WVUMedicine

Glaucoma Screening and Telemedicine

We Need to Find It First

Ronald L. Gross, MD

Oregon Academy of Ophthalmology

March 9-10, 2018

WVUMedicine

Financial Disclosure
Ronald L. Gross, MD

I have the following financial interests or relationships to disclose:

Alcon Laboratories: C

Allergan, Inc.: C,L,S

Aerie Pharmaceuticals: C

Glaucos: C

Reichert Technology: C

Intelligent Retinal Imaging Systems, LLC: C

WVUMedicine

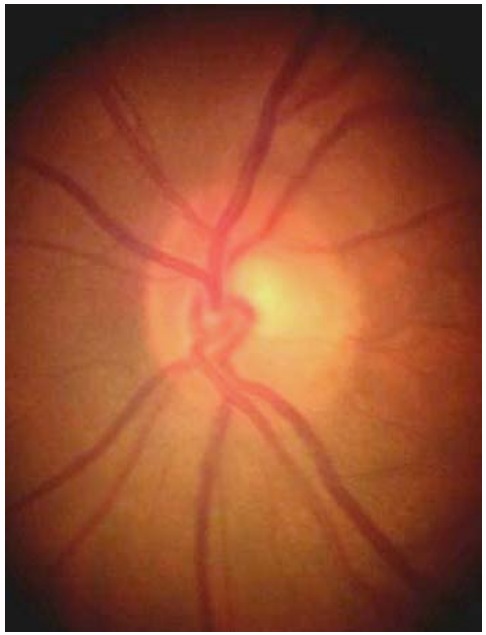
Outline

- Ideal screening test
- Evidence supporting benefits of glaucoma screening
- Prior glaucoma screening efforts
- Ways to improve cost effectiveness of glaucoma screening
- Examples of current screening projects

WVUMedicine

Glaucoma

- Optic neuropathy
- Characterized by progressive injury to retinal ganglion cells and their axons
- Specific pattern of optic atrophy (“cupping”)
- Associated visual function deficit
- IOP not part of the definition



WVUMedicine

Glaucoma Diagnosis: An Historical Perspective

Pre -1980s

- Elevated intraocular pressure (IOP) → glaucoma

1980s - Mid 1990s

- Elevated IOP + visual field (VF) defect → glaucoma

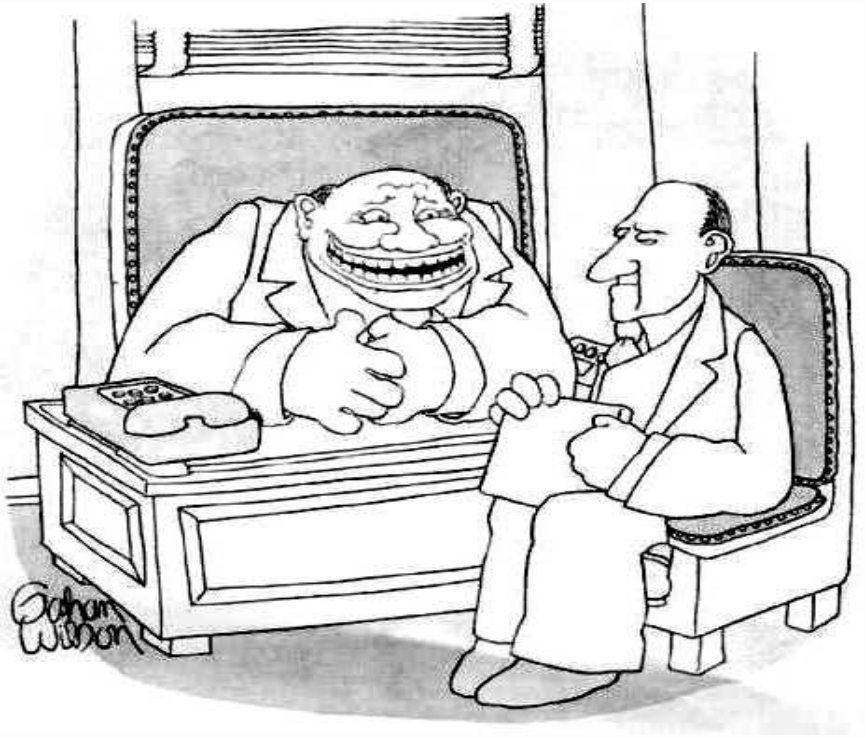
Mid 1990s - present

- Glaucomatous optic disc + retinal nerve fiber layer (RNFL) changes → glaucoma

WVUMedicine

OAG Screening

"I'd like to be straightforward about all this, but, of course, that's out of the question."



WVUMedicine

Should we screen for glaucoma?

Tenets of a screening test:

- The condition is a public health problem.
- There is treatment for the condition.
- Treatment is effective when administered earlier in disease.
- There is a latent or asymptomatic stage of disease.
- The test should be economically balanced, sensitive, and specific.

WVUMedicine

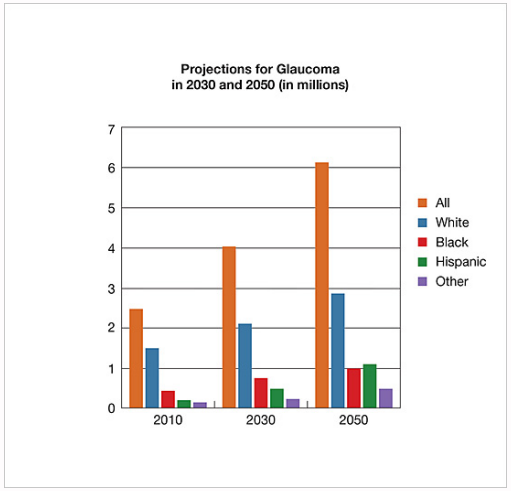
Glaucoma is a public health concern

- Accounts for over 10 million visits to physicians each year
- Major eye disorders care costs $35 billion/ year in direct costs and productivity losses
  - Cost increases with worsening disease
  - $9,000 for moderate disease
  - $16,000 for severe disease

Wong et al. Ophthalmology. 2004 Aug;111(8):1508-14; Kymes et al. Am J Ophthalmol. 2010 July; 150(1): 74-81

Incidence Of Open-angle Glaucoma

- Affects >2 million over the age of 40 in the US (1.9%); expected to exceed 3 million by 2020[1] . Number will grow to over 6 million by 2050
- Average age of onset 54 years of age[2]
- Most patients (63%) have had glaucoma >10 years[2]
- 2nd leading cause of blindness[3]



National Eye Institute

1. Friedman DS et al. *Arch Ophthalmol.* 2004;122:532-538.
2. Gallup Eye Health Survey. 2002.
3. Glaucoma Facts. Available at: www.glaucoma.org/learn/facts.html.

