeating the VF test taking into account each patient's risk factors. Although previous studies evaluated the recommended frequency of VF tests in established glaucoma patients,[13] there is no study to

date investigating the optimal frequency of testing to detect VF progression among ocular hypertensives.

To evaluate better the interval options, we performed computer simulations on four paradigms of testing frequencies for -0.42 dB/year of MD change, based upon the work of Demirel et al,[20] and three levels of risk to conversion to glaucoma. As expected, shorter intervals were necessary for detecting CMPL in high-risk patients (6 months). Nevertheless, long-term results from OHTS demonstrated that only one-fourth of patients showed evidence of VF loss in either eye, while the low-risk patients presented with a cumulative POAG incidence of 31.7%.[9] Thus, our findings suggest a 12-month interval for low-risk patients (as long as they remain, adherent to follow-up visits). We speculate that lower test variability in OHT eyes and differences in endpoints and demographics might contribute to the disparate results from similar studies in VF testing.

Moreover, the actual time necessary to detect conversion to glaucoma may likely be shorter in clinical practice, if one includes all currently available diagnostic modalities, such as optic nerve head examination and optical coherence tomography (OCT).[26] By adding OCT into the clinical approach, relatively longer intervals could be considered in the "real-world" decision-making processes, as well as in further studies on the frequency of VF testing.

Notably, the actual test interval adopted in the OHTS (every 6 months) was the most adequate to detect rapidly progressing eyes, based upon our simulations, even though OHTS primary VF endpoint was an event- and not trend-based one. In clinical practice, rapidly progressing patients should not be missed and adopting a more frequent testing paradigm may have enabled the OHTS investigators to detect such group. Outside the clinical trial realm, where the availability of resources does not always replicate the real world, and in light of the OHTS

findings regarding risk calculation, clinicians can now customize the frequency of testing for each patient once the baseline risk variables are collected. This may ultimately reduce costs to patients and healthcare system as well as minimize risks associated with unnecessary office visits.[15]

This study has some limitations. 1) Although pointwise, event-based, and global trend–based methods have similar performances to detect glaucoma progression,[27] the use of a global metric such as MD does not detect local change, which can miss the conversion from ocular hypertension to glaucoma detected by pointwise changes. 2) These assumptions should be evaluated with caution as we arbitrary used an estimate for CMPL (loss of 3dB) that may not reflect the criteria for conversion from ocular hypertension to glaucoma, as applied in OHTS[8] and we did not investigate what the ideal frequency should be once patients are treated.

In conclusion, ocular hypertensive patients that present two or more reliable VF tests at baseline may be followed up with a 6-month interval for the high and medium risk participants and 12-month interval for the low risk ones. Since previous findings have presumed no clear benefit from intense monitoring of ocular hypertensive patients,[28] a combination of VF tests and structural analyses may enable further spacing of those intervals. Furthermore, our results may help reduce burden frequent office visits, particularly in low-risk patients.

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Table 1. Follow-up duration, number of visits and visual field characteristics (mean and 95% confidence interval) for eyes at low, medium and high baseline 5-year risk of developing Primary Open-Angle Glaucoma of selected eyes evaluated in OHTS.

	Low Risk	**Medium Risk**	**High Risk**	**P value**
Eyes (n)	550	505	520	-
Follow-up Time (yr.)	4.8 (4.8 to 4.9)	4.7 (4.7 to 4.8)	4.8 (4.7 to 4.8)	0.04
Visits (n)	10.4 (10.3 to 10.5)	10.2 (10.1 to 10.4)	10.5 (10.4 to 10.6)	0.04
Baseline MD (dB)	1.25 (1.15 to 1.35)	1.45 (1.33 to 1.56)	1.16 (1.05 to 1.27)	< 0.01
MD slope (dB)	-.02 (-.07 to -.02)	-.04 (-.07 to -.01)	-.13 (-.17 to -.09)	< 0.01

MD = visual field mean deviation

Table 2. Time to Detect Progression at 80% Power According for Testing Intervals of 4, 6, 12 and 24 Months in Eyes with Low, Medium or High baseline Risk of Developing Primary Open-Angle Glaucoma in 5 Years Progressing at -0.42 dB/year.

	Time to Detect Progression (years)			
	4 mos interval	**6 mos interval**	**12 mos interval**	**24 mos interval**
LOW RISK	5.3	6.0	7.2	8.8
MEDIUM RISK	5.4	6.1	7.4	9.1
HIGH RISK	6.2	7.0	8.5	10.4

Table 3. Test Interval to Detect VF loss of -3dB based on progression rate of -0.42 dB/year in Eyes with Low, Medium or High Risk of Developing Primary Open-Angle Glaucoma in 5 Years at 80% power.

Risk of Progression	**Test Interval (months)**
LOW RISK	12
MEDIUM RISK	6
HIGH RISK	6

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Variability and Power to Detect Progression of Different Visual Field Patterns

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Purpose: To compare the variability and ability to detect visual field (VF) progression of 24-2, central 12 locations of the 24-2 and 10-2 VF tests in eyes with abnormal VFs.

Design: Retrospective, multisite cohort.

Participants: A total of 52 806 24-2 and 11 966 10-2 VF tests from 7307 eyes from the Glaucoma Research Network database were analyzed. Only eyes with $\geq$ 5 visits and $\geq$ 2 years of follow-up were included.

Methods: Linear regression models were used to calculate the rates of mean deviation (MD) change (slopes), whereas their residuals were used to assess variability across the entire MD range. Computer simulations (n = 10 000) based on real MD residuals of our sample were performed to estimate power to detect significant progression ($P < 5\%$) at various rates of MD change.

Main Outcome Measures: Time required to detect progression.

Results: For all 3 patterns, the MD variability was highest within the −5 to −20 decibel (dB) range and consistently lower with the 10-2 compared with 24-2 or central 24-2. Overall, time to detect confirmed significant progression at 80% power was the lowest with 10-2 VF, with a decrease of 14.6% to 18.5% when compared with 24-2 and a decrease of 22.9% to 26.5% when compared with central 24-2.

Conclusions: Time to detect central VF progression was reduced with 10-2 MD compared with 24-2 and C24-2 MD in glaucoma eyes in this large dataset, in part because 10-2 tests had lower variability. These findings contribute to current evidence of the potential value of 10-2 testing in the clinical management of patients with glaucoma and in clinical trial design. *Ophthalmology Glaucoma 2021;■:1−7 © 2021 by the American Academy of Ophthalmology*

The main goal of glaucoma therapy is to prevent vision loss and preserve quality of life.[1,2] For this purpose, detection of visual field (VF) change is crucial to clinical management.[3,4] Although glaucoma VF loss has been shown typically to begin in the periphery, central visual field (CVF) damage can occur either after peripheral loss extends to fixation or as the primary location of damage.[5−7] The CVF, the central 10 degrees of the VF, is particularly important in visual function, and its loss has been demonstrated to correlate with self-reported quality of life.[8−10]

Despite the recognition of the importance of CVF, the currently most used 24-2 VF test pattern has limited ability to detect abnormalities and monitor changes in this area,[11−14] compromising the ability to monitor and treat glaucoma, especially at advanced stages when the risk of blindness and impact on quality of life are the greatest. With the 10-2 pattern, there is a significant increase in sampling density of the CVF, which can improve assessment of macular damage.[7,11,13−15] Among eyes with normal 24-2 VF tests, 16% can actually be classified as abnormal when tested with the 10-2 pattern,[13] which can also help confirm glaucoma diagnosis in glaucoma suspects missed by the 24-2 pattern.[16]

Previous studies suggested that CVF progression was more often detected on the 10-2 pattern compared with the central locations of the 24-2 in glaucomatous eyes. Park et al[17] demonstrated a 6-fold increase in detection of progression with 10-2 compared with the central 24-2. However, by using pointwise linear regression analysis, these results could be affected by the higher sampling density of the 10-2. Rao et al[11] showed that the slope of VF mean deviation (MD) for the 10-2 test was significantly more negative compared with the 24-2 test in eyes with more severe glaucomatous VF loss at baseline (MD <12 decibels [dB]). More recently, Wu et al[18] demonstrated in a cohort of 300 eyes that trend-based analyses showed reduced time to detect progression using 10-2 tests compared with the central test locations of the 24-2, but this improvement was only mild (7%−9%).

Large sets of real-world data may complement the findings from these previous studies. By accessing information from a more representative patient population, big data studies are able to find subtle but clinically relevant results that would have remained statistically insignificant in smaller studies.[19] To that end, this study will use the data

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gathered by the Glaucoma Research Network, a research consortium composed of 6 member institutions with VF data contributed by each institution, closely depicting the profile of patients that present to academic eye clinics in the United States.

Given the conflicting reports and insufficient information available pertaining to the power and time to detect progression of different VF patterns, the purpose of this study is to compare the variability and the ability to detect VF progression of 24-2, central 12 locations of the 24-2 VF test, and 10-2 VF tests in eyes with abnormal VFs. We hypothesized that the 10-2 VF test would be associated with a reduced variability and time to detect progression compared with both full and central locations of the 24-2.

Methods

The Institutional Review Boards at all sites approved the creation of the de-identified database of VF tests. The study adheres to the tenets of the Declaration of Helsinki. Written informed consent was waived given the retrospective nature of the study.

Visual field tests were selected from the Glaucoma Research Network database, which comprises all VF tests (standard automated perimetry) performed over varying time periods at its member institutions: Wilmer Eye Institute (Johns Hopkins University), Wills Eye Hospital (Thomas Jefferson University), Bascom Palmer Eye Institute (University of Miami), Massachusetts Eye and Ear (Harvard University), New York Eye and Ear Infirmary (Icahn School of Medicine at Mount Sinai), and Edward S. Harkness Eye Institute (Columbia University). The complete, unfiltered dataset contains 963 913 VFs from 357 602 eyes from 190 144 patients. Patients in the dataset were treated at the discretion of attending physicians.

