SCREENING FOR GLAUCOMA IN INDIA WITH THE FREQUENCY DOUBLING PERIMETRY TEST.

By

Steven L. Mansberger, M.D.

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CERTIFICATE OF APPROVAL

This is to certify that the MPH thesis of

Steven L. Mansberger

Has been approved

Thomas Becker - [redacted]
Professor in charge of thesis

Dongseok Choi- [redacted]
Member

Chris A. Johnso[redacted]
Member

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ABSTRACT

Purpose: To determine the utility of Frequency Doubling Technology perimetry (FDT) for screening for glaucoma in a rural, developing world setting.

Methods: We performed FDT (C-20-5 screening protocol), best-corrected visual acuity, tonometry, anterior segment biomicroscopy, cataract grading with the Lens Opacities Grading System (LOCS), and dilated ophthalmoscopy in participants over 35 years old in Southern Indian villages near Madurai. The FDT was repeated in participants with an abnormal location or an unreliable result. We defined an abnormal FDT as one abnormal location on the FDT printout present on the initial and repeat examination. We determined the diagnostic precision of FDT for the "gold standards" of a glaucomatous optic disc (a cup to disc ratio (C/D) of greater than 0.5 or glaucomatous features), C/D greater than 0.6, and C/D greater than 0.7.

Results: We tested both eyes of 296 participants over three days with a single FDT machine. Because the test was repeated if unreliable or abnormal, 826 FDT examinations were completed. Nineteen percent (114/592) of eyes were unreliable on initial FDT testing but only 5% (30/592) had a repeatable, unreliable FDT. We used one eye for analysis. We excluded 51 eyes due to visual acuity worse than 20/30 (n=5), unreliable FDT results (n=15), or indeterminate FDT results (n=31). When we analyzed one eye of a patient, 2% (6/245) of eyes had a glaucomatous optic disc and a repeatable, abnormal FDT. Sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of FDT for an glaucomatous optic disc were 11%, 87%, 19%, 76%, and 69%, respectively (p=.58, Chi-Square = .30). Sensitivity, specificity, positive predictive

value, negative predictive value, and accuracy of FDT for a C/D >0.6 were 6%, 87%, 3%, 93%, and 81%, respectively (p=.38, Chi-Square = .76). Sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of FDT for a C/D >0.7 were 0%, 87%, 0%, 99%, and 86%, respectively (p=.51, Chi-square = .44).

Conclusion: The FDT screened large numbers of persons for glaucoma rapidly with reliable results. However, FDT testing was not sensitive compared to the gold standards, although specificity was reasonably high.

INTRODUCTION

Glaucoma is an optic nerve disease associated with a loss of peripheral vision. Patients with advanced glaucoma have tunnel vision, which means they are only able to see objects straight in front of them because their peripheral vision is absent. Clinicians diagnose glaucoma by observing typical changes to the optic disc and abnormalities of the visual field. Glaucoma screening is important because it is a major cause of blindness, it is treatable, and it can be detected in the early stages.

Public Health Impact of Glaucoma

Glaucoma is the second leading cause of blindness and an important public health problem worldwide[1]. For example, in the U.S., the total cost of blindness was $4.1 billion in 1990 (vision less than 20/200 in the better eye or visual field extent of less than 10 degrees radius). The cost of vision loss may be even more expensive as these costs do not include the individuals with visual impairments that are less than the definition of legal blindness. More importantly, preventing blindness in persons under 20 years of age and among working-age adults would save the federal budget $1.0 billion per year[2].

In comparison to developed countries, the public health effects of blindness are thought to be more devastating in underdeveloped parts of the world. While the World Health Organization estimated that there are 40 million blind individuals worldwide, an astounding 90% of blind individuals live in developing countries[1]. One adult with bilateral blindness in a rural, agrarian community in the developing world requires up to five individuals to care for him.

Blindness prevents these individuals from participating fully in the labor force and overall production of the family and community diminishes. This burden prevents children from attending school because they need to care for their relative or provide more work in the fields. In this manner, blindness propagates poverty and illiteracy.

In both developed and developing countries, delayed diagnosis is one of the greatest risk factors for blindness due to glaucoma[3]. Only 50% of all glaucoma patients have been diagnosed[4]. This delay in diagnosis may be due to several causes. First of all, glaucoma is without symptoms in the early to moderate stages of the disease process. Without any symptoms, patients may not realize that there is an abnormality with their vision until the late stages of the disease. Patients and primary medical providers may not recognize the importance of routine eye exams. In contrast to the American Academy of Ophthalmology guidelines, which states that Americans over the age of 50 years should have an eye exam once every year, the average Portland adult has an eye exam once every five years[5]. Nationwide, in comparison to Portland, eye exams may be even less frequent because the ratio of eye care providers to the population is smaller. Even if the undiagnosed glaucoma patient makes it to the office, eye care providers vary in their ability to detect early signs of glaucoma[6, 7]. Their abilities are affected by the thoroughness of the eye examination, the test procedures that are employed, and the individual skills of the practitioner.

India is one of the most populated, developing countries. In 1995, India contained 23.5% of the total number of people in the world with bilateral

blindness[8]. Glaucoma causes 23% of blindness in India. It is the second most common cause of blindness (after cataract) and the most common cause of permanent blindness[8]. The prevalence of all types of glaucoma in individuals over the age of 40 years of age is approximately 4%[9-12].

Glaucoma Screening

To decrease the public health impact of glaucoma, an effective glaucoma screening program is needed. Desirable features of this program would include such characteristics as immediate feedback of the results, high sensitivity and specificity, targeted towards populations with high prevalence of disease, and performance without expert personnel. The personnel performing the screening program could have minimal ophthalmic knowledge but be well trained in the use of the screening mechanism. They could identify patients at high risk of blindness and refer them to an eye care center. A screening program including these characteristics would be cost effective, efficient, and a first step towards decreasing blindness worldwide.

Traditional screening techniques for glaucoma include measurement of intraocular pressure by means of tonometry, evaluation of the optic disc, and examination of the visual field. Each of these approaches has a number of pitfalls as described below.

Tonometry

Tonometry is the evaluation of the pressure within the eye, commonly referred to as intraocular pressure (IOP). While IOP is the strongest risk factor for development of glaucoma, it has low sensitivity. The traditional normal cutoff

for IOP is 21 mm Hg. With this cutoff, 50% of patients with glaucoma may not have IOP greater than 21mm Hg[13]. Additionally, the large diurnal variation in IOP[14] makes it difficult to detect abnormalities when present only during certain times of the day. Tonometry requires contact between the instrument and the patient. This contact increases the risk of transferring infections[15] and causing corneal abrasions when compared to optic disc evaluation or visual field testing. Overall, the results of screening for glaucoma by evaluation of IOP have been less than ideal[16].

Optic Disc Evaluation:

Optic disc evaluation presents other difficulties. It requires technical expertise to perform photography of the optic disc and needs expert opinion to grade the optic disc photos. Also, experts disagree when grading optic nerve photos[17]. Additionally, optic disc photos are difficult to obtain because of ocular media abnormalities, lack of technical expertise to perform the test, and limited patient cooperation such as blinking during photography. The difficulty in attaining optic disc photos was highlighted in the Baltimore Eye Study. In this study, optic disc photos were difficult to obtain in 30% of individuals[4].