WVUMedicine

Under-diagnosis Of Open-angle Glaucoma

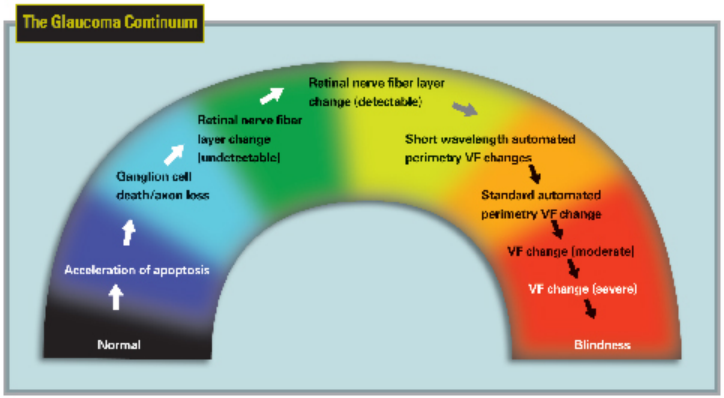
- Population studies suggest over half of all glaucoma cases in the US have not been diagnosed
  - Percentage of patients with undiagnosed glaucoma
    - Baltimore Eye Survey: 56%[1]
    - Proyecto VER: 62%[2]
- Many suffer severe VF loss before diagnosis[3]

1. Sommer A et al. *Arch Ophthalmol.* 1991;109:1090-1095.
2. Quigley HA et al. *Arch Ophthalmol.* 2001;119:1819-1826.
3. Gillespie BW et al. *Invest Ophthalmol Vis Sci.* 2003;44:2613-2620.

WVUMedicine

Treatment

- There is effective treatment for glaucoma
- Early treatment reduces the risks of glaucoma progression
  - AGIS, CIGTS, EMGT, OHTS
- Treatment reduces mean time to blindness in at least one eye from 16-23 years to 35 years with treatment



AGIS IOVS. 2004 Dec;45(12):4346-51.; EMGTS Arch Ophthalmol. 2003 Jan;121(1):48-56; Burr et al. Health Technology assessment 2007 11(41).

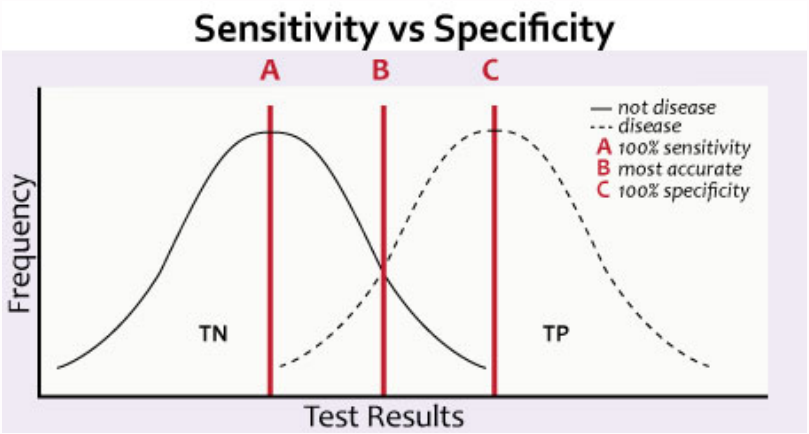
WVUMedicine

Latent or Asymptomatic Stage

- Asymptomatic early in disease
  - 25-40% of retinal ganglion cells may be lost before visual function impairment
- Irreversible vision loss
- Wilson: Natural history of untreated glaucoma in St. Lucia
  - Unilateral blindness in 10 years was about 16% in St. Lucia
  - >50% of these eyes had no or minimal VF loss at baseline
- Treatment is more effective when administered earlier in disease

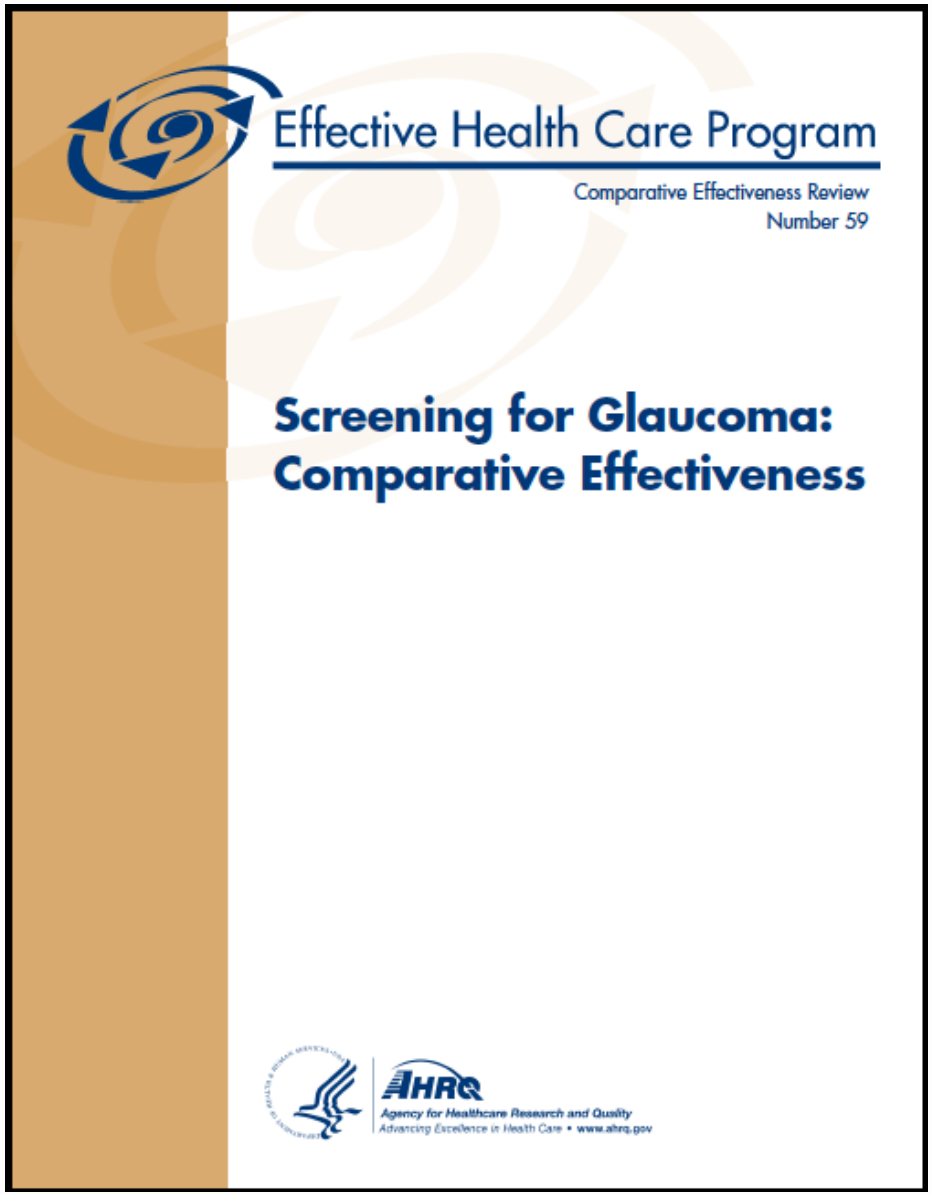
Bowd C et al. *Invest Ophthalmol Vis Sci*. 2001;42:1993-2003; Wilson MR. *Trans Am Ophthalmol Soc.* 2002;100:365-410.