Inclusion and Exclusion Criteria for This Study

The subset of 24-2 and 10-2 VF tests performed using the Swedish Interactive Thresholding Algorithm (Standard and Fast) with white-on-white stimuli of size III were selected. The 12 central point locations of 24-2 were used to create a "central 24-2" VF test (Fig 1). For the C24-2 VF test, a new MD was created with the mean of the total deviation of the central points. We did not use the new 24-2C pattern because not enough data had been collected at the time of this study.

Visual fields that did not meet the established reliability criteria,[20] defined as having less than 15% false-positive errors and less than 20% fixation losses, were excluded. We did not filtrate false-negatives because this could translate to exclusion of advanced glaucoma.[21] Eyes with less than 2 years of follow-up and eyes with less than 5 VF tests were also excluded. Only eyes with a Glaucoma Hemifield Test outside normal limits or pattern standard deviation (SD) probability less than 0.05 on at least 3 of the first VF tests were included.

Global Analysis

To measure the MD variability, ordinary least-squares linear regressions were applied to the 10-2, 24-2, and central 24-2 MD values over time for each eye. The residuals, defined as the difference between the best-fitted MD value and the real MD measurement, were obtained. Individual subjects were grouped into 5-dB intervals to compare the MD variability between each pattern of VF (10-2, 24-2, and central 24-2), and the MD variability was defined as the SD of residuals. Intervals of 5 dB were selected to equalize the sample sizes and to approximate to MD parameters used in clinical practice: >-5 dB to mild glaucoma, -5 to -10 dB to moderate glaucoma, and <-10 dB to severe glaucoma.

Computer simulations were first used to find a criterion that matched the specificities of the trend-based analysis of the 10-2, 24-2, and central 24-2 MD values after 5 years of follow-up. This was achieved by generating 10 000 sequences of VF tests for each VF pattern using their mean of MD residuals and baseline MD from our database. The VF testing paradigm involved 2 tests at baseline and tests at 6-month intervals over a 5-year follow-up period. The P values for the statistically significant MD slope that resulted in a 5% progression rate by the end of the 5-year follow-up period (fifth percentile or 95% specificity) were determined. They were $P = 0.052$, $P = 0.046$, and $P = 0.047$ for 24-2, 10-2, and central 24-2, respectively. These values were used to define progressors in our real database. Because there was no meaningful difference using $P = 0.05$ versus the P value for matched specificity, we opted to use 0.05 for all analyses.

Next, computer simulations were used to find the power and time to detect VF progression by generating 10 000 sequences of VF tests using MD residual values of each severity group for 10-2, 24-2, and central 24-2 MDs from our database and -2 dB as baseline MD. The time of follow-up of the simulation was 10 years plus a confirmation test 6 months later. The rates of change of -0.25, -0.50, and -1.00 dB/year were used in separate analyses for each pattern of VF. The rate of change of 0 dB/year was used to simulate nonprogressors as an estimate of false-positives. The power to detect progression after 2 to 10 years was calculated using ordinary least-squares linear regressions. All statistical analyses and computer simulations were performed using Stata Version 16 (StataCorp LP).

Results

Database Characteristics

A total of 64 772 reliable VF tests (52 806 24-2/central 24-2 and 11 966 10-2) from 7307 eyes of 5476 patients from the Glaucoma Research Network database were analyzed. A total of 11.0% of the 24-2 VF tests were from eyes that also had their 10-2 VF analyzed, and 48.5% of the 10-2 VFs were from eyes that did not have suitable 24-2 VFs to be analyzed in this study. Baseline patient ages ranged from 18 to 80 years, and follow-up ranged from 2.0 to 18.3 years. The characteristics for each pattern of VF are shown in Table 1.

VF Variability

Figure 2 compares the SD of MD residuals for the 10-2, 24-2, and central 24-2 tests. The results show the commonly reported increasing variability with increasing VF damage until -20 dB. There was a lower variability with 10-2 for all MD bins compared with the 24-2 ($P \leq 0.0025$) and the C24-2 (P 0.0015, variance ratio test).

False-Positives

The false-positive rates, estimated by simulating nonprogressors, are shown in Figure 3. The power to detect progression when the MD slope was 0 dB/year varied between 1.01% and 1.76% when tested every 6 months and a follow-up test had to confirm the patient was progressing.

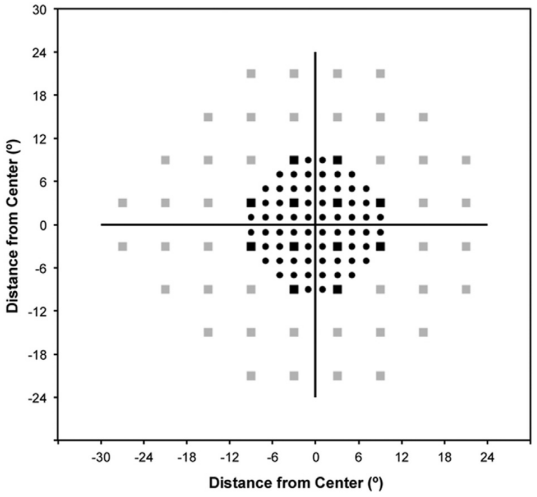

Figure 1. Diagram of the 24-2 **(grey square)**, central 24-2 **(black square)**, and 10-2 **(black circles)** visual field (VF) test locations.[18]

Power and Time to Detect Progression

As shown in Table 2, the power to detect VF progression with 2, 5, and 10 years of follow-up was consistently higher with the 10-2 test. Overall, at 80% power, the 10-2 reduced the time required to detect VF progression by 14.6% to 18.5% when compared with 24-2 and 22.9% to 26.5% when compared with central 24-2 (Table 2). In particular, the time to detect significant progression ($P < 5\%$) at 80% power differed by up to 2 years among 10-2, 24-2, and central 24-2 VF tests when the MD rate of change was −0.50 dB/year. This difference decreased to 1.2 years when the MD slope was −1.00 dB/year.

Additionally, we compared results using moderate (−6 dB) and severe (−12 dB) baseline MD levels with a −1 dB/year progression rate. At 80% power, the 10-2 reduced the time required to detect VF progression by 14.2% when compared with 24-2 and 21.3% when compared with central 24-2 at 5 years using a baseline MD of −6 dB. By using −12 dB as baseline, the reduction was by 31.12% and 25.9% when compared with the 24-2 and central 24-2, respectively.

Discussion

We analyzed the variability and the ability to detect VF progression with different test patterns using simulations based on a large, real-world dataset. We showed increasing variability with worsening of MD values and a consistently lower variability using MD values from 10-2 compared with values from both full and central 24-2. Global trend-based analysis also showed improved ability to detect VF progression with 10-2 when compared with 24-2 and central 24-2. These findings enhance our understanding of the different available strategies to detect VF worsening and corroborate previous studies showing the value of adding 10-2 to routine practice.[11,22–25]

The baseline MD values of 24-2 and central 24-2 were similar, whereas they were lower with 10-2 VF. This finding was expected, because the 24-2 strategy can miss up to 61.5% of CVF damage seen on the 10-2 test.[22,24–26] Furthermore, it is also expected that less severe VFs will be weighted more heavily in the 24-2 database because the 10-2 pattern is usually used in patients with more severe glaucoma, whereas the 24-2 is the main pattern used in clinical practice. It is important to note that the patients in this study were followed at academic centers with large referral bases; thus, the baseline in this study may not refer to the first examination a particular patient has received, but to the first test encountered in the dataset. Moreover, all the patients in this study had at least 3 abnormal VFs at baseline.

The literature shows conflicting data on the extent of the improvement in detection of CVF progression comparing the 10-2 with 24-2. A previous study found that the median rate of MD change in 9 years was 0.19 dB/year and 0.26 dB/year on 24-2 and 10-2 fields, respectively, and this difference increased in eyes with worse MD.[11] Park et al,[17] using a pointwise linear regression analysis, detected progression in 48%, 22%, and 8% of glaucoma eyes with 10-2, 24-2, and central 24-2, respectively. The significantly higher mean global progression rate in 10-2 VF can be partially attributed to the fact that all subjects in this referred study had an initial parafoveal scotoma at baseline that was limited within the central 10 degrees. Furthermore, despite being a helpful tool in detecting VF progression,[23,27] pointwise linear

Table 1. Database Characteristics

	10-2	24-2	Central 24-2	*P* Value
No. of eyes	1404	6641	6641	—
OD	667	3195	3195	0.91
OS	737	3446	3446	
No. of participants	1063	5048	5048	—
No. of VFs	11 966	52 806	52 806	—
Baseline MD, dB (SD)*	−13.69 (±7.95)	−9.16 (± 6.5)	−8.47 (±6.84)	<0.01
Follow-up, yrs (SD)*	6.3 (±2.7)	6.6 (±2.7)	6.6 (±2.7)	<0.01
Age, yrs (SD)*	63.2 (±11.5)	63.9 (±11.1)	63.9 (±11.1)	<0.01

dB = decibels; MD = mean deviation; OD = right eye; OS = left eye; SD = standard deviation; VF = visual field.
*Mean and SD.