Visual Field Testing:

In contrast to photos, visual field testing has good diagnostic precision[18, 19]. However, visual field testing has other disadvantages. One disadvantage is that the machines to perform visual field testing can be expensive and difficult to transport. For example, a popular visual field machine made by Humphrey Instruments (HFA II, Humphrey Instruments Inc., Dublin, CA) weighs 80 lbs and

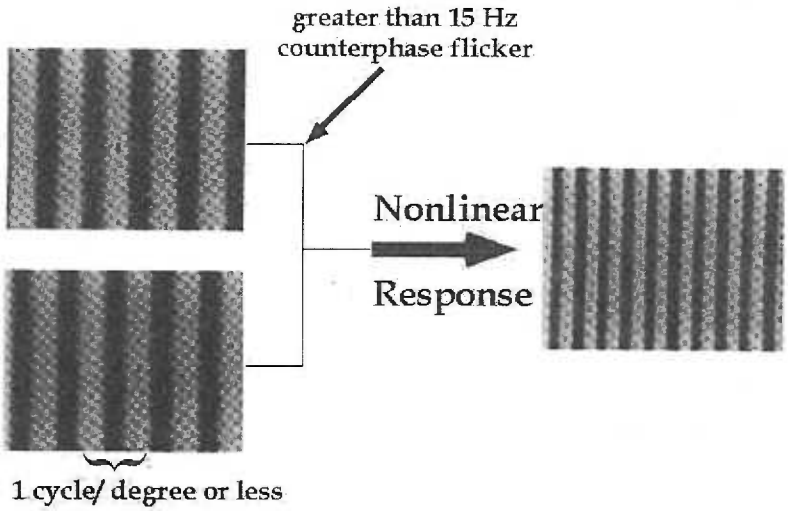
costs approximately $30,000. Also, the testing is time consuming requiring up to 15 minutes per eye. Furthermore, the testing can be tedious for the patient and examiner because it requires a great deal of concentration by the patient to recognize a stimulus that is close to the visual threshold.

Because the stimulus is so close to the visual threshold, patients have trouble being reliable in recognizing the stimulus appropriately, especially those inexperienced in perimetry[20]. Also, visual field testing requires a great deal of time by the examiner because a novice patient may require constant reinforcement and encouragement. Additionally, interpretation of test results for visual field screening procedures is difficult because normative data is not available and clinical validation studies have not been performed to determine their performance characteristics. Finally, abnormalities of the visual field can occur due to small pupil size[21-23], uncorrected refractive error[24, 25], fatigue[26], and learning effects[27-31].

Visual field testing uses full threshold and suprathreshold procedures. The full threshold testing strategy presents visual stimuli above and below the detection threshold to determine the exact sensitivity of a particular location of the visual field. In contrast, suprathreshold testing presents a predetermined stimulus contrast that 95% of a normal sighted population can detect. If the patient does not recognize the initial stimulus, the instrument increases the intensity until the stimulus is seen. Investigators use suprathreshold testing most commonly for screening because of reduced test duration.

Frequency Doubling Technology (FDT) perimetry is a new method of visual field testing for glaucoma and other eye diseases. The basis of FDT perimetry is the frequency doubling effect. The frequency doubling effect occurs when a low spatial frequency sinusoidal grating (less than 1.0 cycles per degree) undergoes high temporal frequency counterphase flicker (greater than 15 Hertz). Under these conditions, twice as many light and dark bars appear in the grating than are physically present, i.e. the spatial frequency of the grating appears to be doubled **(Figure 1)**.

Figure 1: Frequency Doubling Effect.



The retina detects the FDT stimulus by using a subset of the total ganglion cell receptive fields[32]. Because only a subset of cells are used for detection of the stimulus, loss of these cells would result in abnormal sensitivity at an earlier time when compared to standard perimetry. Short wavelength automated perimetry, which similarly evaluates a subset of ganglion cell receptive fields,

demonstrated a decrease in sensitivity up to five years earlier than standard perimetry in ocular hypertensive patients converting to glaucoma [33, 34].

The FDT determines the contrast sensitivity for detecting the frequency doubling stimulus at either 17 (C-20 stimulus pattern) or 19 (N-30 stimulus pattern) visual field locations within the central visual field. The C-20 pattern consists of sixteen 10 degree by 10 degree squares (4 per quadrant) and a central circular 10 degree diameter stimulus. The N-30 pattern is identical, except that it includes two additional squares just above and below the horizontal midline between 20 and 30 degrees eccentricity for detection of subtle nasal steps. **Figure 2** illustrates the C-20 and N-30 presentation patterns.

Figure 2: The C-20 and N-30 presentation patterns for the left eye.

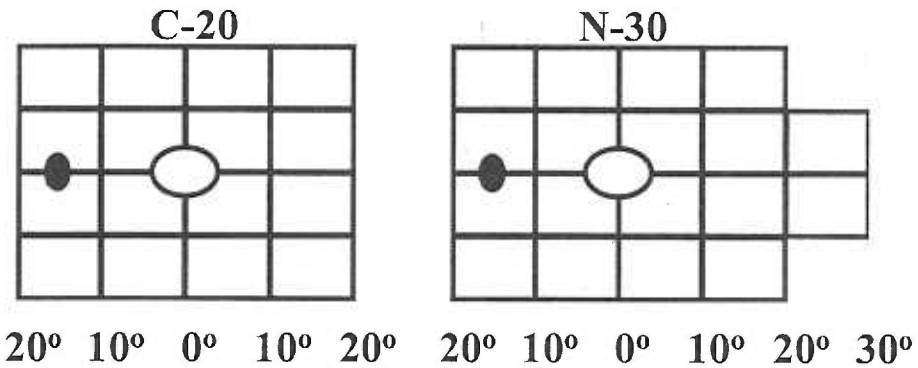


Figure 1

Both full threshold and suprathreshold procedures are available for the FDT. The full threshold procedure requires approximately 5 minutes per eye to perform. The suprathreshold procedure requires only about 35 to 45 seconds per eye. Because of this reduced test time, investigators use the FDT suprathreshold procedure most commonly for screening.

If the sensitivity of the location is worse than 95% of age matched normals (P<5%), the machine identifies the location with shading. The possibilities for shading on the FDT printout are no shading, gradually increasing shading corresponding to a P<5%, P<1%, and P<0.5%, and dark shading corresponding to a maximal stimulus.

Research has proven FDT perimetry to be highly specific and sensitive for detecting glaucoma using either the full threshold or the rapid screening mode in well-defined glaucoma and normal patients[35-38]. The FDT screening mode has reduced test duration as compared to standard perimetry but with comparable diagnostic precision[39].

In addition to its clinical performance characteristics, FDT perimetry has several other advantages for screening purposes in comparison to standard perimetry. The machine is portable because it weighs less than 15 lbs. It can be used on any stable surface such as a tabletop. The FDT is simple to operate requiring just a few buttons to be pressed. In addition to being simple to operate, participants find it easy to take the test[38]. Another advantage is that the test procedure is relatively unaffected by moderate amounts of uncorrected refractive error (up to 6 diopters). Additionally, pupil size does not affect the result as long as the pupil is 2mm in diameter or greater[36]. Finally, individuals taking the FDT test can wear their glasses, even if they contain a bifocal segment. For all of the above reasons, FDT perimetry appears to be well suited as a screening procedure for glaucoma but has not been tested in a community based, developing world setting.