Cost Effective, Sensitive and Specific Test



- Qualities:
  - Economic
  - Easy to administer,
  - Reproducible,
  - Sensitive, few false negatives
  - Specific, few false positives
- Prevent Blindness America recommended screening test >85% sensitivity and at least 95% specificity.

WVUMedicine



WVUMedicine

Conclusion

Conclusions. We did not identify any systematic review or study that provided evidence for direct or indirect links between glaucoma screening and visual field loss, visual impairment, optic nerve damage, intraocular pressure, or patient-reported outcomes. Early treatment is important in determining the indirect chain of evidence for screening; the treatment of glaucoma is addressed in the report Treatment for Glaucoma: Comparative Effectiveness. There have been improvements in screening devices, yet there is limited evidence on the effects of screening for OAG.

- No link between glaucoma screening and the disease- Does screening change the disease?
- Early glaucoma treatment is important
- Glaucoma Screening is improving
- Limited evidence that glaucoma screening effective

WVUMedicine

AAO/AGS Response

Summary:

When the medical evidence described above is viewed in its proper context, it suggests several important conclusions:

1. There is, in fact, a clear chain of evidence that connects glaucoma screening by eye care professionals with meaningful preservation of visual function and quality of life, through the reduction of worsening of glaucoma.
2. Community glaucoma screening will result in detection of patients with meaningful loss, since most will already have significant visual field loss in excess of – 4 dB.
3. Visual field loss at the -4 dB level has a demonstrable and clinically significant impact on patient visual functioning and vision-related quality of life.
4. There is documented cost-effectiveness from the societal perspective in treating this level of visual field loss.
5. Glaucoma screening, defined as including an eye examination that detects all other conditions that threaten sight in the elderly and thus will result in significant benefit for older Americans in key indicators as important as IADL's and ADL's.

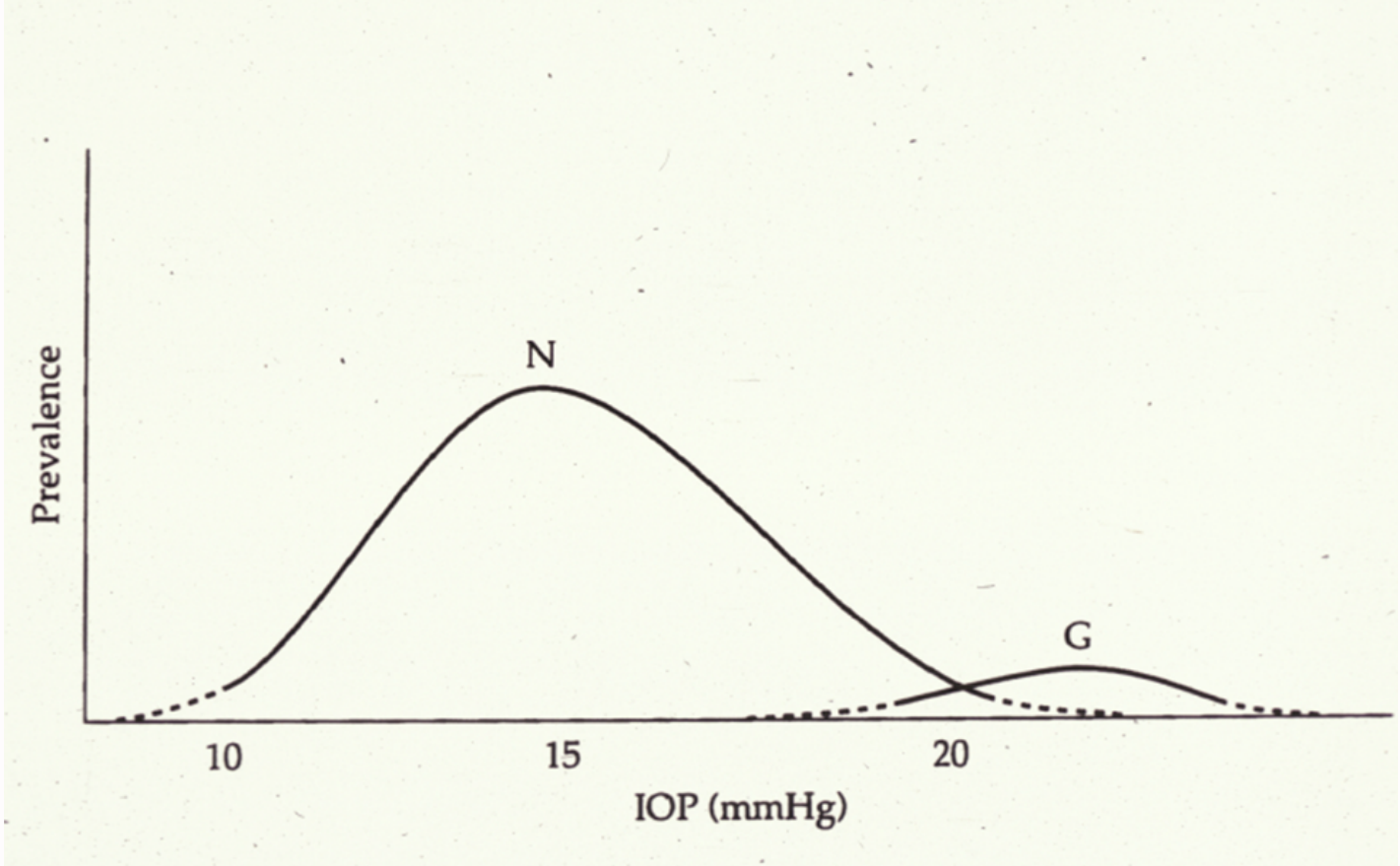
WVUMedicine

Glaucoma Screening

Options:

- IOP
- Structure
- Function
- Other
  - Family History
  - Age
  - Race
  - Diabetes