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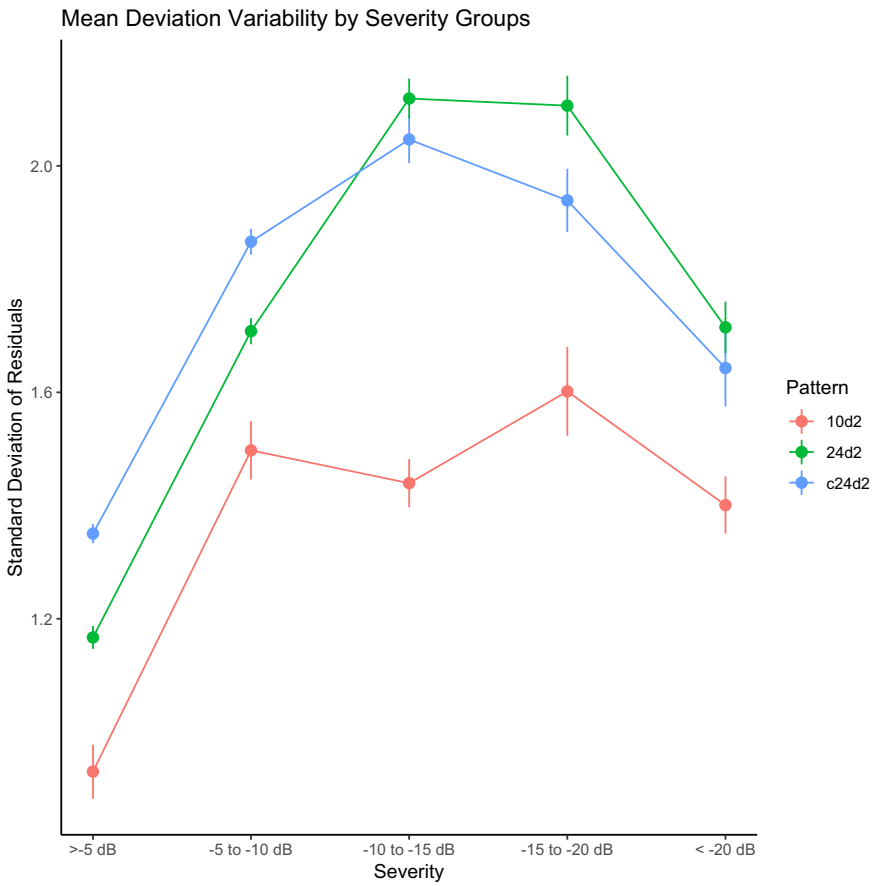

Figure 2. Standard deviation (SD) of mean deviation (MD) residual over predicted MD for the 3 VF patterns. For all 3 patterns, variability was lower with MD −5 and −20 decibels (dB) and consistently lower with the 10-2 compared with 24-2 or central 24-2. Error bars represent SD.

regression analysis only requires a single location to exhibit a statistically significant negative slope and the 24-2 tests 4 points (plus the foveal sensitivity) in the central area compared with 68 test points with the 10-2;[12] therefore, this increase could be overestimated and achieved simply by chance at the expense of a higher rate of false-positives.

A recent study by Wu et al[18] used linear-regression analysis and observed that the time to detect progression was only mildly reduced (7%−9%) using the 10-2 compared with the central 24-2. This improvement was likely due to the marginal reduction in measurement variability with the 10-2 test, because the SDs of all the residuals of the 10-2 and central 24-2 MD used in the simulations were 0.7 dB and 0.9 dB, respectively. By analyzing real-world data from a large population, we attained more representative results, which might explain the significantly greater reduction (22.9% to 26.5%) found in our study using the same method for analysis.

Visual field test variability is strongly correlated with the ability to detect progression. In this study, we controlled the follow-up duration and analyzed progression based on the different residuals of the 3 patterns. The SD of all residuals was lower with 10-2 compared with 24-2 and central 24-2 (Fig 1), which is in accordance with previous studies that show 10-2 has a lower variability than central 24-2[18] and that central test points have lower test−retest variability than peripheral points.[26,28,29] Given the design and findings of this study, the improved ability to detect CVF progression with the 10-2 test using global trend-based analysis is probably due to the reduction in variability.

Our findings are clinically relevant because they suggest that the 10-2 tests could be a useful addition to routine clinical practice. Using the 10-2 as a complement to the 24-2 should result in a moderate increase in the ability to detect progression centrally, without compromising the clinician's assessment of noncentral regions. Given the significant impact of CVF loss on vision-related quality of life,[30–32] this improvement could translate to less loss of central vision. New hybrid modalities of testing that incorporate more points of the 10-2 to the 24-2 are currently under

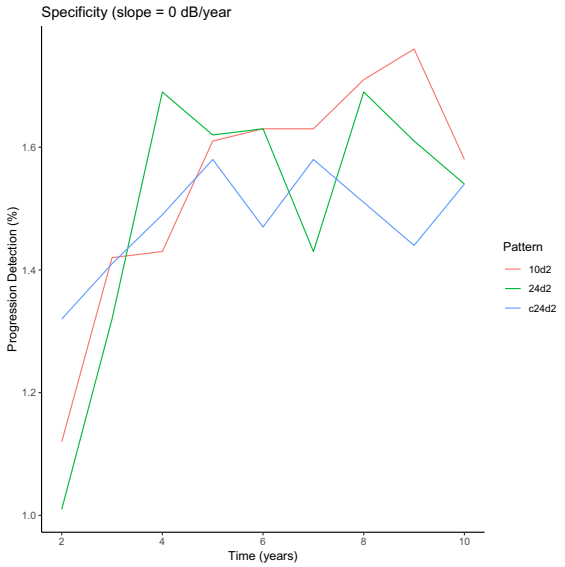

Figure 3. Power to detect progression (%) of MD in stable eyes (MD slope = 0 dB/year) with different VF patterns (10-2, 24-2, and central 24-2) at 6-month intervals, estimating false-positive rates. dB = decibels.

investigation and may help address this issue.[33] In addition to its clinical use, from a research perspective, using the 10-2 pattern as primary outcome could allow for clinical trials with smaller sample size and shorter duration.[34]

Study Limitations

The study was retrospective, which may have influenced our results. Because we did not have access to diagnosis, some data from patients with diseases other than primary open-angle glaucoma could have been included in the analyses. We minimized this possibility by only selecting patients with multiple fields performed over a 2-year follow-up and at least 3 initial VF tests with Glaucoma Hemifield Test outside normal limits or a pattern SD probability less than 0.05. Another limitation that arises with the use of this dataset is that patients may have undergone eye surgery during the course of their follow-up, which could influence their measured rate of VF loss. However, this is unlikely to affect the outcome of this study considering the large population and the fact that this influence would be applicable to all 3 patterns of VF analyzed. Further, previous work using this database has validated this approach.[20,35–39]

In addition, we did not calculate pointwise VF sensitivity values in this study. There is no developed model for that approach using the 10-2 VF test, and pointwise analyses perform similarly to the global trend-based analyses[40] used in this study. Finally, we applied ordinary least-squares linear regressions to measure the MD variability, which includes the assumption of linearity for the rate of VF worsening. Although glaucomatous VF loss can be nonlinear over the course of the disease,[41] we do not believe the assumption of linearity for MD would affect our results because our mean follow-up was only 6.5 years. Additionally, a similar study also relied on this assumption and supports its robustness.[18] Finally, commercially available algorithms rely largely on linear trends, which make our findings more easily applicable to clinical settings.

In conclusion, the 10-2 tests showed improved detection of VF progression and reduced variability when compared with the full and central test locations of the 24-2 tests, using trend-based analysis of MD. These data reiterate the potential value added of MD trend-based assessment of central 10-2 and provide evidence-based guidance on performing 10-2 VFs in patients with glaucoma, especially those with advanced disease. Future studies are needed to better determine whether other analytical methods are best suited to analyze progression and compare VF patterns.

Table 2. Time and Power to Detect Visual Field Progression for Different Rates of Mean Deviation Change over Time When Tested at 6-Month Intervals

	Power to Detect (%)			Time to Detect (Yrs)	
	2 Yrs	*5 Yrs*	*10 Yrs*	*80% Power*	*90% Power*
−0.25 dB/yr					
10-2	3.93	25.61	96.17	8.27	9.14
24-2	2.79	16.46	83.69	9.68	10.67
Central 24-2	2.76	13.02	71.29	10.74	11.8
−0.50 dB/yr					
10-2	9.97	79.37	100	5.05	5.73
24-2	6.65	58.26	99.85	6.13	7.1
Central 24-2	5.54	45.84	99.19	6.87	7.8
−1.00 dB/yr					
10-2	33.58	99.08	100	3.26	3.76
24-2	22.40	95.22	100	4	4.6
Central 24-2	16.43	90.94	100	4.34	4.95

dB = decibels.

Footnotes and Disclosures

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HUMAN SUBJECTS: Human subjects were included in this study. The institutional review boards at all sites approved the creation of the de-identified database of visual field tests. All research adhered to the tenets of the Declaration of Helsinki. Written informed consent was waived given the retrospective nature of the study.

No animal subjects were used in this study.

Author Contributions:

Conception and design: Susanna, Melchior, De Moraes

Data collection: Susanna, Melchior, Paula, Boland, Myers, Wellik, Elze, Pasquale, Shen, Ritch, Hood, Liebmann, De Moraes

Analysis and interpretation: Susanna, Melchior, De Moraes

Obtained funding: N/A; Study was performed as part of regular employment duties at Columbia University. No additional funding was provided.

Overall responsibility: Susanna, Melchior, Paula, Boland, Myers, Wellik, Elze, Pasquale, Shen, Ritch, Susanna, Hood, Liebmann, De Moraes

Abbreviations and Acronyms:
CVF = central visual field; **dB** = decibels; **MD** = mean deviation; **SD** = standard deviation; **VF** = visual field.

Keywords:
Glaucoma, Macula, Progression, Visual field.

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5. Discussão

Até este momento, há poucos dados que apoiem as recomendações refinadas de frequência de testes para acompanhamento do glaucoma e detecção precoce de sua progressão. No mundo real, em que a disponibilidade de recursos dos grandes estudos clínicos quase sempre não é replicada, é importante o direcionamento clínico a respeito da frequência ideal de testes para, simultaneamente, otimizar a detecção de progressão no glaucoma, assim como reduzir os custos para o paciente e para o sistema de saúde, evitando consultas e exames desnecessários.