OBJECTIVE

To determine the utility of Frequency Doubling Technology perimetry (FDT) for screening for glaucoma in a rural, developing world setting.

METHODS

We used a community based, cross sectional study design to examine the ability of FDT to screen for glaucoma in the developing world.

APC Study:

The Internal Research Board and Ethics Committee at Aravind Eye Hospital and Legacy Heath System, Portland, OR approved this study as a corollary to the Antioxidants in Prevention of Cataract (APC) Study. All of the investigations are in accordance with the guidelines of the Declaration of Helsinki. Each subject gave informed consent. **(Appendix)**

The APC Study is a prospective, randomized, placebo-controlled, triple-masked clinical trial to assess the ability of antioxidants (vitamins A, C, and E) to slow the rate of cataract progression. The study is based in five villages in the southern state of Tamil Nadu near the city of Madurai, India. Hindi is the language spoken by all villagers. The villages are primitive without running water, or a sewage system. Electricity is uncommon and thus exposure to modern media such as television is rare. The villagers produce rice and goat products. They complete their work without machinery by using manual techniques. The

villages were chosen because of their suspected stable population and the number of residents aged 35 to 50 years.

The inclusion criteria for the APC study were a best-corrected visual acuity of 20/40 or better and age 35 to 50 years old. Exclusion criteria were a visual acuity worse than 20/40 in either eye at recruitment, age other than 35 to 50 years old during recruitment, history of ocular surgery, history of diabetes, history of radiation therapy, history of corticosteroid therapy, present use of vitamin supplements, traumatic or congenital cataract in either eye, infectious keratitis in either eye, occludable angle (by Von Herrick sign) in either eye, and random glucose greater than 140. **Table 1** shows the number of people screened, included, and excluded from APL study enrollment.

Table 1:

Total number of eligible subjects in target villages*	4,007
Total number of subjects screened	954
Number of subjects with exclusion criteria	83
Best corrected visual acuity less than 20/40	61
History of Diabetes	4
Previous Intraocular surgery	None
History of Radiation therapy	None
History of corticosteroid therapy	None
Present use of vitamin supplements	5
Presence of significant or traumatic congenital cataract	None
Presence of active infectitious keratitis	None
Narrow anterior chamber angle	None
Random blood glucose of greater than 140mg%	8
Other Medications	5
Number of subjects meeting inclusion and exclusion criteria	871
Number of subjects who declined enrolment	73
Number of subjects intially enrolled	798

* Meeting general screening inclusion criteria of 35 –50 years old with pinhole vision of 20/40 or better.

Study coordinators interviewed the participants regarding their alcohol and tobacco ingestion, drug use, diet, and sun exposure at enrollment. In addition,

during each year of the study, the interviewer determined if there were changes in ocular history, medical history, and medications. Testing in all patients included best corrected visual acuity with the ETDRS (Early treatment Diabetic Retinopathy Study) protocol, manifest refraction, intraocular pressure evaluations with the Tono-Pen® XL (Medtronic Solan, Jacksonville, FL. 32116-0980. USA), systemic blood pressure, and anterior chamber depth with a flashlight. After dilation with 0.8% tropicamide and 5.0% phenylephrine hydrochloride eye drops (Milmet Ltd. India, Ahmadabad, India), three clinicians independently completed a slit lamp evaluation of the lens, fundus, and optic nerve. They graded the lens using the Lens Opacification Classification System III (LOCS III) method[40]. At the conclusion of the grading, the final examiner performed a fundus and optic disc examination with a 90-diopter lens at the slit lamp.

The final examiner used a forced-choice design to grade the optic nerve as abnormal or normal based on its clinical appearance. The criteria for an abnormal optic nerve included any one or more of the following features: a cup to disc ratio (C/D) greater than 0.5, glaucomatous characteristics, or other abnormalities such as pallor or optic disc edema. Also, the examiner graded the C/D to the nearest 0.1 on an ordinal scale from 0.1 to 1.0. Finally, the examiner determined if the fundus was normal or abnormal and if abnormal, a description was written.

FDT Screening

The APC study was started in 1998. In 2001, the third year of the APC study, we added the FDT to the examination in two out of the five villages. While dilating and prior to slit lamp evaluation, the participants performed FDT testing in both eyes. Because the villages had recently attained electricity and were subject to random blackouts, diesel powered portable generators were brought to each testing site to provide emergency power for the FDT. We performed the FDT screening protocol, C-20-5 (FDT version 2.6, visual field version 1.02) indoors with uniform lighting conditions. The FDT downloaded and stored the results to a portable computer. Because many of the participants were unfamiliar with buttons and had never seen video games or television, they practiced with pushing and releasing the FDT button until they were familiar with using the FDT button. Using interpreters, we taught the participants to recognize and respond to the stimulus while maintaining fixation at the central target. To practice responding to the FDT stimulus, the participants used the simulation presented by the FDT during the entering of age and identifying information. Once the participant voiced understanding of the test and responded appropriately to the stimulus, we started the FDT testing. During the testing, we gave each participant constant supervision and encouragement.

If the FDT printout was abnormal (defined as one area of abnormal sensitivity) or unreliable (defined as over 33% fixation losses or false positive responses), we repeated the FDT. We completed the FDT a maximum of two times per eye. We performed a pilot study in a different village prior to the start

of this study. We found that the predictive ability was maximized with this approach. The results of a different study have similar findings[41]. The investigators performing the analysis of the optic disc and retina were masked to the results of the FDT testing and vice versa. The tests performed are listed in **Table 2**.

Table 2: Tests performed on participants

1. Systemic blood pressure
2. Finger stick glucose level
3. Best corrected visual acuity
4. Refraction
5. Tonometry by Tonopen® measurement
6. Pupil exam
7. Anterior segment biomicroscopy
8. Grading of cataract with the Lens Opacities Grading System III (LOCS) method
9. Dilated ophthalmoscopy of the fundus and optic disc
10. Frequency Doubling Technology perimetry (C-20-5 screening protocol)

Reliability Determination:

Each examiner viewed a selection of 10 optic disc stereo photographs from a database of glaucoma and normal patients. We calculated the kappa statistic to determine inter-observer reliability for the dichotomous outcome of

optic disc grading (glaucoma and normal). The kappa values were 0.80 (p=0.01), 0.78 (p=0.01), and 0.60 (p=0.04) between reviewer 1 and 2, reviewer 2 and 3, and between reviewer 3 and 1, respectively. A kappa value below 0.40 represents poor agreement, 0.40 to 0.75 indicates intermediate to good agreement, and greater than 0.75 indicates excellent agreement[42]. Therefore, the reliability was excellent to good for grading abnormal and normal optic discs.

For inter-observer reliability of C/D, we calculated a gamma statistic for each pair of reviewers[43]. The gamma statistic ranges from –1 to 1. A value of zero indicates no relationship. The gamma values were 0.80 ($p<0.001$), 1.00 ($p<0.001$), and 0.846 ($p<0.001$) between reviewer 1 and 2, reviewer 2 and 3, and between reviewer 3 and 1, respectively. These gamma values indicate excellent to good agreement for grading C/D.

Data Preparation:

We excluded from statistical analysis participants with visual acuity of 20/40 or worse due to cataract or ocular disease (other than glaucoma) that would be likely to cause a visual field defect (n=5). Because abnormal (defined as one area of abnormal sensitivity) and unreliable (defined as greater than 33% fixation losses or false positive responses) results on initial FDT testing were repeated, we used a combination of initial and repeat FDT testing for the final result.