IOP Screening



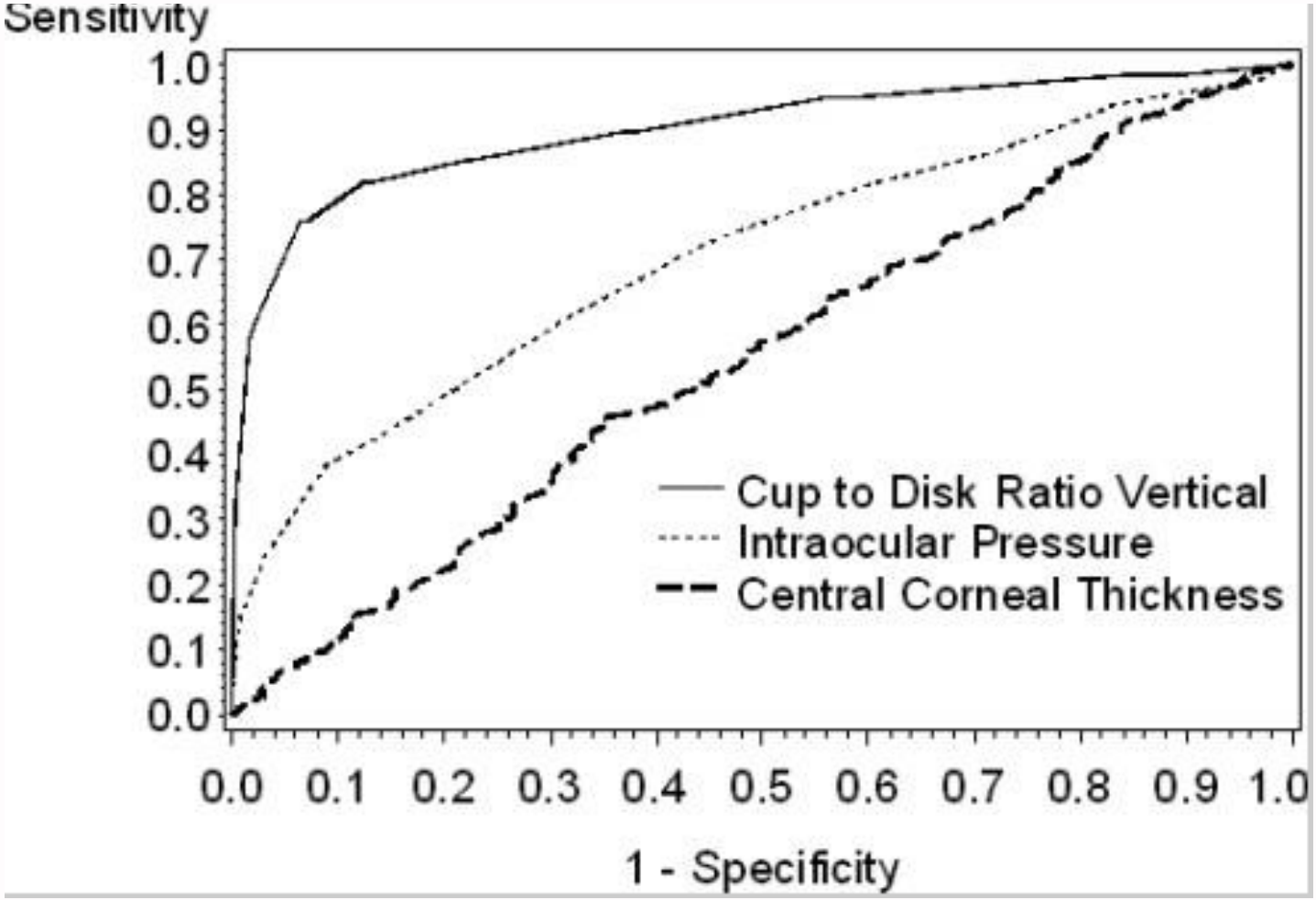
WVUMedicine

IOP Screening

- Lots with elevated IOP never develop glaucoma damage
  - Up to 90%
  - OHTS
  - Many more “normals” than glaucomas
- Lots with “normal” IOP still develop glaucoma damage
  - Up to 33%
  - Beaver Dam Eye Study

WVUMedicine

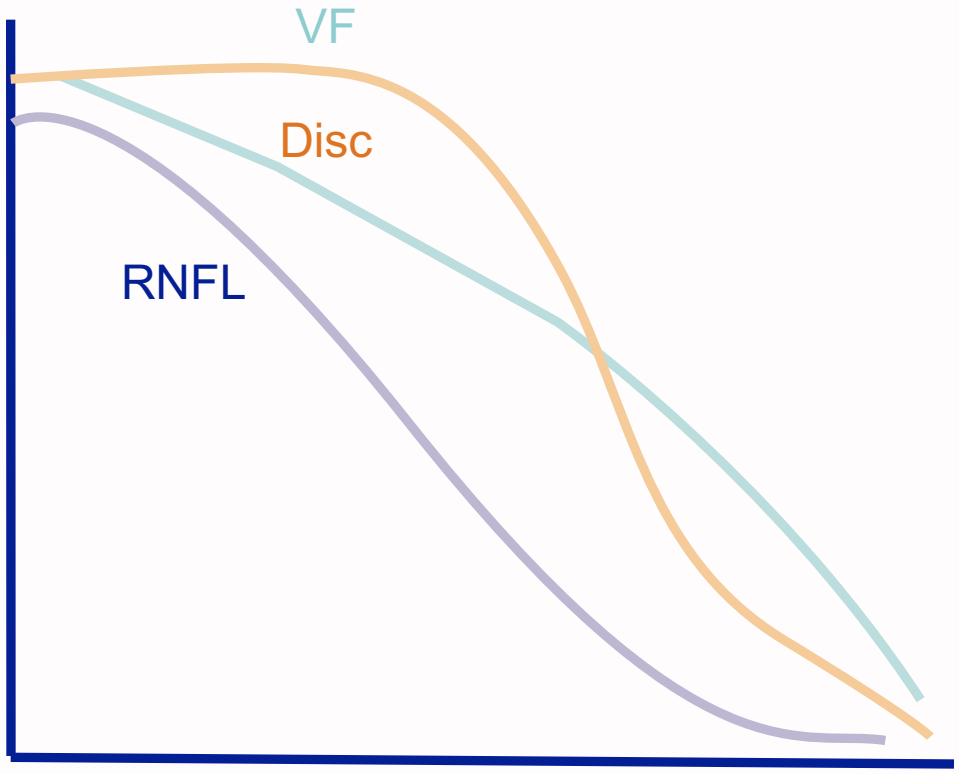
IOP Screening



Francis, Varma, et al. Invest Ophthalmol Vis Sci 2011; 52: 6257-64.

WVUMedicine

Structure And Function In Glaucoma



WVUMedicine

Glaucoma Screening

Table 1. Traditional glaucoma screening tests

	Sensitivity (%)	Specificity (%)
Elevated intraocular pressure	20–70	80–95
Visual field	55–96	77–99
Disc imaging	29–98	83–98

McManus and Netland, Curr Opin Ophthalmol 2013; 24:144-9.

WVUMedicine

Structural Damage Precedes Functional

- NFL injury can be observed up to 6 years before VF defects[1]
  - Mean number of axons[2] in normal ON ~800,000–1,200,000
  - 25-40% of ON fibers can be lost from an eye that retains a normal visual field[2,3]
- VF loss by SAP does **NOT** mean early disease
  - By the time VF loss is detected by SAP, substantial structural damage may exist[1,4]
  - Functional loss may be detected earlier using selective tests (eg, FDT, SWAP)[4]

1. Sommer A et al. *Arch Ophthalmol*. 1991;109:77-83.
2. Quigley HA et al. *Arch Ophthalmol*. 1982;100:135-46.
3. Kerrigan-Baumrind LA et al. *Invest Ophthalmol Vis Sci*. 2000;41:741-748.
4. Bowd C et al. *Invest Ophthalmol Vis Sci*. 2001;42:1993-2003.