Nos artigos desta tese, foram estudados intervalos para a realização de testes para detectar progressão nas SAPs de hipertensos oculares e nas OCTs de pacientes com glaucoma, assim como as diferenças entre os programas de SAP 10-2, 24-2 e os 12 pontos centrais da SAP 24-2 em relação ao poder e tempo de detecção de progressão do glaucoma.

Estudos prévios demonstraram que a progressão no campo visual central foi melhor detectada quando utilizada a SAP 10-2, comparada à SAP 24-2,[77-79] com diferentes estratégias para a detecção de progressão. Em glaucomas avançados (com MD inicial < -12 dB), a SAP 10-2 apresentou taxa de progressão do MD mais acentuada que a 24-2.[77] Wu et al.[79] também demonstraram, por meio de análise de tendência discreta, diminuição no tempo de detecção de progressão (7 a 9%) utilizando a SAP 10-2, quando comparado aos pontos centrais do 24-2. Estudos com *big data* podem ajudar nessa análise ao resultarem em achados clinicamente significativos por terem amostra mais representativa da população real, que de outra forma poderiam permanecer estatisticamente insignificantes em amostras menores.[80] Neste sentido, os resultados do presente estudo corroboram os achados dos estudos prévios: houve maior habilidade para detectar a progressão com a SAP 10-2 ao ser comparada com a SAP 24-2 e os pontos centrais da SAP 24-2, por meio de análise de tendência do MD como variável de estudo. Também foi encontrada menor variabilidade com a SAP 10-2, achado também condizente com estudos prévios, que demonstraram menor variabilidade do 10-2 quando comparado aos pontos centrais do 24-2.[79] Assim, devido aos achados e desenho do presente estudo, a maior habilidade para detectar progressão com a SAP 10-2, aplicando a análise de tendência de medida global (MD), se deveu, provavelmente, à sua menor

variabilidade quando comparada à SAP 24-2 e aos seus pontos centrais. Assim, estes achados aumentam o entendimento sobre as diferentes estratégias de SAP e reforçam a importância de adicionar a estratégia 10-2 na prática clínica, o que pode resultar em maior habilidade para detectar progressão glaucomatosa e, assim, prevenir a perda visual. A inclusão da SAP 10-2 pode ser uma ferramenta útil no seguimento rotineiro do glaucoma também pela importância do campo visual central na qualidade de vida. Novas estratégias híbridas adicionando mais pontos da SAP 10-2 na SAP 24-2 estão em investigação e podem ajudar a solucionar esta questão na prática clínica.[81]

Para estudar a frequência de exames nos hipertensos oculares, utilizou-se o banco de dados do OHTS, o estudo clínico com maior tempo de seguimento dessa condição clínica.[13] Foram analisadas simulações de computador com quatro frequências de teste (4, 6, 12 e 24 meses) em SAP, com taxa de progressão de -0,42 dB/ano (baseado no estudo de Demirel et al)[69] divididos em três grupos de risco de conversão para glaucoma, para detectar progressão clinicamente significativa de -3dB no MD. Como esperado, no grupo de alto risco foram necessários intervalos menores para realização de testes (seis meses), enquanto intervalos de 12 meses se mostraram suficientes nos grupos de baixo risco. Essas recomendações devem ser avaliadas com cautela; uma vez que se estabeleceu, arbitrariamente, um desfecho de progressão (perda de -3dB no MD da SAP), que pode não corresponder aos critérios de conversão de hipertensos oculares para glaucoma e também não foram avaliados os pacientes com hipertensão intraocular em tratamento. Na prática clínica, progressores rápidos podem necessitar de frequência menor de testes a fim de que se detecte progressão a tempo de se evitar perda visual. Ademais, o tempo de detecção de conversão para glaucoma pode ser menor quando aliadas outras ferramentas clínicas e diagnósticas, como análise clínica da CNO, retinografias seriadas e OCT, por exemplo. Assim, ao adicionar a OCT na investigação clínica, estudos futuros poderão possivelmente encontrar intervalos maiores para realização de testes para detecção de conversão em hipertensos oculares. Essa análise não foi possível no presente estudo devido à ausência de OCT no início do OHTS.

A frequência ideal de testes de SAP para detectar progressão em pacientes com glaucoma foi previamente estudada usando simulações de computador.[64] Vários modelos já foram propostos para definir intervalos clinicamente aceitáveis para a aplicação de testes, considerando tempo e poder de detecção de progressão estatisticamente significativa, baseado em análise de tendência de medidas globais do SAP, como o MD. Nesses estudos observou-se que 80% dos progressores rápidos (taxa de progressão pior que -2,0 dB/ano) serão detectados em dois a três anos, se testados a cada seis meses.[64] Porém, enquanto as medidas da SAP são subjetivas e têm muita variabilidade nas regiões centrais e periféricas em curto e longo prazo,[64,71,82] a OCT é um biomarcador mais objetivo para o seguimento de pacientes com glaucoma e se correlaciona bem com a progressão na SAP.[83,84] Assim, usando estratégia semelhante aos estudos com SAP, verificou-se, no presente estudo, que 80% dos olhos considerados rápidos progressores (taxa de progressão da pp-CFNR de -2,5 µm/ano) terão progressão detectada em 2,8, 2,5 e 2,5 anos se testados a cada quatro meses e identificadas em 3,1, 2,9 e 2,7 anos se testados a cada seis meses em olhos com danos leve, moderado e avançado à OCT, respectivamente.

Considerando, por meio de análise de gráficos estrutura-função usando SD-OCT,[85-87] uma perda de 6 µm na pp-CFNR como medida aproximadamente correspondente à perda clinicamente significativa de 3dB na SAP,[27,71] tanto seis quanto quatro meses de intervalo para realização de teste podem ser considerados razoáveis para se detectar progressão à SD-OCT. Porém, dadas as modestas diferenças no poder de detecção de progressão com esses intervalos, testes realizados a cada seis meses parecem fornecer equilíbrio entre poder estatístico e custos para o paciente e para o sistema de saúde. Entretanto, pacientes de alto risco podem se beneficiar com intervalos menores, como quatro meses, principalmente aqueles com glaucoma leve, nos quais a variabilidade da OCT é maior. Estes achados são semelhantes aos de estudos prévios com SAP.[64] Um achado importante deste estudo foi que os pacientes negros apresentaram maior variabilidade na OCT do que os brancos, o que se assemelha com achados prévios com a SAP;[88] cuja relevância clínica é que o aumento da variabilidade aumenta o tempo para detecção de progressão, podendo ser mais demorada entre os negros.

Assim, na prática clínica, é preciso considerar um intervalo de testes menor para pacientes negros.

Como já observaram Wu et al.,[64] o aumento da frequência de testes, apesar de diminuir o tempo para detecção da progressão da doença, aumenta a taxa de falsos positivos; porém testes confirmatórios podem reduzir essa taxa, havendo diminuição expressiva com um teste confirmatório ao se detectar progressão (porém, a magnitude dessa diminuição se reduz com testes adicionais). Por isso, é necessário balancear a frequência de testes com a taxa de falsos positivos e com os custos para o sistema de saúde e para o paciente.

Os estudos utilizados para o desenvolvimento desta tese também apresentaram algumas limitações. A frequência de testes ideal precisa considerar a expectativa de vida, qualidade de vida e os custos e benefícios para prevenção de perda visual. Entretanto, esses parâmetros não foram avaliados nesses estudos e precisam de maiores investigações. Além disso, cada estudo analisou apenas um exame (SAP ou OCT); porém, o uso concomitante de diferentes testes pode abreviar a detecção de progressão glaucomatosa. Assim, por exemplo, avaliando SAP juntamente com OCT, é possível que o intervalo de testes possa aumentar na vida real; sendo, inclusive, essa abordagem necessária para novos estudos. A falta de um teste padrão-ouro para determinação de progressão no glaucoma também afeta a inferência dos falsos-positivos, que nesses estudos foram calculados a partir da taxa de detecção de progressão em simulações com olhos estáveis. Ademais, a variabilidade pode ser maior em períodos mais longos comparados a períodos mais curtos,[88] o que pode também afetar a inferência da especificidade no presente estudo.

A abordagem estatística foi a mesma aplicada aos três estudos e se baseou no uso de análises de tendência com medidas globais da SAP ou OCT. Apesar de demonstrar que as análises de tendência e de evento com medida global possuem desempenho similar para detectar progressão do glaucoma na perimetria,[73] medidas globais podem perder alterações pontuais, o que pode interferir na identificação de alteração perimétrica, como por exemplo na conversão para glaucoma em hipertensos oculares.

Por fim, foi aplicado teste de regressão linear com quadrados mínimos para medir a variabilidade do MD e da medida global da pp-CFNR, assumindo a taxa de progressão linear da SAP e da OCT, respectivamente. Apesar de ser provável que a progressão glaucomatosa não seja linear no curso da doença,[89] a presunção de linearidade provavelmente não afeta os resultados deste estudo, já que a média de tempo de seguimento variou entre apenas 4,0 a 6,6 anos entre os cenários dos artigos. Outro estudo similar também chegou a essa mesma conclusão,[79] endossando os achados do presente estudo.

Em resumo, os resultados deste estudo podem servir de base para a optimização da frequência de testes de OCT e SAP para detecção de progressão glaucomatosa, podendo ser utilizados para desenvolver guias para uso clínico. Estes achados podem ajudar a diminuir os custos para o sistema de saúde e para os pacientes, especialmente os de baixo risco.

6. Conclusões

Após análise dos resultados concluiu-se que:

- Como esperado, as SD-OCTs mais frequentes resultaram em menor tempo para detectar a progressão glaucomatosa. Embora houvesse clara desvantagem para testes em intervalos de 24 *versus* 12 meses (22,4% de tempo [25 meses] de aumento no tempo para detecção de progressão) e em intervalos de 12 *versus* seis meses (22,1% de tempo [20 meses] de aumento), a mudança no tempo para detectar a progressão foi menos pronunciada ao comparar seis *versus* quatro meses (11,5% de redução do tempo [10 meses]). Dadas as modestas diferenças entre intervalos de quatro e seis meses para SD-OCT, parece ser razoável o uso de seis meses como equilíbrio entre poder estatístico e custos para os pacientes e para os sistemas de saúde. Grupos de alto risco podem se beneficiar com intervalos de quatro meses, especialmente os pacientes com glaucoma inicial, que apresentam maior variabilidade na SD-OCT e, por isso, levam mais tempo para se detectar progressão.