A participant had a normal final result of FDT if any of the following three combinations occurred: a reliable, normal result on initial FDT testing; reliably abnormal on initial testing but reliably normal on repeat FDT testing; or unreliable

on initial testing but reliably normal on repeat FDT testing. A participant had an abnormal FDT result if there was a reliable, abnormal FDT result on initial testing and reliable, abnormal results on repeat testing. Finally, a participant had a indeterminate result if any of these three combinations occurred: unreliable result on repeat testing; an unreliable result on initial testing but a reliably abnormal on the subsequent testing; or an abnormal or unreliable result on initial testing but refused subsequent testing. Finally, a participant had a repeatable, unreliable result if there was an unreliable result on initial and subsequent FDT testing.

We excluded 51 eyes due to visual acuity worse than 20/30 (n=5), unreliable FDT results (n=15), or indeterminate FDT results (n=31). **Table 3** is a cross table diagram of the possible combinations of results of the initial and repeat FDT testing and the final result of FDT testing for statistical analysis.

Table 3: Cross Table Diagram of indicating the possible combinations of initial and repeat FDT testing with the final result determination*. Blank cells indicate that no participant had that particular combination of results.

		Repeat FDT Testing			
		Reliably Abnormal	Reliably Normal	Unreliable	Test not Performed
Initial FDT Testing	Reliably Abnormal	A	B	D	D
	Reliably Normal				B
	Unreliable	D	B	C	D
	Test not Performed				D

***A=abnormal result (n=31), B=Normal Result (n=214), C=Unreliable (n=15, excluded from statistical analysis), D=Indeterminate result (n=31, excluded from statistical analysis)**

After the final FDT results were determined, we chose the eye with the worst optic disc appearance for analysis. If the eyes were similar in optic disc appearance, a computerized random number generator determined the eye used for statistical analysis. We selected the worst eye of a participant because a participant limited to monocular disease would still be referred for diagnosis and treatment in most screening protocols.

Statistical analysis:

We used SPSS® (version 10.0, SPSS Inc., Chicago, IL 1999.) for all statistical analyses.

The main objective was to determine the diagnostic precision of the FDT as a screening test for optic disc features typical of glaucoma. To determine this, we assessed the sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of FDT for the following commonly used gold standards: a glaucomatous optic disc (C/D greater than 0.5 or glaucomatous features), C/D greater than 0.6, or a C/D greater than 0.7. We determined the association of the FDT with these criteria by using a chi square test. Our cutoff for statistical significance was a p-value of 0.05. Because investigators have previously used IOP as a screening test, we determined the diagnostic precision of IOP greater than 20 mm Hg for these same gold standards.

We used a reverse, stepwise logistic regression equation to determine if any variables were associated with the dependent variables of an abnormal optic nerve, C/D > 0.6, and C/D > 0.7, and an abnormal FDT. This model will determine single variate as well as multivariate combinations that are associated with the dependent variables. The model included the independent variables of age, gender, IOP, systolic blood pressure, and diastolic blood pressure. The model used a score value probability of 0.05 and 0.10 for entrance and removal from the model, respectively.

Results

Demographics:

Two hundred ninety six subjects participated in this study. Patients with glaucomatous optic discs were older than patients with normal optic discs **(Table 4).** Otherwise, the demographic characteristics were similar.

Table 4: Demographics (mean ± SD, (range))

Variable	Overall (n=296)	Normal Optic Discs (n=215)*	Glaucomatous Optic Discs (n=76)*	P value
Age	44.6 ± 6.5 (35-65)	44.1 + 6.5 (30-65)	46.0 + 6.4 (35-63)	0.03
Male Gender, N (%)	119 (40%)	86 (39%)	33 (43%)	0.58
Intraocular Pressure	13.2 ± 3.4 (4-23)	13.2 ± 3.3	13.3 ± 3.5	0.82
Ethnicity	100% Asian Indian	215 (100%)	76 (100%)	0.99

*Intraocular pressure was not determined in 4 normal and 1 glaucomatous optic discs

FDT Testing Results:

We completed FDT testing in both eyes of 295 (590 eyes) participants. One person refused to complete the testing during the first eye examination. We repeated FDT testing in 42% of participants due to being abnormal (114/590 (19%)) and/or unreliable 131/590 (22%)). With repeat testing, only 30/590 (5%) eyes had a repeatable, unreliable FDT. Nine eyes did not have repeat FDT testing despite having an abnormal or unreliable result on initial FDT testing. With both eyes tested and repeat testing for unreliable and abnormal visual fields, we performed 826 FDT examinations over three days with a single FDT machine.

When one eye of a patient was used for analysis, 2.4% (6/245) of eyes had a glaucomatous optic disc and repeatable abnormal FDT. Overall, the diagnostic precision of FDT indicated low sensitivity but high specificity for the outcome criteria of a glaucomatous optic nerve, a C/D > 0.6, or a C/D > 0.7 **(Table 5).**

Table 5: Diagnostic Precision of FDT for the gold standard tests: glaucomatous optic nerve, cup to disc ratio (C/D) greater than 0.6, and C/D greater than 0.7.

	Sensitivity	Specificity	PPV*	NPV*	Accuracy	Chi square value (p value)
Glaucomatous Optic Nerve	11%	87%	19%	76%	69%	.30 (.58)
C/D > 0.6	6%	87%	3%	93%	81%	.76 (.38)
C/D > 0.7	0%	87%	0%	99%	86%	.44 (.51)

*PPV=positive predictive value, NPV=negative predictive value
+ - Zero patients had a C/D greater than 0.7 and an abnormal FDT.

FDT Result and Cup to Disc Ratio:

Table 6 is a cross table of FDT result and C/D. The data show an increase in the percentage of abnormal FDT results in the columns representing a C/D equal to 0.3 and 0.4. Because this distribution does not show a relationship between increasing C/D with abnormal FDT, changing the requirements for an abnormal optic nerve by C/D will not improve the predictability of the FDT. In addition, changing the requirements for an abnormal FDT would not appreciably increase the diagnostic precision either.

Table 6: Cross table analysis of FDT result vs cup to disc ratio (C/D)

	C/D of the Worst Eye by Structure									
	.0	.1	.2	.3	.4	.5	.6	.7	.8	Total
Abnormal FDT	1	1	3	18	6	2	0	1	0	32
Normal FDT	1	14	46	83	28	19	11	13	3	218
Total	2	15	49	101	34	21	11	14	3	250

Intraocular Pressure as the Screening Test:

Using IOP greater than 20 mm Hg in place of FDT as the screening test shows low sensitivity and high specificity for the outcome criteria of a glaucomatous optic disc, C/D greater than 0.6, and a C/D greater than 0.7 **(Table 7).** In this table, IOP > 21 was statistically associated with C/D >0.6 (chi square =.1, p=0.02)

Table 7: Diagnostic Precision of IOP > 20 mm Hg for the gold standard tests: glaucomatous optic nerve, cup to disc ratio (C/D) greater than 0.6, C/D greater than 0.7.