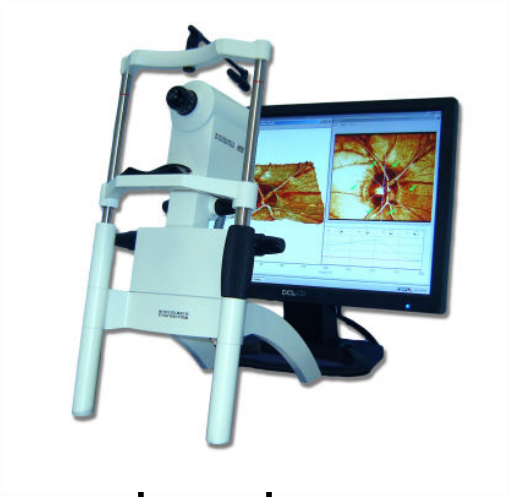
WVUMedicine

First OHTS POAG Endpoint Per Participant

	Medication		Observation	
	n	%	n	%
Visual field	15	41.7	29	32.6
Optic disc	18	50.0	51	57.3
Concurrent visual field and optic disc	3	8.3	9	10.1
Total	**36**	**100.0**	**89**	**100.0**

Kass MA et al. *Arch Ophthalmol.* 2002;120:701-713

Analysis of optic nerve head



- Mainstream in clinical practice
- Evolving role in screening programs
  - Expensive and inconvenient
  - Limited in evaluation of the optic nerve head
  - Poor signal strength
- HRT II
  - Sensitivity up to 77% and specificity up to 84% for detection of glaucoma in high-risk populations
- OCT
  - SD-OCT still currently lacks the diagnostic performance for glaucoma screening

Population Being Screened

Example: HRT

	Sensitivity	Specificity
General Population		
Blue Mountains (10 yr fu)	46%	91%
Abnormal MRA		
Tajimi (Japan)	39%	96%
Glaucoma Clinic		
Meta Analysis – MRA	86%	89%

Healey, et al. Ophthalmology 2010; 117:1667-74
Saito, et al. Ophthalmology 2009; 116:1854-61
Mowatt, et al. Inv Ophthal Vis Sci 2008;49:5373-8

WVUMedicine

Functional Screening

TABLE 3. Diagnostic Results of Each Criterion of the Three Tests Studied: Frequency Doubling Technology (FDT), Tendency Orientated Perimetry (TOP), and Humphrey's SITA-Fast (HSF)

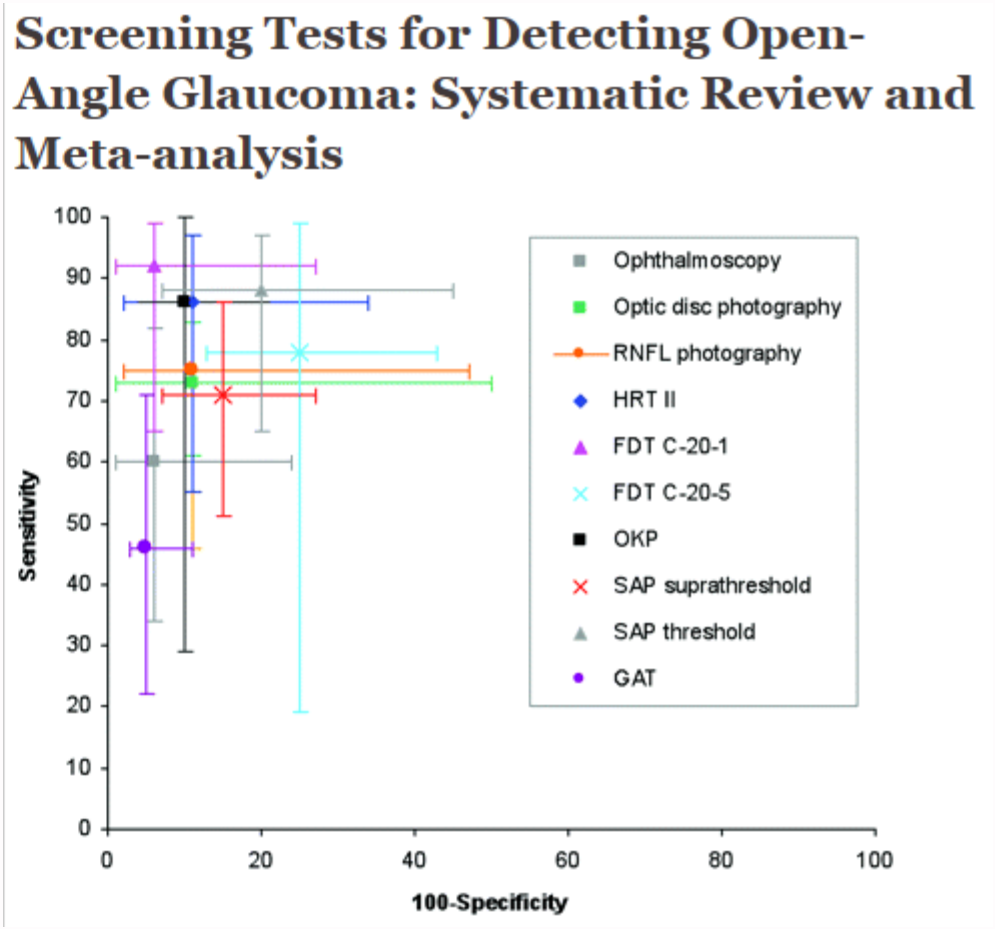
Test	FDT-a	FDT-b	TOP-a	TOP-b	HSF-a	HSF-b	HSF-c
Sensitivity (%)	91.4	80.0	97.1	94.2	98.5	95.7	94.2
Specificity (%)	96.4	100	67.8	82.1	67.8	75.0	82.1
Positive predictive value (%)	98.4	100	88.3	92.9	88.4	89.3	92.9
Negative predictive value (%)	81.8	66.6	90.4	85.1	95.0	87.5	85.1
Area under the ROC curve (%)	93.9	90.0	82.5	88.2	83.2	85.4	88.2

HSF-a = Glaucoma Hemifield Test (GHT) being "borderline" or "outside normal limits"; HSF-b = pattern deviation probability plot showing a cluster of three or more nonedge points at $p < 5\%$, one of which at $p < 1\%$; HSF-c = PSD had a value at $p < 5\%$; FDT-a = at least one abnormal location; FDT-b = presence of two or more abnormal points on FDT; TOP-a = MD > 2 dB and/or LV > 6 dB; TOP-b = at least seven points with sensitivity decreased 5 dB or more, three of them being contiguous.

Wadood, et al. Am J Ophthalmol 2002; 133:327-32.