- Considerando o tempo para detectar a progressão glaucomatosa em hipertensos oculares com poder de 80%, observou-se benefício maior para testes realizados a cada seis *versus* 12 meses e 12 *versus* 24 meses (aproximadamente 18% de redução do tempo em ambos), em comparação com quatro *versus* seis meses (aproximadamente 11,5% de redução de tempo), considerando a progressão de -0,42 dB/ano. Olhos com hipertensão ocular de pacientes com alto e médio risco de conversão para glaucoma, que apresentem duas ou mais perimetrias iniciais, podem ser seguidos a cada seis meses, enquanto aqueles com baixo risco podem ser reavaliados a cada 12 meses.

- Entre os diferentes padrões de SAP, o tempo para se detectar progressão significativa com poder de 80% foi menor com a SAP 10-2, com diminuição de 14,6% a 18,5% quando comparada à SAP 24-2 e redução de 22,9% a 26,5%, quando comparada aos pontos centrais da SAP 24-2. A variabilidade da SAP 10-2 foi menor em relação ao 24-2 e aos pontos centrais do 24-2, provavelmente a causa do menor tempo de detecção de progressão obtido pela SAP 10-2 entre os padrões estudados.

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8. Anexos

ANEXO A - COMPROVANTES DE APROVAÇÃO DO COMITÊ DE ÉTICA

ADAGES

Columbia University Human Subjects Protocol Data Sheet

General Information

Protocol:	AAAO6901(M00Y08)	**Protocol Status:**	Approved
Effective Date:	05/05/2022	**Expiration Date:**	05/04/2023
Originating Department Code:		OPH Ophthalmology (753000X)	
Principal Investigator:		Liebmann, Jeffrey (jml2314)	
From what Columbia campus does this research originate:		Medical Center	
Title:	African Descent and Glaucoma Evaluation Study (Bridge Funding for the African Descent and Glaucoma Evaluation Study (ADAGES II)		
Protocol Version #:		**Abbreviated Title:**	ADAGES II
Was this protocol previously assigned a number by an IRB:			No

Is the purpose of this submission to obtain a "Not Human Subjects Research" determination?
No

IRB Expedited Determination

5. Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for nonresearch purposes (such as medical treatment or diagnoses).
7. Research on individual or group characteristics or behavior or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodology.

Renewal Information

Enrollment status:
Closed to further enrollment: remaining research activities are limited to data analysis only
Provide any additional information necessary to explain the study status:
Since the last renewal:
Have there been any changes in the relevant literature that would affect the study design or procedures?
No
Have there been any interim findings associated with this study?
No
Have there been any publications resulting from this study?
No
Have any participants been enrolled using the Short Form process?
No
Is there a Data Monitoring Committee (DMC), Data Safety Monitoring Board (DSMB), or other monitoring entity for this study?
No
Is an annual Progress Report required by the funding organization or coordinating center for this study?
No
Does this submission include a modification?
No
Has the consent form been revised in this submission?

No

Does this submission include a report of a protocol violation?

No

Attributes

Special review type: Check all that apply or check "None of the Above" box.

[ ]Review for 45 CFR 46.118 Determination (involvement of human subjects is anticipated but is not yet defined)

[ ]Funding review for Administrative IRB approval (such as for Center or Training Grants)

[x]None of the above

IRB of record information: Will a Columbia IRB be the IRB that is responsible for providing review, approval, and oversight for this study?

Yes

Select the most appropriate response:

Columbia will be the IRB of record for the study procedures conducted by Columbia researchers (Note: this response will apply to most submissions).

Is this research part of a multicenter study?

Yes

Indicate Columbia's involvement by checking all applicable roles below

[x] Columbia is a study site

Does this submission describe and seek approval for the study procedures at Columbia?

Yes

[ ] Columbia is the Lead Institution

[ ] Columbia is serving as the Clinical Coordinating Center

[ ] Columbia is serving as the Data Coordinating Center

[ ] Columbia is serving as the site for a repository of biological specimens related to this study

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Please indicate if any of the following University resources are utilized:

[ ] Cancer Center Clinical Protocol Data Management Compliance Core (CPDM)

[ ] CTSA-Irving Institute Clinical Research Resource (CRR)

[ ] CTSA- Irving Institute Columbia Community Partnership for Health (CCPH)

[x] None of the above

Background

Abbreviated Submission:

The IRB has an abbreviated submission process for multicenter studies supported by industry or NIH cooperative groups (e.g., ACTG, HVTN, NCI oncology group studies, etc.), and other studies that have a complete stand-alone protocol. The process requires completion of all Rascal fields that provide information regarding local implementation of the study. However, entering study information into all of the relevant Rascal fields is not required, as the Columbia IRBs will rely on the attached stand-alone (e.g., sponsor's) protocol for review of the overall objectives.

If you select the Abbreviated Submission checkbox and a section is not covered by the attached stand-alone

protocol, you will need to go back and provide this information in your submission.

Study Purpose and Rationale:

Provide pertinent background description with references that are related to the need to conduct this study. If this is a clinical trial, the background should include both preclinical and clinical data. Be brief and to the point.

[x] Abbreviated Submission - This information is included in an attached stand-alone protocol. Proceed to the next question

---

Study Design:

Describe the methodology that will be used in this study, covering such factors as retrospective vs. prospective data collection, interventional vs. non-interventional, randomized vs. non-randomized, observational, experimental, ethnography, etc.

[x] Abbreviated Submission - This information is included in an attached stand-alone protocol. Proceed to the next question

---

Statistical Procedures:

Provide sufficient details so that the adequacy of the statistical procedures can be evaluated including power calculations to justify the number of participants to be enrolled into the study. Definitions of subject terms such as enrolled and accrued as used for Rascal submissions can be found in the Subjects section.

[x] Abbreviated Submission - This information is included in an attached stand-alone protocol. Proceed to the next question

Exempt and Expedited

Is the purpose of this submission to obtain an exemption determination, in accordance with 45CFR46.101(b):

No

Is the purpose of this submission to seek expedited review , as per the federal categories referenced in 45CFR46.110?

No

Funding

Is there any external funding or support that is applied for or awarded, or are you the recipient of a gift, for this project?

No

Locations

Location Type	Facility Name	Domestic or International	Geographic Location	Local IRB Ethics Approval	Local Site Approval
Columbia/CUMC	880 3rd Ave. New York, NY 10022				

Location Type	Facility Name	Domestic or International	Geographic Location	Local IRB Ethics Approval	Local Site Approval
Columbia/CUMC	Harkness Eye Institute				

Personnel

UNI/Phone	Name	Role	Department	Edit/View	Obtaining Informed Consent
jml2314 516-662-2803	Liebmann, Jeffrey	Principal Investigator	OPH Ophthalmology (753000X)	Edit	Y
al4195 646-826-9307	Leshno, Ari	Investigator	OPH Ophthalmology (753000X)	Edit	N
kkb20 212-305-6716	Bauer, Kara	Non-Engaged Personnel	OPH Ophthalmology (753000X)	View	N
	Roles and Experience: Administration (Grant)				
ma3448 917-403-6751	Atakulova, Marzhan	Coordinator	OPH Ophthalmology (753000X)	Edit	N
nh2651 917-664-8530	Harizman, Noga	Investigator	OPH Ophthalmology (753000X)	View	N

Training and COI

The PI must ensure that each individual that is added as personnel has met the training requirements for this study (http://www.cumc.columbia.edu/dept/irb/education/index.html). For help identifying which research compliance trainings you may be required to take, visit the Research Compliance Training Finder.

UNI	Name	COI	HIPAA	HSP (CITI)	Research with Minors (CITI)	FDA-Regulated Research (CITI)	S-I	CRC	Good Clinical Practice (GCP)	GCP - Third-party tracking	GCP Refresher	Genetic Research Consent
jml2314	Liebmann, Jeffrey	09/29/2021	01/27/2015	09/09/2020	09/09/2020	09/09/2020			01/08/2022			
al4195	Leshno, Ari	07/30/2021	07/15/2021	07/07/2021		07/07/2021			07/15/2021			
kkb20	Bauer, Kara	08/24/2021										
ma3448	Atakulova, Marzhan	09/13/2021	01/28/2015	12/07/2020	01/29/2020	05/20/2014		02/05/2015	08/23/2019			11/22/2019
nh2651	Harizman, Noga	10/08/2021	04/30/2020	04/30/2020		11/03/2014			04/30/2020			

Departmental Approvers

Electronic Signature: Jeffrey Liebmann (753000X) - Principal Investigator — Date: 04/19/2022

Electronic Signature: Bonnie Wang (753000X) - Department Administrator — Date: 04/27/2022

Privacy & Data Security

Indicate the methods by which data/research records will be maintained or stored (select all that apply):

[x]Hardcopy (i.e., paper)

Describe where and how the data will be stored:

Hard copy data in form of case report forms and research questionnaires may contain coded ID, DOB, and DOVs. Patient's name will not be present on any research forms. All hard copy data will be securely stored at the Edward S. Harkness Eye Institute, Research Annex (618), accessible only to pertinent research staff. Temporary storage at the approved 880 3rd avenue may be utilized, where same safety measures discussed above will be in place.

[x]Electronic

Where will the data be stored?

Y

[x]On a System

[x]On an Endpoint

Identify what type of endpoint will be used (select all that apply):

[x]Desktop Computer

[ ]Laptop Computer

[x]Mobile Device

[ ]Other

Does this study involve the receipt or collection of Sensitive Data?