	Sensitivity	Specificity	PPV*	NPV*	Accuracy	Chi square value (p value)
Glaucomatous Optic Nerve	4%	98%	43%	75%	74%	1.16 (.28)
C/D > 0.6	10%	98%	29%	94%	92%	5.08 ** (.02)
C/D > 0.7	0%	98%	0%	98%	96%	0.13 (.72)

*PPV=positive predictive value, NPV=negative predictive value
**Statistically significant

Other Variables Tested:

Other variables were sampled for their association for the dependent variables of a glaucomatous optic disc, C/D >0.6, or C/D >0.7 using a single variate and multivariate logistic regression equation **(Table 8).** Age is a weak predictor of an glaucomatous optic nerve with F statistic of 4.5 (p= 0.04) with one degree of freedom. However, the dependent variables of C/D > 0.6 and >0.7, did not have a statistically significant predictive variable (p >0.05).

Table 8: T score (p values) of single variate logistic regression for the dependent variables of abnormal optic nerve, cup to disc ratio (C/D) >0.6, and C/D>0.7 with the predictor variables of intraocular pressure, hypertension, age, and gender.

Variable	Glaucomatous Optic nerve	C/D > 0.6	C/D > 0.7
Intraocular pressure	0.31(0.76)	-0.76 (0.45)	0.15 (0.88)
Systolic Blood Pressure	0.98 (0.33)	0.35 (0.73)	0.15 (0.87)
Diastolic Blood Pressure	0.38 (0.71)	0.26 (0.79)	0.44 (0.66)
Age	4.5 (0.04)*	1.2 (0.25)	0.34 (0.73)
Gender	0.06 (0.95)	1.0 (0.30)	-0.43 (0.67)

*statistically significant

To determine if there were any variables predictive of FDT performance, we completed a similar procedure using the FDT result as the dependent variable **(Table 9).** We found no statistically significant predictor variable for the FDT result.

Table 9: T score (p values) of single variate logistic regression for the dependent variable of FDT result with the predictor variables of intraocular pressure, cup to disc ratio (C/D), hypertension, age, and gender.

	FDT result
Intraocular pressure	-0.76 (0.45)
C/D	0.44 (0.66)
Systolic Blood Pressure	-0.66 (0.51)
Diastolic Blood Pressure	0.09 (0.93)
Age	-0.63 (0.53)
Gender	0.13 (0.90)

DISCUSSION

The results of FDT testing were not significantly associated with any of the criteria used for the definition of glaucoma including: the clinical appearance of the abnormal optic disc, a cup-to-disc-ratio > 0.6, or a cup-to-disc ratio > 0.7. Several other studies using FDT contradict these results. The amount of compliance with the evaluation of a diagnostic test, the methodological standards used, and low correlation of optic disc and visual fields explain some of the discrepancies in predictability between our study and previous studies.

Compliance with Methodological Standards:

Methodological standards for the evaluation of diagnostic tests have been discussed in the literature [44, 45]. **Table 10** delineates ten standards for evaluation of a diagnostic test. Authors should specify the participant population. This should include information regarding the age and sex distribution, the recruitment method, and the inclusion and exclusion criteria. This is important because it allows the reader to decide whether the results of the study in question can be applied to a particular patient population.

In addition, authors should analyze all pertinent subgroups entered in the study. Like the first standard, this allows readers to determine whether the results of the study apply to their patient population. For example, if researchers perform a screening test for glaucoma in participants with a higher proportion of diabetes than is found in the population of interest, the results may not be

applicable. One can expand this standard to recommend that a test should detect early, moderate and advanced glaucoma and not just the latter.

Furthermore, a study should be designed to prevent work-up bias. Work-up bias occurs when all patients recruited into the study do not have both the diagnostic as well as the gold standard test. This affects the results of the study because only patients that fail certain criteria are referred for the definitive exam. Work-up bias increases specificity because all patients that passed the baseline criteria (including being normal on the diagnostic test) are called normal. It increases the positive predictive value because the prevalence of abnormal eye conditions is higher. Work-up bias occurred In the Baltimore Eye Study[4] because only the patients who failed the evaluation tests were referred for a definitive ophthalmologic examination. Also, forty percent of the patients did not have a dilated eye exam. Therefore, investigators classified patients as normal based on the results of baseline testing but may have classified them differently if they had completed a dilated eye exam. This discrepancy between the clinical diagnosis of the optic disc and the visual field result can occur frequently[46].

Additionally, investigators should avoid review bias. Review bias occurs when there is not an independent review of the diagnostic and the gold standard test. An example of this bias would be an examiner who has access to the information from the gold standard test and the screening test while performing the eye exam for final diagnosis of the patient. The examiner may diagnose a patient as normal, even though they had a normal visual field result but an

abnormal optic disc to coincide with the diagnostic test. Review bias may either increase or decrease the sensitivity and specificity of the diagnostic test.

In addition, Investigators should present the variability of the results by including the confidence interval or standard error. In addition to presenting the variability, one should determine whether a statistical association is present between the disease and the diagnostic test.

Furthermore, one should present indeterminate results or at least a description of the analysis completed for patients that were not clearly defined into a diagnostic group. For example, a study design may exclude from analysis patients with an enlarged cup-to-disc ratio but normal visual fields instead of evaluating them similarly. Separating borderline cases decreases the variability of each group tested, more clearly differentiates the groups, and improves both sensitivity and specificity.

Investigators should reference inter- and intrareliability of the testing procedure and gold standard. In addition to reliability, investigators should indicate if repeat testing for a procedure is required. If repeat testing is needed, the methods should indicate whether the initial or repeat test result is used for the final diagnosis. With visual fields, this is particularly important as a learning curve is possible[27-31]. Also, repeating visual fields may decrease the feasibility of efficient screening.

Finally, the methods should clearly define the gold standard. This guideline helps readers compare studies.

Table 10: Criteria for evaluating a diagnostic test for glaucoma screening
1. Specification of the participant population. a. Including age, race, gender, severity of glaucoma, type of glaucoma
2. Analysis of all pertinent subgroups entered in the study. a. This should including evaluation of early, moderate and advanced glaucoma when possible.
3. Prevention of work-up bias. a. All patients recruited into the study should have both the diagnostic testing as well as the gold standard.
4. Prevention of review bias by ensuring independent interpretation of both The diagnostic test and the gold standard procedure.
5. Presenting the variability of the results by including confidence intervals, standard errors, and receiver operator curves of the measures of diagnostic precision.
6. Appropriate statistical tests should be applied to determine the associations of the disease of interest with the diagnostic test.
7. Results should be presented in all patients tested including indeterminate test results. a. If not, a description should be provided of the number of patients excluded and the reasons for exclusion.
8. The reliability of the testing and evaluation procedures should be indicated or referenced in the study.
9. Presentation of the number of times a test needed to be repeated. a. This helps determine applicability, an important part of a screening test.
10. The gold standard should be widely accepted and clearly described to compare screening programs evaluating similar machines.

Previous FDT studies have variable compliance with the standards for evaluation of a diagnostic test **(Table 11).** In particular, the third criterion that all diagnostic testing should be completed in all participants was observed in 100% of studies. In contrast, criterion six (appropriate statistical testing was completed to determine associations between the screening and gold standard test) had the least compliance and was completed in only 11% of studies.

In individual studies, the compliance with the 10 criteria ranged from 40 to 80%. When compared to studies examining other diagnostic tests for glaucoma screening[44], the compliance with these standards was similar.

Table 11: Compliance with the 10 Criteria (see Table 10) for evaluation of a diagnostic test for glaucoma screening in frequency doubling perimetry screening studies (Y=yes, N=no, U=unknown).