WVUMedicine

Functional v Structural Screening



Mowatt, et al. Inv Ophthal Vis Sci 2008;49:5373-8

Age

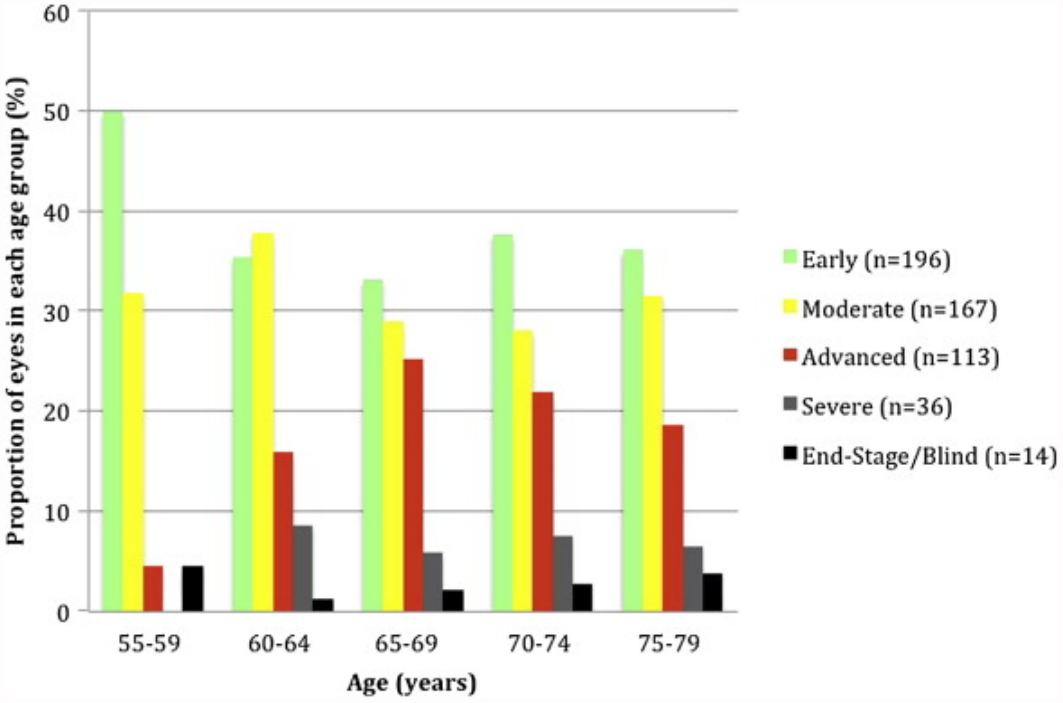


Figure 1 Stages of glaucomatous visual field loss in eyes with newly detected disease. The severity of field loss was similarly distributed from age 60 years and more, with 30% to 40% at the early stage and more than ≥25% at advanced, severe, or end stages...

Anders Heijl , Boel Bengtsson , Sigridur Erla Oskarsdottir

Prevalence and Severity of Undetected Manifest Glaucoma : Results from the Early Manifest Glaucoma Trial Screening

Ophthalmology, Volume 120, Issue 8, 2013, 1541 - 1545

WVUMedicine

Glaucoma Screening: APD

Estimation of Retinal Ganglion Cell Loss in Glaucomatous Eyes With a Relative Afferent Pupillary Defect

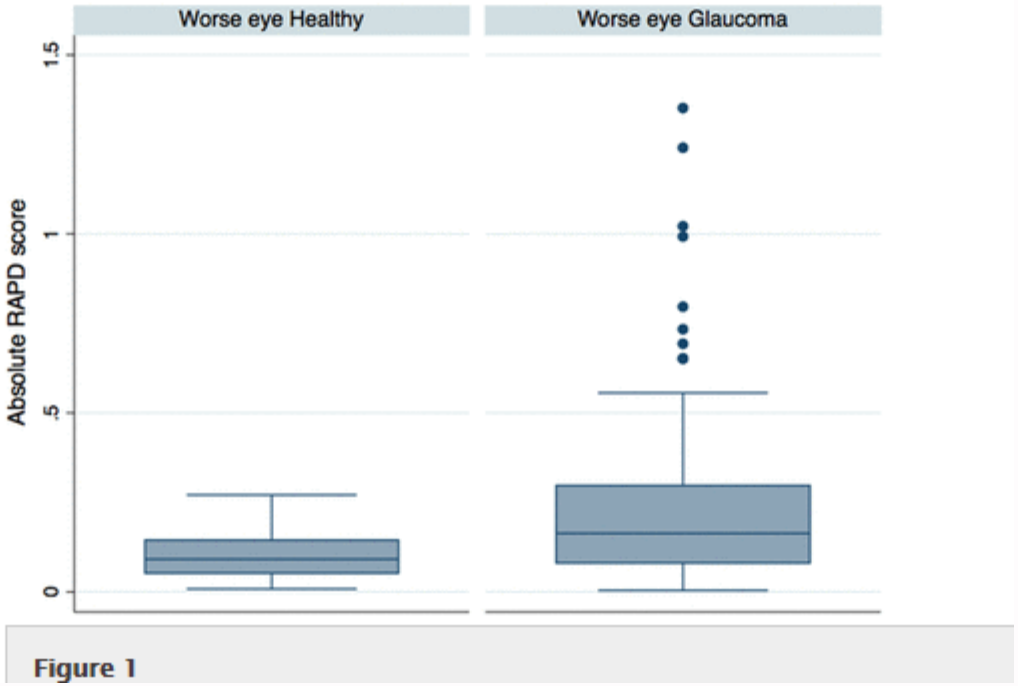


Figure 1

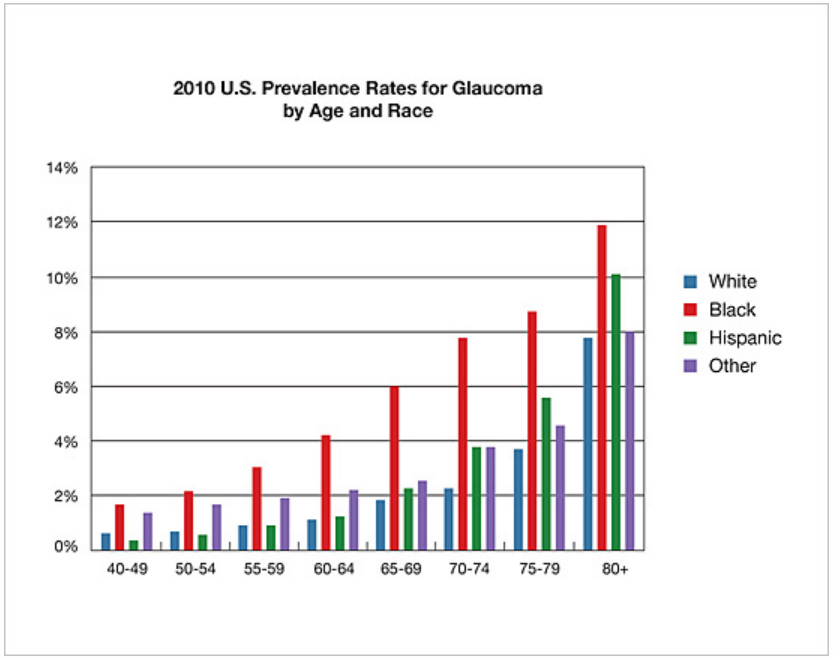
DIGS: Tatham, et al. Invest Ophthalmol Vis Sci 2014;55:513-22

WVUMedicine

Screen High-Risk Populations

AAO: Screenings may be useful in populations of high glaucoma prevalence

- Family History of Glaucoma
- African Americans
- Hispanic Americans
- Elderly



AAO PPP, NIH National Eye Institute

WVUMedicine

Glaucoma Screening
Family History

TABLE 2. Differences in Age at Diagnosis in Different Types of Glaucoma Between Patients With and Without Family History of Glaucoma