Yes

If any Sensitive Data is lost or stolen as part of your research protocol, you must inform both the IRB and the appropriate IT Security Office (CUMC IT Security if at CUMC; CUIT if at any other University campus).

What type of Sensitive Data will be obtained or collected? Select all that apply:

[ ]Personally Identifiable Information (PII), including Social Security Numbers (SSN)

Will Social Security Numbers (SSNs) be collected for any purpose?

[x]Protected Health Information (PHI), including a Limited Data Set (LDS)

If any PHI is lost or stolen, you must inform both the IRB and the Office of HIPAA Compliance.

Indicate plans for secure storage of electronic sensitive data: check all that apply

[ ]Sensitive data will not be stored in electronic format

[ ]Sensitive data will be stored on a multi-user system

[x]Sensitive data will be stored on an encrypted endpoint

By Selecting an Endpoint Device and approving this protocol for submission to the IRB, the PI is attesting that the device and any removable media that may be used have been or will be registered and/or will be maintained in compliance with the University's Information Security Charter and all related policies. It is

important that this information is updated, during the course of the study, as new devices are added.

Provide a description of how the confidentiality of study data will be ensured, addressing concerns or protections that specifically relate to the data storage elements identified above (e.g. hard copy, electronic, system, and/or endpoint):
Visual field and imaging data will contain unique study IDs.

Visual field data will be exported and ultimately sent to the data coordinating center at UCSD using an approved encrypted endpoint device(s), encrypted email and/or the University approved "DatAnywhere"(http://cumc.columbia.edu/it/howto/remote/dn.html).

All data related to photos/imaging will ultimately be exported from FORUM and the Heidelberg Spectralis Eye Explorer, respectively. All data relating to imaging will be sent to the data coordinating center at UCSD via the same methods as described for visual fields. All data will be shipped using FedEx and can be tracked accordingly.

Lastly, patient data will be sent electronically to the main coordinating center at UCSD via a UCSD generated software program (“EyeChart”) on an encrypted, UCSD-provided iPAD. Data transmission via the iPad requires WiFi. For onsite secure internet connectivity, “Athens” will be used by all study personnel. No names will be provided to UCSD at any time.

If your project is not NIH funded, has a Certificate of Confidentiality (CoC) been requested for this research?
No

Provide a description of the protections in place to safeguard participants' privacy while information is being collected:
Participant identification will be communicated by ID codes and not by name for all communication between Columbia University and the Central Coordinating Site/Data Coordinating Site at UCSD.Confidentiality will be maintained in all publications derived from this study. Mean data, not individual data, will generally be reported. If individual data is reported in a publication, no identifying information (such as names, initials, birth dates) will be provided. Every effort will be made to protect each patient's confidentiality. Only the patients' ophthalmologists, pertinent clinic personnel, and study staff will have access to the information collected. Any research-related communication will be handled in a discrete manner to prevent unintentional disclosure.

Procedures

Is this project a clinical trial?
Yes
Is this project a clinical trial that requires registration with www.clinicaltrials.gov?
Yes
Has this study been registered with www.clinicaltrials.gov?
Yes
Please provide the registration number:
NCT00221923
Is this project associated with, or an extension of, an existing Rascal protocol?
No
Do study procedures involve any of the following?

Analysis of existing data and/or prospective record review
Yes
Audio and/or video recording of research subjects
No
Behavioral Intervention?
No
Biological specimens (collection or use of)
No
Cancer-related research
No
Drugs or Biologics
No
Future use of data and/or specimens
Yes
Genetic research
No
Home Visits
No
Human embryos or human embryonic stem cells
No
Imaging procedures or radiation
No
Medical Devices
No
Surgical procedures that would not otherwise be conducted or are beyond standard of care
No

Will any of the following qualitative research methods be used?
Survey/interview/questionnaire
Yes
NOTE: You must attach a PDF version of the survey(s)/interview(s)/questionnaire(s) to this protocol prior to submission.
Systematic observation of public or group behavior
No
Program evaluation
No

Will any of the following tests or evaluations be used?
Cognitive testing
No
Educational testing
No
Non-invasive physical measurements
No
Taste testing
No

Is there an external protocol that describes ALL procedures in this study?
Yes
[ ]Check here if all procedures being conducted by Columbia researchers are detailed in the stand-alone protocol, or provide a detailed description of which procedures are being conducted by Columbia researchers.

***At this time, the only research-related activities are the administration of three research questionnaires/letters to existing research patients as described below, data clean-up (eCRF,CRF...etc), data export, and data analysis.

No actual study visits/recruitment are taking place.

Three research questionnaires will be administered only once to research patients (SF-36v2 Health Survey, NEI Visual Functioning Questionnaire-25, and The University of Illinois at Chicago Fear of Falling Measure Scoring Sheet). These will be provided to patients via regular mail or in person at the patient's next SOC visit. These questionnaires attempt to assess the health, visual function, and issues related to perceived mobility. These questionnaires will be self-administered.

Analysis of Existing Data and/or Prospective Record Review

Indicate whether the data that will be collected or utilized for the proposed study are in existence as of the current IRB submission date.

Some of the data are in existence and some will be generated in the future.

Provide the date range of the existing data, documents, or records (e.g., medical charts, school records, census data)

Beginning Date: 01/01/2011
End Date: 12/31/2015

As this research involves the collection of some data that will be generated after the IRB protocol is submitted, informed consent and HIPAA Authorization may be required from subjects

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Data will be obtained from (select all that apply):

[x] Columbia and/or NYP (e.g., departmental databases/systems, patient charts, Eclipsys, WebCIS, administrative/billing records, etc.)

Select all that apply:

[ ] Data to be analyzed were or will be collected for clinical care

[ ] Data to be analyzed were or will be collected for nonresearch purposes other than for clinical care (e.g., student records, class evaluation, administrative records, etc.,)

[ ] Data originate from an IRB approved protocol

[x] Other

Describe
Data to be collected prospectively will be for research purposes only via three research questionnaires as described elsewhere. Data collected retrospectively will be obtained via EMR records.

[ ] Outside Columbia and/or NYP:

Will a member of the research team be abstracting data directly from source documents?

Yes

If there is a data abstraction document/spreadsheet, attach it to the submission to complete study records. Though the IRB does not approve these documents, for reference purposes they are extremely helpful in understanding the scope of the proposed data collection.

Select the applicable responses:

[x] The data, documents, or records to be reviewed/abstracted are those to which a member of the research team has legitimate access for non-research purposes (e.g., departmental patient database, physicians' patient clinical records, student records).

[ ] Special authorization is necessary to review the records as the research team does not have access to the data, and a request will be or has been made to access the data.

If any existing data was obtained from a prior research study, was any member of the current research team involved (e.g., obtained consent, performed study procedures, conducted data analysis) in the project or procedures that collected and/or used identifiable information?

N/A

Indicate the manner in which the existing data and/or the records to be reviewed prospectively will be collected or received:
(Select all that apply. At least one must be selected.)

[x] Contains direct identifiers (e.g., name, MRN, date of birth)
[x] Coded and the research team has the key and can link the data to direct identifiers
[ ] Coded and the research team does not have access to the key to link data to direct identifiers
[ ] Prior to the receipt of the data by the research team submitting this protocol, the identifiers will be removed and no link will remain.
[ ] The information was originally or will be collected without identifiers

If data are collected or received at any point in time with direct identifiers or linked to identifiers, then the data are considered to be identifiable, and the requirements for Informed Consent (or a waiver, if applicable) and HIPAA Authorization (or a waiver, if applicable) apply. The necessary information will need to be included in the respective sections of the submission.

Future Use

For what materials do you anticipate future research use? Select all that apply.

[x]Data

[ ]Biological Specimens

Please indicate how data and/or specimens will be retained for future use:

[x]Some or all data and/or specimens, as applicable, will be retained by Columbia researchers for future use.

How are the materials intended to be used for research in the future?

Current PI will retain the materials and there is no intent to create a repository or share with other CU researchers. Note: Information provided in original consent forms will be considered when an addition of future uses is submitted via modification.

What future uses are anticipated?

Retained data may be used for re-analysis if new technologies become available in the future or new discoveries suggest that patients could benefit from re-analysis. All data are non-identifiable at retained center (see MOP). Additional IRB approval will be requested IF future use of data becomes necessary.

How will the data and/or specimens, as applicable, be labeled during storage for future uses.

[ ]In the same manner as during collection (e.g., with direct identifiers, coded, de-identified, anonymous)

[x]In a different manner than during collection. Select all that apply:

[ ]Specimens will be labeled with, and/or data will contain, direct identifiers

[ ]Specimens and/or data will be labeled with a code and the research team will have the key and can link specimens/data to direct identifiers. Specimens and/or data would be considered to be identifiable.

[x]Specimens and/or data will be labeled with a code and the research team will not have access to the key to link specimens/data to direct identifiers. Specimens and/or data would be considered to be de-identified.

Specify who will maintain the link:

PI at CUMC

[ ]Identifiers will be removed prior to the receipt of the specimens/data by Columbia researchers and no link will remain.

[ ]Data and/or specimens were originally or will be collected without identifiers.

Describe the physical storage for the specimens/data, including location.

[x]In the same manner as during collection

[ ]In a different manner than during collection

Describe who will have access to the stored data and/or specimens.

PI and co-investigators

[x]Some or all data/specimens will be released to a non-Columbia entity for future use and Columbia researchers will not have direct control.

Indicate to whom the data/specimens will be released

[ ]Sponsor

[x]Non-Columbia repository

[ ]Other

Describe plans for release of data and/or specimens.

Detailed outline of the collection, processing and shipment of data/specimens is provided in attached MOP.

Recruitment And Consent

Recruitment:

Will you obtain information or biospecimens for purposes of screening or determining eligibility?

No

Describe how participants will be recruited:

New enrollment has closed.