	Criteria										
Study	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**% of criteria met per study**
Khong, et al	Y	N	Y	U	Y	Y	Y	N	N	Y	**60**
Patel, et al	Y	Y	Y	U	N	N	N	N	N	Y	**40**
Quigley	Y[a]	N	Y	Y	N	N	Y	N	Y	Y	**60**
Paczka, et al	Y	Y	Y	Y	Y	N	Y	N	N	Y	**70**
Johnson, et al	Y[a]	Y	Y	Y	Y	N	Y	Y	N	Y	**80**
Trible, et al	Y	Y	Y	Y	N	N	N	N	N	Y	**50**
Yamada, et al	N	Y[b]	Y	Y	Y	N	N	N	Y	Y	**60**
Burnstein, et al	Y	U[c]	Y	Y	Y	N	N	N	Y	Y	**60**
Cello, et al	Y[a]	Y	Y	U	Y	N	Y	N	N	Y	**60**
% of all studies that met criteria	**89**	**67**	**100**	**67**	**67**	**11**	**56**	**11**	**22**	**100**	

a=No mention of type of glaucoma, race
b=For diagnostic precision, only compared normals vs glaucomas
c=No mention of severity of glaucoma

Differences in Study Methods for FDT Evaluation:

Differences exist in study methods for the evaluation of the FDT **(Table 12)**. The only study, which recruited patients from the community, was Yamada et al[47]. However, instead of using the screening test in the community, the investigators performed all testing within the clinic. Related to subjects' ability to attend a clinic, one would expect selection bias for participants motivated to come because of preexisting glaucoma, symptoms of glaucoma, or family history of glaucoma. Some have advocated the use of the FDT in high pedestrian traffic areas such as shopping malls[48] but research evaluating the FDT in this type of environment has not been completed.

Table 12: Summary of FDT screening studies' methods

Study	Recruitment Site	Testing Site	Gold Standard	Criteria*	Diagnostic Test	Sensitivity/ Specificity
Current Study	Community	Community	ON	Any Defect at 5% level	C-20-5	11/87
Khong, et al	Clinic	Clinic	HVF/ON	2 or more defects abnormal at 1% level	Screening FDT	100/69
Patel, et al	Clinic	Clinic	HVF/GHT	Any defect at 1% level	Screening FDT	80/93
Quigley	Clinic	Clinic	HVF	2 or more defects at 1% level	Screening FDT	90/95[a]
Paczka, et al	Clinic	Clinic	HVF/ON	Any defect at 1% level	Screening FDT	84/100
Johnson, et al	Clinic	Clinic	HVF/ON	ROC	Full Threshold FDT	65/85[b]
Trible, et al	Clinic	Clinic	HVF/ON	Any defect at 1% level	Screening FDT	39,86,100[c] /95
Yamada, et al	Community	Clinic	HVF/ON	Any defect at 1% level	Screening FDT	92/93
Burnstein, et al	Clinic	Clinic	HVF/GHT	Any defect at 1% level	Screening FDT	86/83
Cello, et al	Clinic	Clinic	HVF/ON	ROC	Full Threshold FDT	85/90[b]

*Not all criteria for gold standard and diagnostic test results are presented
a=includes borderline cases, b=determined from logistic regression developed ROC (receiver operator curve), c=Sensitivity for early, moderate, and advanced glaucoma, respectively, HVF=Humphrey visual field, GHT=glaucoma hemifield test, ON=optic disc, ROC=Receiver Operator Curve

Other than the study by Yamada et al[47], all of the other studies recruited participants from a referral, university based setting. These studies included

glaucoma patients with typical glaucomatous optic discs and visual field results. The patients were experienced in the completion of visual field testing. In conjunction, the normal patients were experienced visual field takers as well. Using typical glaucoma patients decreases variability of the disease. Patients experienced in visual field testing are more reproducible. Both of these characteristics increase the diagnostic precision of the FDT.

Another important methodological difference concerns the definition of the gold standard for glaucoma in these studies. All of the studies used the Humphrey visual field (HVF) as part of the definition. Using the HVF as the gold standard test when evaluating the FDT creates bias in that both are measuring similar visual tasks and may artificially increase the diagnostic precision. An example could be two gun detection machines for baggage. One machine, the newest machine, detects only one metal that is present in all guns. A second machine, the gold standard, may be used to compare the diagnostic precision of the newest machine. It detects all metals including the one metal unique to guns. Because these machines are measuring the same thing, the diagnostic precision of the first machine is increased. To properly evaluate the newest machine, a different test that is unrelated, such as a manual check of bags, should be used.

With this in mind, it can be argued that a structural measure such as an optic disc evaluation should be used as the gold standard in evaluating a functional test such as the FDT. Unfortunately, the correlation of a glaucomatous optic nerve to a visual field result is low [49]. In our study, this low correlation may have decreased the diagnostic precision of the FDT.

In summary, our results showed lower diagnostic precision than previously reported because the previous studies have differences in compliance with evaluating a diagnostic test, study design, and the gold standards. Trible, et al[37] had results similar to ours with a sensitivity and specificity of 39% and 95%, respectively for early glaucoma. In regard to location of recruitment, our study is similar to Yamada et al[47]. He found higher diagnostic precision with FDT but excluded 63 out of 240 subjects because they were glaucoma suspects or ocular hypertensives. Therefore, they did not comply with the criteria that results should be presented in all patients. If all patients had been included, the range of sensitivity and specificity would be 97-26% and 95-65%, respectively.

Improving Glaucoma Screening:

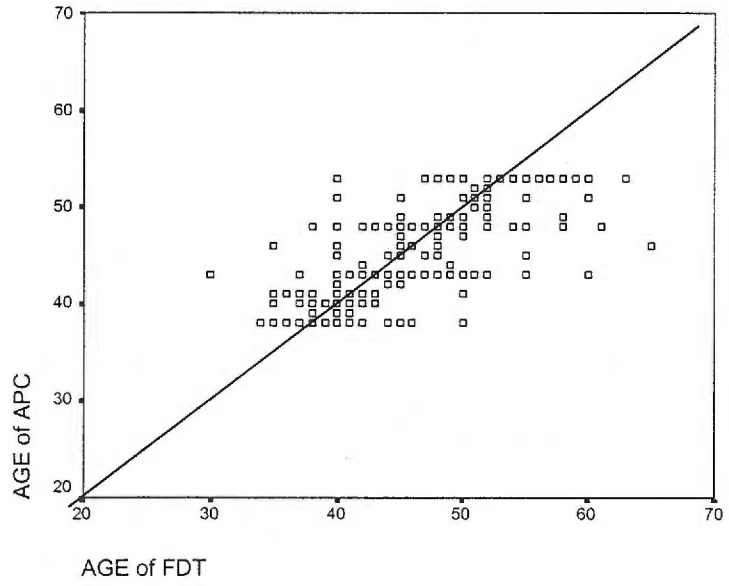
As stated in the introduction, the public health impact of blindness due to glaucoma will increase. We need to investigate better methods of screening for glaucoma. Because undiagnosed glaucoma is one of the major risk factors for blindness, we should screen for glaucoma in the community. The community environment has distractions such as noise, patient movement, and weather conditions. The performance of a functional test may be different in this situation. When a diagnostic test is used in the environment of interest, then the diagnostic performance can be accurately determined.