Type of Glaucoma	Patients With FHG, *n*	Mean Age at Diagnosis, y	Patients Without FHG, *n*	Mean Age at Diagnosis, y	Earlier Diagnosis in Patients With FHG	Age Difference, y	*P* Value
POAG	533	51.6 ± 12.8	741	57.1 ± 11.9	Yes	−5.5	0.0001
PACG	97	52.1 ± 13.4	124	59.2 ± 11.4	Yes	−7.1	0.0001
OH	53	48.3 ±13.1	80	53.0 ± 10.9	Yes	−4.7	0.03
PG	17	35.4 ± 9.3	32	48.2 ± 12.6	Yes	−12.8	0.0002
NTG	50	56.8 ± 13.0	97	57.4 ± 13.7	No	−0.6	0.8
PEX	14	62.6 ± 8.0	51	66.4 ± 7.7	No	−3.8	0.1

Gramer, et al. IOVS 2014;55:259-64

WVUMedicine

Glaucoma Screening
Family History

Investigative Ophthalmology & Visual Science

TABLE 3. Frequency of Glaucoma or Ocular Hypertension in 12 Groups of Relatives of Patients With POAG, NTG, and OH

Group of Relatives	POAG			NTG			OH		
	Total Number of Patients Who Provided Information on This Group of Relatives	Number of Patients in Whose Relatives Glaucoma or OH Had Been Diagnosed	%	Total Number of Patients Who Provided Information on This Group of Relatives	Number of Patients in Whose Relatives Glaucoma or OH Had Been Diagnosed	%	Total Number of Patients Who Provided Information on This Group of Relatives	Number of Patients in Whose Relatives Glaucoma or OH Had Been Diagnosed	%
Siblings	656	194	29.6	76	14	18.4	67	19	28.4
Children	866	64	7.4	92	2	2.2	95	7	7.4
Mother	873	212	24.3	98	23	23.5	94	25	26.6
Father	747	109	14.6	86	13	15.1	79	9	11.4
Maternal									
Grandmother	319	44	13.8	39	8	20.5	32	6	18.8
Grandfather	289	21	7.3	35	4	11.4	27	2	7.4
Aunts	311	51	16.4	38	8	21.1	33	4	12.1
Uncles	287	27	9.4	32	6	15.6	28	3	10.7
Paternal									
Grandmother	255	27	10.6	33	3	9.1	32	4	12.5
Grandfather	237	19	8.0	31	1	3.2	28	0	0
Aunts	245	33	13.5	33	2	6.1	24	0	0
Uncles	227	13	5.7	30	0	0	25	0	0

Gramer, et al. IOVS 2014;55:259-64

WVUMedicine

The Prevalence of Definite Open-Angle Glaucoma as Reported in Other Studies

Study	Racial/Ethnic Group	Age-Specific Prevalence					
		Age Groups (yrs)					
		40–49	50–59	60–69	70–79	80+	Total
Baltimore Eye Study[1]	African American	1.27	4.15	6.19	8.88	12.87	4.97
Barbados Eye Study[2]	Afro-Caribbean	1.4	4.1	6.7	14.8	23.2	6.8
LALES	Latino	1.32	2.92	7.36	14.72	21.76	4.74
Proyecto VER[3]	Latino	0.50	0.59	1.73	5.66	12.63	1.97
Baltimore Eye Study[1]	NHW	0.18	0.32	1.53	3.33	1.94	1.44
Blue Mountains Eye Study[4]	NHW	0.4*		1.3	4.7	11.4	3.0
Visual Impairment Project[5]	NHW	0.5	1.5	4.5	8.6	9.9	3.4
Beaver Dam Eye Study[6]	NHW						2.1
Roscommon[7]	NHW		0.72	1.76	3.2	3.05	1.88

LALES = Los Angeles Latino Eye Study; NHW = non-Hispanic White

WVUMedicine

Screen high-risk population

- Glaucoma is 6 to 8 times more common in African Americans than Caucasians.
- African Americans are 15 times more likely to be blind from glaucoma than Caucasians.

Rudnicka et al.. Ophthalmol. Vis. Sci. October 2006 vol. 47 no. 10 4254-4261
Tielsch JM, et al J.. JAMA. 1991 Jul 17;266(3):369-74.
Varma et al. Ophthalmology. 2004; 111: 1439-48

WVUMedicine

Projected Clinical Outcomes of Glaucoma Screening in African American Individuals

Joseph A. Ladapo, MD, PhD; Steven M. Kymes, PhD; Jonathan A. Ladapo, PhD; Veronica C. Nwosu, PhD; Louis R. Pasquale, MD

Objectives: To project the clinical impact of routine glaucoma screening on visual outcomes in middle-aged African American individuals and help guide glaucoma screening policy.

Methods: Using data from the Eye Diseases Prevalence Research Group and Baltimore Eye Study, we developed a microsimulation model to project visual outcomes in African American individuals screened for glaucoma under a national screening policy using frequency-doubling technology. We projected the impact of universal screening on glaucoma-related visual impairment (acuity worse than 20/40 but better than 20/200 in the better-seeing eye) and blindness (acuity 20/200 or worse in the better-seeing eye). The diagnostic characteristics of frequency-doubling technology and the hazard ratio for glaucoma progression in treated patients were informed by meta-analyses of randomized controlled trials.

Results: Implementation of a national glaucoma screening policy for a cohort of African American individuals between the ages of 50 and 59 years without known glaucoma would reduce the lifetime prevalence of undiagnosed glaucoma from 50% to 27%, the prevalence of glaucoma-related visual impairment from 4.6% to 4.4% (4.1% relative decrease), and the prevalence of glaucoma-related blindness from 6.1% to 5.6% (7.1% relative decrease). We project the cost of the program to be $80 per screened individual, considering only the cost of frequency-doubling technology and confirmatory eye examinations. The number needed to screen to diagnose 1 person with glaucoma is 58. The number needed to screen to prevent 1 person from developing visual impairment is 875.

Conclusions: Routine glaucoma screening for middle-aged African American individuals is potentially clinically effective but its impact on visual impairment and blindness may be modest. However, we did not assess the impact on visual field loss.

Arch Ophthalmol. 2012;130(3):365-372

Screen High-Risk Communities

- Projections for national glaucoma screening of African Americans 50 to 59 years old.
- Reduce the lifetime prevalence of undiagnosed glaucoma from 50% to 27%.

Table 3. Model Predictions of Visual Impairment Prevalence in African American Individuals With Glaucoma

Age, y	Usual Care Visual Impairment, %[a]	Screening Policy		
		Visual Impairment, %[a]	Absolute Reduction	Relative Reduction, %
50-59	1.7	1.6	−0.1	−3.5
60-69	3.7	3.5	−0.2	−6.2
70-79	6.6	6.3	−0.3	−3.9
≥80	10.5	10.1	−0.3	−3.0
Overall[a]	4.6	4.4	−0.2	−4.1

Ladapo JA, Kymes SM, Ladapo JA, Nwosu VC, Pasquale LR. Arch Ophthalmol. 2012 Mar;130(3):365-72.

WVUMedicine

Where to screen?