Select all methods by which participants will be recruited:

[ ] Study does not involve recruitment procedures
[x] Person to Person
[ ] Radio
[ ] Newspapers
[ ] Direct Mail
[ ] Website
[ ] Email
[ ] Television
[x] Telephone
[ ] Flyer/Handout
[ ] Newsletter/Magazine/Journal
[ ] ResearchMatch
[ ] CUMC RecruitMe

Additional Study Information: Please add a description of your study as you would like it to be displayed on the RecruitMe website.

Informed Consent Process:

Informed Consent Process, Waiver or Exemption: Select all that apply

[x] Informed consent with written documentation will be obtained from the research participant or appropriate representative.

Documentation of informed consent is applicable to:

The study in its entirety

Identify the portion of the study (e.g., prospective portion, focus groups, substudy 2) or subject population for which documentation of consent will be obtained::

Documentation of participation will be obtained from::

[x] Adult participants
[ ] Parent/Guardian providing permission for a child's involvement

[x] Legally Authorized Representatives (LARs)

Describe how participants' written consent will be obtained:
Patients will be consented in person at the time of their study visit.

[x] Informed consent will be obtained but a waiver of written documentation of consent (i.e., agreement to participate in the research without a signature on a consent document) is requested.

If applicable, remember to attach the Information Sheet that will be provided/mailed to those subjects who agree to participate. If permission will be obtained over the phone, attach the Verbal Consent Script to be used to introduce the study to potential participants

Waiver of written documentation of consent is applicable to:
The study in its entirety

Waiver of documentation of consent applies to:
[x] Adult participants
[ ] Parent/Guardian providing permission for a child's involvement
[ ] Legally Authorized Representatives (LARs)

Select the applicable basis for the waiver request: This study qualifies for a waiver of Written Documentation of Consent as per 45CFR46.117(c) as the following criteria are met in this study
The only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. Each subject, or parent/LAR if applicable, will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern

Provide justification:
Questionnaires would only contain study ID, DOB. The consent form could link name with questionnaires (study ID), unnecessarily. There are link(s) already in existence that would only be privy to pertinent research/clinic staff.

Describe how participants' consent will be obtained and whether an information sheet will be used:
Telephone script informing patient of questionnaires and verbal consent would be used.

[ ] A waiver of some or all elements of informed consent (45 CFR 46.116) is requested.

[ ] Planned Emergency Research with an exception from informed consent as per 21 CFR 50.24.

[ ] This is exempt research.

Subject Language

Enrollment of non-English speaking subjects is expected.

Languages anticipated:
Russian

Spanish

As you plan on enrolling non-English speaking subjects, administrative IRB approval of the translated documents (e.g., consent, recruitment materials, questionnaires) in the above selected languages are required. Please see the IRB's policy on the Enrollment of Non-English Speaking Subjects in Research for further details

(http://www.cumc.columbia.edu/dept/irb/policies/documents/Nonenglishspeakingsubjects.Revised.FINALDRAFT.111909.website.doc).

Capacity to Provide Consent:

Do you anticipate using surrogate consent or is research being done in a population where capacity to consent may be questionable?
No

Research Aims & Abstracts

Research Question(s)/Hypothesis(es):

The overall aim is to identify what factors account for the differences in glaucoma onset and rate of progression found between individuals of African Descent and those of European Descent and to determine whether accounting for these differences can be used to optimize algorithms for detection of glaucoma and for monitoring progression.

Scientific Abstract:

Several epidemiologic studies have demonstrated a greater susceptibility to primary open-angle glaucoma and higher rates of blindness in populations of African descent (AD) compared with those of European descent (ED).1- 6 These racial differences in the susceptibility to glaucomatous injury prompted the initiation of the National Eye Institute–funded African Descent and Glaucoma Evaluation Study (ADAGES).7 ADAGES enrolled AD and ED individuals who were healthy or who had suspected glaucoma, ocular hypertension, or glaucoma. ADAGES is the first prospectively designed observational cohort study to follow up a well-characterized AD patient population covering all stages of glaucoma (excluding end-stage disease). Each ADAGES participant undergoes a variety of measures of visual function and optic nerve and retinal nerve fiber layer (RNFL) structure and documentation of clinical, ocular, systemic, and demographic risk factors. The 3-site collaboration includes the Department of Ophthalmology and the Hamilton Glaucoma Center at the University of California, San Diego (UCSD), which served as the data coordinating center; the Department of Ophthalmology, New York Eye and Ear Infirmary (NYEE); and the Department of Ophthalmology, University of Alabama, Birmingham (UAB). The baseline characteristics and study design have been described in a previous publication. The present study evaluated differences in optic disc topography, RNFL, and macular measurements obtained with confocal scanning laser ophthalmoscopy using Heidelberg retina tomography (HRT) (HRT II; Heidelberg Engineering, Inc, Heidelberg, Germany) and optical coherence tomography (OCT)

(Stratus OCT; Carl Zeiss Meditec, Inc, Dublin, California) between healthy AD and ED subjects to determine structural differences between these groups in ADAGES.

Lay Abstract:

Objective To identify factors accounting for differences in glaucoma onset and rate of progression between individuals of African descent and European descent. Design A prospective, multicenter observational cohort study of 1221 participants of African descent and European descent with no glaucoma (normal), suspected glaucoma, and glaucoma. Six hundred eighty-six patient participants in the African Descent and Glaucoma Evaluation Study will be followed up longitudinally. Four hundred thirty-six participants of European descent from the Diagnostic Innovations in Glaucoma Study (DIGS) were also included. Baseline demographics, visual function (standard automated perimetry, short-wavelength automated perimetry, frequency doubling technology perimetry), optic nerve structure (retina tomography, optical coherence tomography), clinical status, and risk factors were measured. Results Individuals of African descent had (1) thinner corneas (P<.001) across all diagnostic groups, (2) a higher percentage of reported diabetes mellitus (P<.001) and high blood pressure (P<.001) and a lower percentage of reported heart disease (P=.001), and (3) worse pattern standard deviation for standard automated perimetry fields overall (P=.001) and within normal limits (P=.01) than individuals of European descent. No differences were present for mean intraocular pressure (P=.79). Conclusions Significant baseline differences were found in a number of clinical findings between persons of African descent compared with European descent. Longitudinal data from the African Descent and Glaucoma Evaluation Study will be important for determining which baseline features are important and predictive for accurate diagnosis and follow-up in this high-risk group.

Risks, Benefits & Monitoring

Abbreviated Submission:

The IRB has an abbreviated submission process for multicenter studies supported by industry or NIH cooperative groups (e.g., ACTG, HVTN, NCI oncology group studies, etc.), and other studies that have a complete stand-alone protocol. The process requires completion of all Rascal fields that provide information regarding local implementation of the study. However, entering study information into all of the relevant Rascal fields is not required, as the Columbia IRBs will rely on the attached stand-alone (e.g., sponsor's) protocol for review of the overall objectives. .

If you select the Abbreviated Submission checkbox and a section is not covered by the attached stand-alone protocol, you will need to go back and provide this information in your submission.

Potential Risks:

Provide information regarding all risks to participants that are directly related to participation in this protocol, including any potential for a breach of confidentiality. Risks associated with any of the items described in the Procedures section of this submission should be outlined here if they are not captured in a stand-alone protocol. Risks of procedures that individuals would be exposed to regardless of whether they choose to participate in this research need not be detailed in this section, unless evaluation of those risks is the focus of this research. When applicable, the likelihood of certain risks should be explained and data on risks that have been encountered in past studies should be provided.

[x] Abbreviated Submission - This information is included in an attached stand-alone protocol. Proceed to the next

question

Potential Benefits:

Provide information regarding any anticipated benefits of participating in this research. There should be a rational description of why such benefits are expected based on current knowledge. If there is unlikely to be direct benefit to participants/subjects, describe benefits to society. Please note that elements of participation such as compensation, access to medical care, receiving study results, etc. are not considered benefits of research participation.

[x] Abbreviated Submission - This information is included in an attached stand-alone protocol. Proceed to the next question

---

Alternatives:

If this research involves an intervention that presents greater than minimal risk to participants, describe available alternative interventions and provide data to support their efficacy and/or availability. Note, participants always have the option not to participate in research.

[x] Abbreviated Submission - This information is included in an attached stand-alone protocol. Proceed to the next question

---

Data and Safety Monitoring:

Describe how data and safety will be monitored locally and, if this is a multi-center study, how data and safety will be monitored across sites as well.

[ ] Abbreviated Submission - This information is included in an attached stand-alone protocol. Proceed to the next question

Please see chapters 16-17 of the ADAGES protocol version 2009 (attached in the documents section).

Subjects

Unless otherwise noted, the information entered in this section should reflect the number of subjects enrolled or accrued under the purview of Columbia researchers, whether at Columbia or elsewhere.

Target enrollment:

750

Number enrolled to date:

678

Number enrolled since the last renewal or, if this is the first renewal, since the initial approval:

0

Number anticipated to be enrolled in the next approval period:

0

Does this study involve screening/assessment procedures to determine subject eligibility?

No

Of the number of subjects enrolled, or the number accrued for interventional studies with a screening process:

How many remain on the study?

0

How many are off study?

678

How many completed the study?
674
Have any withdrawn of their own initiative?
Yes
How many?
2
Please explain:
Possible reasons due to commute and mobility, a few patients have decided not to continue with the study.
Have any been removed by PI?
No
Have any been lost to follow-up?
Yes
How many?
0
Please explain:
Lost to follow-up number may change after further review. Will keep IRB posted.
Have any died while on study?
Yes
How many?
2
Please explain, including whether death was related to participation in this study:
Since this is an observational study, cause of death of patients were unrelated to any study-related procedures. Deaths may have occurred prior to initial approval at Columbia.

Have any subject complaints been received?
Yes
How many?
1
Please explain:
Complaint was in regards to billing. Corrective action plan have been implemented.