Screening in the Developing World:

The developing world has more difficulties with screening when compared to the developed world. One difficulty is that age determines the specific stimuli to be presented for FDT. In our study, we found a discrepancy in the age that

the patient indicated upon enrollment in the APC Study in comparison to the age given when performing the FDT test. The mean difference in age (age of APC minus age of FDT) was -0.5 $\pm$ 4.2 (range –19 to +13) years. Because patients received free eye care as subjects in the APC study, they may have altered their age to enroll but gave an accurate age for the FDT testing. Another possibility is that their age is not known by Western standards. Some cultures determine age by counting the number of harvests or full moons. We do not know why this discrepancy occurred. **Figure 3** seems to indicate a random distribution around the APC age. If the participant's age were chosen randomly, nondifferential informational bias would result. Nondifferential information bias increases variability, thus decreasing statistical differences.

Figure 3: Scatterplot of Age reported as part of the APC study vs Age while performing the FDT



Our patients had limited experience with buttons because they used manual methods of farming. In addition, they had little access to television or other forms of mass media. They had never played video games. It is unclear how the learning curve for perimetry is affected by these differences. In our study, the patients were given instruction using the button until they seemed to have an accurate response. While using a button may seem like second nature in the developed world, we found this instruction to be extremely important. Finally, Welch-Allyn created the normative distributions for determining differences for FDT in developed countries such as the United States and England. It is possible that the normative distributions are different in the developing world.

Experts argue whether sensitivity or specificity should be paramount in screening. A test with high sensitivity has a low proportion of false negatives and a patient with glaucoma would not be missed with the examination. However, because of a high number of false positives, patients may be referred inappropriately. In contrast, a test with high specificity has a low proportion of false positives and patients are not referred inappropriately for evaluation. In the developing world, one can argue that high specificity is more important than high sensitivity. A screening program with high specificity but low sensitivity may miss early glaucoma; but the moderate to advanced stage glaucoma patients would be detected. Moderate and advanced stage glaucoma patients are at highest risk of developing blindness and would receive sight-saving treatment. High

specificity would decrease the referral of patients with normal eyes for costly examinations in an environment with a limited supply of practitioners.

Limitations:

A second functional test such as Humphrey visual field perimetry was not used to confirm the visual field of the FDT. Therefore, it is difficult to know whether the decreased diagnostic precision of the FDT is due to the FDT or whether it is due to the participants having difficulties with functional testing. A second limitation not particular to this study but to all glaucoma screening evaluations is that we do not have an accurate gold standard structural test. Harper, et al [50] showed that a cup-to-disc ratio of >0.6 and >0.7 determined by direct ophthalmoscopy had a sensitivity of 60% and 55%, respectively for well-defined glaucoma patients. When a gold standard is inaccurate even in well-defined glaucoma patients, the diagnostic test will be limited to the sensitivity of the gold standard. It may be possible to model differences in screening predictability based on the accuracy of the gold standard. Alternately, investigators should agree on a gold standard for glaucoma screening so diagnostic precision between different tests can be compared.

Future Directions

An instrument that objectively determined structural features of the optic disc consistent with glaucoma would be helpful in glaucoma screening. Confocal scanning laser ophthalmoscopy (CSLO) is an objective method of evaluating the optic disc topography and has been found to be highly sensitive and specific for

glaucoma[51, 52]. This test could be used as the gold standard test, a diagnostic test in parallel, or as a diagnostic test in series.

Used as the gold standard, the subjective variability of optic disc evaluation would be decreased. If variability of the gold standard decreased the predictive ability of the FDT, increased diagnostic precision would result. If this CSLO were used in parallel with the FDT (i.e. an abnormal result on either test would result in the patient being referred), the sensitivity for glaucoma detection would increase. If CSLO were used in series (with abnormal results on both the CSLO and FDT required for a patient to be referred), the specificity would increase. Because our results show low sensitivity of the FDT, future research should use the FDT as the gold standard test or in parallel with the FDT.

Conclusion

In conclusion, the FDT was found not to be a sensitive indicator of glaucoma in this study in comparison to the gold standards of a glaucomatous optic disc, a C/D > 0.6, and a C/D > 0.7, although specificity was reasonably high.

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APPENDICES

Initiated: 1964

17.C
Original: English

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly
Helsinki, Finland, June 1964
and amended by the
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
and the
52nd WMA General Assembly, Edinburgh, Scotland, October 2000

A. INTRODUCTION

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.

2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.

3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.

6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must

continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.

7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.

8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.

9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

10. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.

11. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.

12. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

13. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.

14. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.

15. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.

16. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.

17. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.

18. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.

19. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.

20. The subjects must be volunteers and informed participants in the research project.

21. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

22. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.

23. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.

24. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.

25. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.

26. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.

27. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

28. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.

29. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.

30. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.

31. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.

32. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

♣ ♣ ♣

7.10.2000 09h14

David C. Gritz
50 Hazel Rd.
Berkeley, California 94705
510-649-1496
david.c.gritz@kp.org

February 14, 2002

To Whom It May Concern:

Dr. Steve Mansberger is participating in a collaborative study between the University of California, San Francisco and the Aravind Eye Hospital, Madurai, India. His study, regarding screening patients for glaucoma, is utilizing some of the subjects and data that is part of the Antioxidants in Prevention of Cataract (APC) Study. The APC Study is a randomized, placebo-control, triple-blind clinical trial to see if the progression of cataracts can be slowed with the use of antioxidant vitamins.

If you have any questions, please feel free to contact me.

Sincerely,

David C. Gritz, MD, MPH
(Electronic transmission, unable to sign)

Assistant Clinical Professor of Ophthalmology
University of California, San Francisco and the
Francis I. Proctor Foundation for Research in Ophthalmology

Regional Cornea and Uveitis Consultant
Kaiser Permanente Northern California Region

LEGACY
Health System

COPY

Legacy IRB: FWA00001280

February 7, 2002

Steven Mansberger, M.D.
1040 NW 22nd Ave., Suite 200
Portland, OR 97210

Dear Dr. Mansberger:

As Chairman of the Legacy IRB, I have a reviewed and approved your proposal "Glaucoma Screening Using Frequency Doubling Perimetry in Rural India". Your study qualified for this expedited review according to 45CFR46.101(b)(4) "Research involving the collection or study of existing data...if the information is recorded in such a manner that subjects cannot be identified."

Please be advised that you should notify the IRB if there are any changes in your protocol, or if any problems emerge. Approval of your study is valid for one year from this date.

Sincerely,

J Michael Albrich MD.

J. Michael Albrich, M.D.
Chair, IRB-01

Purpose and Background

Dr. David Gritz is conducting a study to evaluate the effectiveness of antioxidants (vitamin A, C, E, and carotene) as a way to decrease to cataract development. I am being asked to participate in this study as the investigator believes that my early cataract may be prevented from progressing.

DEC 07 2000

Procedures:

If I agree to be in this study, the following will occur:

1/17/2001

1. I will have a 50/50 chance of being placed in one of two study groups. Neither my doctor nor I will make the choice so that bias in the study is reduced. If I am in one group, I will receive oral vitamins (500 mg. vitamin C, 400 I.U. vitamin E, and 15mg. beta carotene) one tablet three times a week for three years for my cataracts. If I am in the other group, I will receive an inactive substance in tablet form three times a week for three years. My specific form of treatment will not be known to the examiner who will examine my eyes every year for three years.