- In-office comprehensive eye exam
  - Not available to those with barriers to healthcare and access to office
- Community screening
  - Screen high-risk groups in their communities
  - Bring the test to the patients

The Philadelphia Glaucoma Detection and Treatment Project

- initiative aimed at improving the detection, treatment, and follow-up of high risk subjects
    - African Americans >= 50 years, others >= 60 years, family history
- VA, IOP, pachymetry, optic nerve examination, VF (Octopus), fundus photography
    - Awareness workup beforehand
- 1649 subjects from 43 community centers
- 39.1% glaucoma-related diagnoses, 9.2% narrow angles, 10% glaucoma

WVUMedicine

Philadelphia Glaucoma Detection and Treatment Project

- Initiative aimed at improving the detection, treatment, and follow-up of high risk subjects
  - African Americans >= 50 years
  - Others >= 60 years, family history
- VA, IOP, pachymetry, optic nerve examination, VF (Octopus), fundus photography
- Awareness workup beforehand
- 1649 subjects from 43 community centers
  - 39.1% glaucoma-related diagnoses,
  - 9.2% narrow angles,
  - 10% glaucoma

Am J Ophthalmol. 2017 Sep;181:114-124

WVUMedicine

Eye Screening New York Project

- Community based glaucoma screening program in high risk communities
  - VA, IOP, FDT, and optic nerve cup/disk ratio (C/D)
- Glaucoma suspects
  - IOP ≥ 21 mm Hg, abnormal FDT, or cup/disc ≥ 0.5.
- 2,118 subjects (25%) were referred as glaucoma suspects
  - 610 (28.8%) followed up
  - 52% confirmed to have glaucoma

Al-Aswad et al., *Cogent Medicine* (2017), 4: 1367059

WVUMedicine


Clinical and Epidemiologic Research

Population and High-Risk Group Screening for Glaucoma: The Los Angeles Latino Eye Study

Brian A. Francis,[1] Rohit Varma,[1,2] Cheryl Vigen,[2] Mei-Ying Lai,[2] Jonathan Winarko,[1] Betsy Nguyen,[1] Stanley Azen,[1,2] and the Los Angeles Latino Eye Study Group[3]

- Largest & most comprehensive screening study to date.
- 6082 patients underwent population screening with HVF, FDT, IOP, CCT, optic nerve evaluation
- Dichotomized results:
  - HVF: as examined by experts
  - FDT: any/ no defect
  - CCT: ≤504 microns
  - IOP ≥ 21 mmHg
  - C:D ≥0.7 or 0.8

WVUMedicine

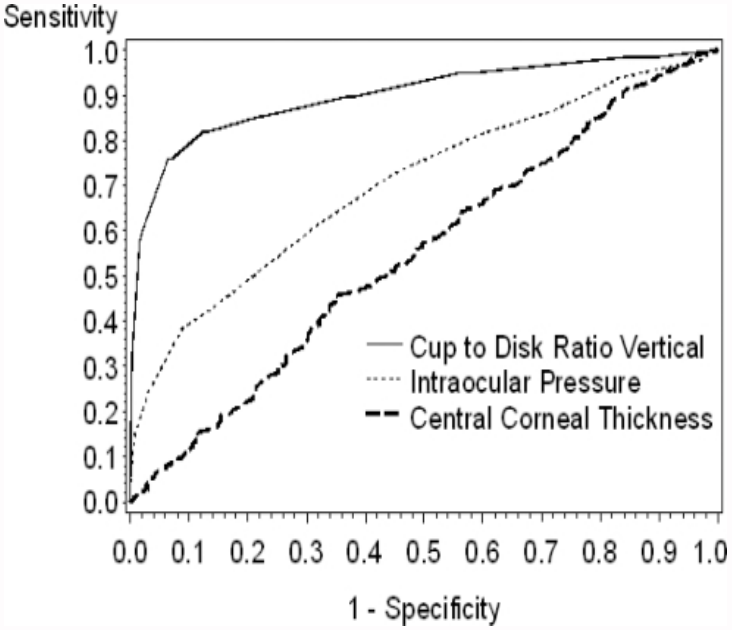
Clinical and Epidemiologic Research

Population and High-Risk Group Screening for Glaucoma: The Los Angeles Latino Eye Study

Brian A. Francis,[1] Rohit Varma,[1,2] Cheryl Vigen,[2] Mei-Ying Lai,[2] Jonathan Winarko,[1] Betsy Nguyen,[1] Stanley Azen,[1,2] and the Los Angeles Latino Eye Study Group[3]

- No single parameter was useful for Glaucoma screening

- Combination of vertical C/D ratio, HVF, and IOP provides the best sensitivity/specificity
  - Sensitivity .98
  - Specificity .80



WVUMedicine

Teleophthalmology

- New screening and diagnostic tool
  - Remote or underserved communities
- Digital photograph of the optic nerve head and/or retina
  - Qualitative and quantitative information
    - Interpretation by trained personnel
    - Automated classification using image analysis
- Combination with visual field exams
  - Combination of tests may improve sensitivity and specificity
- Active area of research

WVUMedicine

ORIGINAL STUDY

Glaucoma Detection Using Optic Disc Images From the English National Screening Programme for Diabetic Retinopathy

Hon Shing Ong, MBBS, Samantha Levin, FRCOphth, FRANZCO, and Gillian Vafidis, FRCOphth

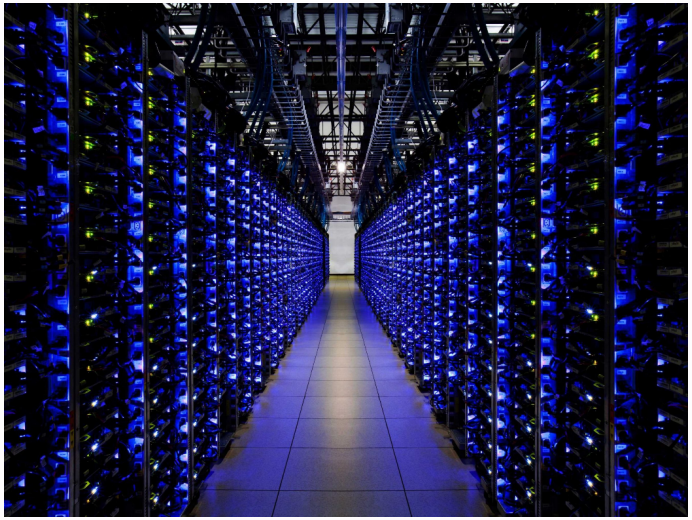
Diabetic Retinopathy Screening Program UK

- 11,565 DRE Patients
- 216 suspected glaucoma- graders (1.87%)
- 170 identified as glaucoma
- 113 true positive
- 22 false positive

J Glaucoma 2012

Artificial Intelligence

- Automated tool for diagnosis
- Google Brain - deep learning AI system
    - detect diabetic retinopathy in fundus photograph
- Visulytix (AI platform for optic disc assessment and diabetic retinopathy)



WVUMedicine

Conclusion

- Glaucoma is a public health problem that would benefit from a screening program.

- No current tests meet the desired combinations of sensitivity, specificity, cost, and ease-of-use required for population screening.

- Focusing on screening
- High risk populations
- Sight-threatening glaucoma

- Teleophthalmology can help expand glaucoma screening to large populations economically.

WVUMedicine

"By God, For A Minute There It Suddenly All Made Sense!"