Is this a multi-center study?
Yes
Target number of eligible subjects to be included at all sites:
1,540

Does this study have one or more components that apply to a subset of the overall study population (e.g. Phase 1/2, sub-studies)?
No

Of the number enrolled, or the number accrued for interventional studies with a screening process, indicate:
Population Gender

Females	Males	Non Specific
50%	50%	0%

Population Age

0-7	8-17	18-65	>65	Non Specific
0%	0%	30%	70%	0%

Population Race

American Indian/Alaskan Native	Asian	Native Hawaiian or Other Pacific Islander	Black or African American	White	More than One Race	Non-Specific
0%	0%	0%	50%	50%	0%	0%

Population Ethnicity

Hispanic or Latino	Not Hispanic or Latino	Non-Specific
30%	70%	0%

Vulnerable Populations as per 45 CFR 46:

Will children/minors be enrolled

No

Will pregnant women/fetuses/neonates be targeted for enrollment?

No

Will prisoners be targeted for enrollment?

No

Other Vulnerable Populations:

[ ]Individuals lacking capacity to provide consent

[ ]CU/NYPH Employees/Residents/Fellows/Interns/Students

[x]Economically disadvantaged

[x]Educationally disadvantaged

[x]Non-English speaking

Please ensure that your plan to enroll subjects in their primary language is described on the Informed Consent page.

[ ]Other Vulnerable populations

[ ]None of the Populations listed above will be targeted for Enrollment

Subject Population Justification:

Patients have already been enrolled in the past. No new enrollment is taking place.

Does this study involve compensation or reimbursement to subjects?

No

Attached HIPAA Forms

Number	Type	Title	Status
AAAL7005	A	ADAGES 2 Form A	Approve

Documents

Archived	Document Identifier	Document Type	File Name	Active	Stamped	Date Attached	Created By
No	Central Site IRB Approval 2016	Local IRB/Ethics/Site Approval	140276_2015_12_07_APPROVE_NSR.PDF	Y	No	08/07/2016	Jeremy Reimann (jr3538)
No	ADAGESII-IV 2019-2020 publications	Other	ADAGESII-IV 2019-2020 publications.docx	Y	No	06/30/2020	Marzhan Atakulova (ma3448)

Archived	Document Identifier	Document Type	File Name	Active	Stamped	Date Attached	Created By
No	IT Letter_Systems	Other	CDO IT Data Information.pdf	Y	No	09/22/2016	Jeremy Reimann (jr3538)
No	Publication ADAGES 2 2015	Other	Publication ADAGES 2 2015.pdf	Y	No	02/18/2016	Carlos Gustavo De Moraes (cvd2109)
No	Protocol	Standalone/Sponsor's Protocol	ADAGES October 2009.pdf	Y	No	07/20/2018	Carlos Gustavo De Moraes (cvd2109)

Tasks

Section	Task	Required for submission	Completed	Created By	Date Created
Subjects	Previous requests made in approval correspondence dated 10/24/2017 has yet to be addressed: Prior to your next renewal submission, please enter “678” in “how many are off study?”	No	Yes	Elizabeth Baez (eb2441)	2021-06-07 12:31:47.0

OHTS

COLUMBIA|RESEARCH
Human Research Protection Office
Institutional Review Boards

September 8, 2022

Jeffrey Liebmann
753000X - OPH Ophthalmology

Protocol Number: IRB-AAAQ2510
Title: Ocular Hypertension Treatment Study: 20 Year Follow-Up
Protocol Version #: 1
Grant #: UG1EY025181;FWA00002284
Approval Date: 09/01/2022 Expiration Date: 08/31/2023
Event Identifier: Renewal (Y08M00)

The above-referenced event was reviewed by Columbia University IRB Exp.

Level of review and outcome: Approved by Expedited review

To view a list of documents that were included in this approval (if applicable) and all other currently approved documents for this study, please refer to the Print Menu for this Event in Rascal. It is important to confirm the status of each document, e.g., active, stamped, etc. Only stamped, active documents can be used with research participants.

Study Status: Closed to further enrollment: remaining research activities are limited to data analysis only

Electronically signed by: Halinski, Ashley

154 Haven Avenue, 1st Floor New York, NY 10032 212-305-5883 Tel 212-305-1316 Fax
615 West 131st Street, 3rd Floor New York, NY 10027 212-851-7040 Tel 212-851-7044 Fax

IRB-AAAQ2510 Renewal (Y08M00)

Researcher Responsibilities:

Any proposed changes in the protocol must be immediately submitted to the IRB for review and approval prior to implementation, unless such a change is necessary to avoid immediate harm to the participants.

Any unanticipated problems that involve risks to subjects must be reported to the IRB in accordance with the Unanticipated Problems: Reporting to the IRB of Unanticipated Problems Involving Risks policy. All submissions for modifications and unanticipated problems must be submitted through Rascal.

Renewal applications should be submitted 60 days before the expiration date of this study through Rascal. Failure to obtain renewal of your study prior to the expiration date will require discontinuance of all research activities for this study, including enrollment of new subjects.

You must file a Closure Report in Rascal when your study has been completed.

GRN

COLUMBIA|RESEARCH
Human Research Protection Office
Institutional Review Boards

April 24, 2023

C.Gustavo De Moraes
753000X - OPH Ophthalmology

Protocol Number: IRB-AAAP9831
Title: Glaucoma progression research network
Approval Date: 04/18/2023 Expiration Date: 04/17/2024
Event Identifier: Renewal (Y07M00)

The above-referenced event was reviewed by Columbia University IRB Exp.

Level of review and outcome: Approved by Expedited review

To view a list of documents that were included in this approval (if applicable) and all other currently approved documents for this study, please refer to the Print Menu for this Event in Rascal. It is important to confirm the status of each document, e.g., active, stamped, etc. Only stamped, active documents can be used with research participants.

Study Status: Closed to further enrollment: remaining research activities are limited to data analysis only

Electronically signed by: Halinski, Ashley

154 Haven Avenue, 1st Floor New York, NY 10032 212-305-5883 Tel 212-305-1316 Fax
615 West 131st Street, 3rd Floor New York, NY 10027 212-851-7040 Tel 212-851-7044 Fax

IRB-AAAP9831 Renewal (Y07M00)

Researcher Responsibilities:

Any proposed changes in the protocol must be immediately submitted to the IRB for review and approval prior to implementation, unless such a change is necessary to avoid immediate harm to the participants.

Any unanticipated problems that involve risks to subjects must be reported to the IRB in accordance with the Unanticipated Problems: Reporting to the IRB of Unanticipated Problems Involving Risks policy. All submissions for modifications and unanticipated problems must be submitted through Rascal.

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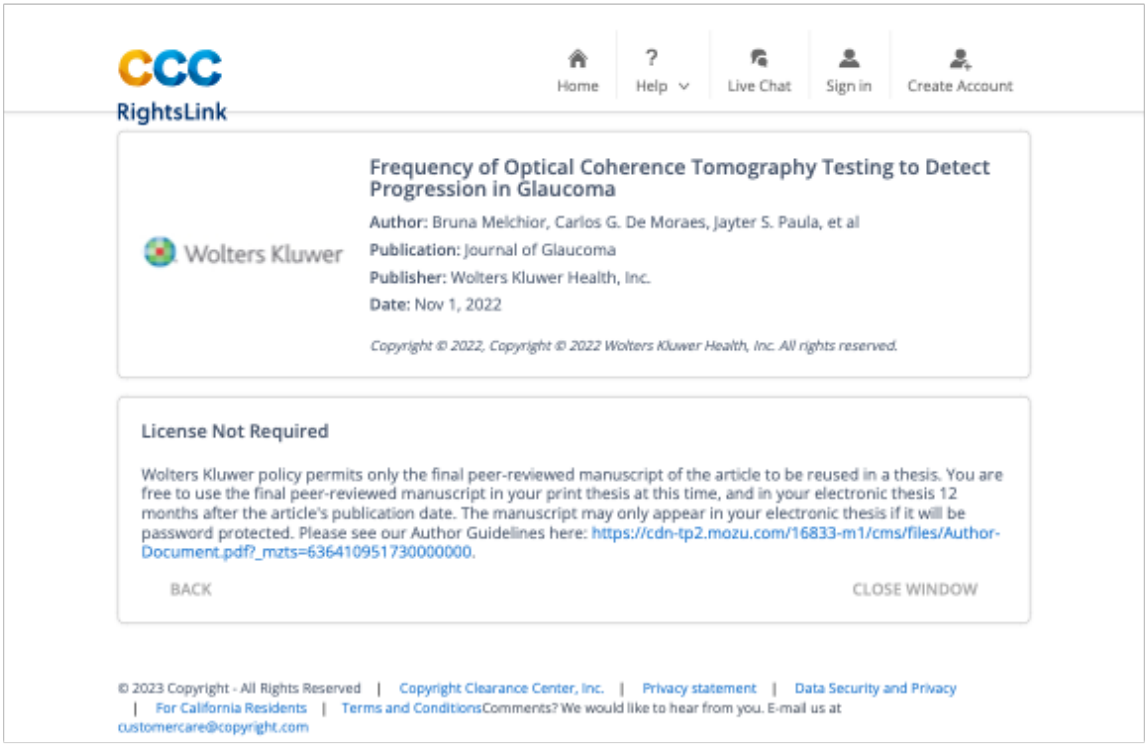
You must file a Closure Report in Rascal when your study has been completed.

ANEXO B - COMPROVANTES DE AUTORIZAÇÃO DE USO DAS EDITORAS



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Wolters Kluwer

Frequency of Optical Coherence Tomography Testing to Detect Progression in Glaucoma

Author: Bruna Melchior, Carlos G. De Moraes, Jayter S. Paula, et al

Publication: Journal of Glaucoma

Publisher: Wolters Kluwer Health, Inc.

Date: Nov 1, 2022

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