2. Prior to entering the study, I will be examined to determine that I do have a cataract and how advanced the cataract is.

3. During the study, I will have a complete eye examination performed once or twice a year.

4. Several times per year at unspecified times, my urine will be collected for study.

Risks/Discomforts:

1. The intake of this dose of vitamins should be totally safe.

2. There may be some inconvenience for me to participate in the study. I will need to meet with my field worker to recieve the vitamins three times per week and have an interview three times a year. The exact timing will be coordinated with my field worker for minimal incovenience. The annual eye examination will take place in my village in June or July of each year and will be scheduled several months in advance for the entire village.

3. The pills may not taste good

4. The intake of the tablets will turn my urine slightly yellow.

5. I will be assigned to a treatment program by chance. If I receive the inactive substance, it may prove to be less effective than the vitamin treatment group or other available treatments. This will not be known until after the study is completed and the data has been analyzed.

6. Confidentiality: Participation in research may involve a loss of privacy. My records will be kept as confidential as is possible within the law. Representatives from the Food and Drug Administration in the United States may be allowed to see my records to check on the study. No individual identities will be used in any reports or publications resulting from this study.

7. Treatment and compensation for injury: If I am injured as a result of being in the study, treatment will be available. The cost of said treatment may be covered by the Aravind Eye Hospital.

Benefits:

The treatment I am assigned to may later be shown to retard cataract formation.

Alternatives:

If I elect to not participate in this study, I can take vitamin supplements on my own or receive no treatment at all for my early mild cataract.

Cost/Reimbursement:

There is no reimbursement for participation in this study. I will receive a free eye and medical examinations during the study. I will be given priority should I develop cataracts that require surgery.

Questions:

If I have any questions, I can call Dr. Srinivasan or Mr. Thulasiraj at the Aravind Eye Hospital.

Consent:

Participation in research is voluntary. I have the right to decline to participate or to withdraw at any point in this study without jeopardy to my medical care. If I wish to participate, I should sign this form.

Date	Subject's Signature
	Translator's Signature
Person Obtaining Consent	Witness's Signature

UCSF COMMITTEE ON HUMAN RESEARCH

APPLICATION COVER PAGE

Principal Investigator (Must be an eligible faculty member)

Name and degree	University Title	Department
John P. Whitcher, MD, MPH	**Professor Clin Ophth**	**Francis I. Proctor Foundation**
Campus Mailing Address (Box No.)	Phone Number	E-mail Address
Box 0944	**415-731-1075**	**nepal@itsa.ucsf.edu**

Co-Principal Investigator

Name and degree	University Title	Department
David C. Gritz, MD, MPH	**Assistant Professor Clin Ophth**	**Francis I. Proctor Foundation**
Campus Mailing Address (Box No.)	Phone Number	E-mail Address
Box 0944	**415-731-1075**	**gritz@home.com**

Send correspondence to (check only one): ☐ PI only ☒ PI and Co-PI ☐ PI and Contact Person identified below:

Name	University Title	Department
Campus Mailing Address (Box No.)	Phone Number	E-mail Address

Study Title (may not exceed 300 characters):

Retardation of Cataracts by Antioxidants

Application Type:

☐ New Full Committee Application

☐ New Subcommittee Application
Expedited Review Category #: ___

☐ Modification ☒ Renewal
Current CHR #: H7933-08640-07

Expiration date: 12-11-01

Other Investigators:

Name and Degree/Department/Site

Site(s) (check all that apply):

☐ Parnassus ☐ SFGH ☐ VAMC
☐ Mt. Zion ☐ Stanford ☐ UC Berkeley
☒ Foreign Country ☐ Other: ___

☐ GCRC (Parnassus)
☐ GCRC (SFGH)
☐ PCRC

Special Subject Populations (check all that apply):

☐ Minors (i.e., under 18 years of age)
☐ Individuals with HIV Infection
☒ Those Unable to Speak or Read English
☐ Those Unable to Consent for Themselves
☐ Fetuses, Pregnant Women
☐ Prisoners

How many subjects will be enrolled here? 0

Will subjects be paid? ☐ Yes ☒ No

Special Study Procedures:

Check all that apply:
☐ Genetic Testing ☐ HIV Testing
☐ Tissue Banking ☐ Gene Therapy

☐ Chart Review Only

Drugs and Devices:

Investigational drugs/devices (and IND/IDE No. from FDA):

Approved drugs/devices:

Is a Non-Significant Risk (NSR) determination requested for study devices? ☐ Yes ☒ No

Funding (All sections must be completed even if funding is pending):

Will study be funded?
☒ Yes ☐ Pending ☐ No

If not, how will study costs be managed? _____

Funding award will be made through:
☒ UCSF ☐ *Gallo* ☐ *Gladstone*
☐ *NCIRE* ☐ VA Research Admin.
☐ *DPH* ☐ *GIOA*
Other: **Francis I. Proctor Foundation**

Name of sponsor: **Francis I. Proctor Foundation**

Award No. (if known): **Private Donations**

Sponsor is (check all that apply):
☐ Federal Gov. ☐ Other Gov.
☐ *Pharmaceutical/Device Co.** ☒ Other Private
☐ Campus/UC-Wide Program ☒ Dept. Funds

* If study is industry sponsored, identify the Administering Dept./ORU and appropriate financial contact person:

Other Approvals:

Does research require review by:
☐ Biosafety Committee If so, BSC approval #: ___

Principal Investigator's Signature:

Signature John P. Whitcher David C. Gritz Date 10/11/01

COMMITTEE ON HUMAN RESEARCH
OFFICE OF RESEARCH ADMINISTRATION, Box 0962
UNIVERSITY OF CALIFORNIA, SAN FRANCISCO
www.ucsf.edu/ora/chr

CHR APPROVAL LETTER

TO: John P. Whitcher, M.D.
Box 0944

David C. Gritz, M.D.
Box 0944

RE: Retardation of Cataracts by Antioxidants

The Committee on Human Research (CHR), the UCSF Institutional Review Board (IRB) holding Department of Health and Human Services Multiple Project Assurance #M-1169, has reviewed and approved this application to involve humans as research subjects. This included a review of all documents attached to the original copy of this letter.

APPROVAL NUMBER: H7933-08640-09 .This number is a UCSF CHR number and should be used on all correspondence, consent forms and patient charts as appropriate.

APPROVAL DATE: December 7, 2000. **Full Committee Review**

EXPIRATION DATE: December 7, 2001. If the project is to continue, it must be renewed *by the expiration date*. See reverse side for details.

ADVERSE EVENT REPORTING: All problems having to do with subject safety must be reported to the CHR within ten working days. All deaths, whether or not they are directly related to study procedures, must be reported. Please review Appendix A of the CHR *Guidelines* for additional examples of adverse events or incidents which must be reported.

MODIFICATIONS: Prior CHR approval is required before implementing any changes in the consent documents or any changes in the protocol which affect subjects.

QUESTIONS: Please contact the office of the Committee on Human Research at (415) 476-1814 or campus mail stop, Box 0962, or by electronic mail at chr@itsa.ucsf.edu.

Sincerely,

Patricia S.A. Sparacino

Patricia S.A. Sparacino, RN, MS, FAAN
Vice Chair
Committee on Human Research

cc: Drug Information and Analysis Service