WHAT ARE YOU GOING TO DO ABOUT SUBCLINICAL EYE DISEASE?

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FINANCIAL DISCLOSURES

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- Konan Medical

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SUBCLINCAL DISEASE

Medical Definition

An illness that is staying below the surface of clinical detection

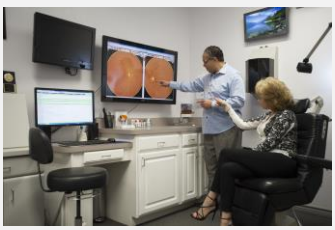
A disease that has no recognizable clinical findings

It is distinct from clinical disease, which has signs and symptoms that can be recognized during a clinical examination

Ophthalmologic Examination

- Patient history
- General medical observation
- Gross visual fields
- Basic sensorimotor examination
- External examination
- Adnexal examination
- Biomicroscopy
- Ophthalmoscopy

Current Procedural Terminology Codebook Service Components



Clinical Examination = Clinical Diagnosis

A clinical diagnosis is a determination based on the knowledge obtained from the patient's medical history and from the results of the eye examination alone, without the benefit of diagnostic tests or procedures

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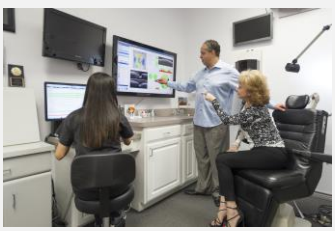
SUBCLINCAL DISEASE

- A problem in which symptoms are mild or inapparent, and may not be diagnosed other than by more advanced testing measures
- Subclinical does not mean that the problem is insignificant or that there is no change in physiologic function, but instead it reflects that conventional measures that have been used to evaluate a patient for the presence of disease may not detect changes early in the natural history of the condition
- The presence of subclinical disease is a strong risk factor for disease progression compared to no detectable subclinical disease
- Measurement of subclinical eye disease requires "non-traditional" thinking and modern technology



Physical Examination = Physical Diagnosis

A physical diagnosis is a determination supported by various diagnostic tests and procedures (i.e., OCT retinal imaging, threshold visual field exam, etc)

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SUBCLINICAL DIABETIC RETINOPATHY

- Regarding the vascular form of the disease, subclinical diabetic retinopathy is the development of vascular abnormalities prior to the development of funduscopically-evident diabetic retinopathy
- In diabetes, a structure-function relationship exists between neurodegeneration and vision loss and in many patients, subclinical retinal neurodegeneration may be detected without visible retinal vasculopathy
- Up to 36% of patients with no clinical diabetic retinopathy have OCTA-detected vascular abnormalities

Mapher C, Johnson SL. Imaging Motion: A Review of OCT-A. Review of Optometry. Vol 154 Number 3 March 2017. 36-48.

Leclerc-Collet A. Evaluation of Retinal Function and Flicker Light-Induced Retinal Vascular Response in Normotensive Patients with Diabetes without Retinopathy. *Invest Ophthalmol Vis Sci.* 2011;52:2861-2867

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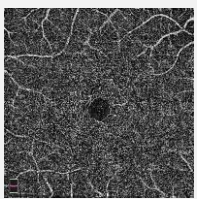
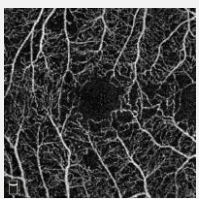
RETINAL BLOOD MICROCIRCULATION

OCTA RETINAL IMAGING NORMAL ANGIOGRAM



OCTA RETINAL IMAGING SUBCLINICAL RETINOPATHY



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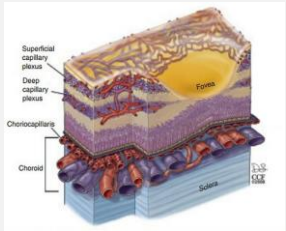
RETINAL BLOOD MICROCIRCULATION

From the optic disc, the major retinal arteries and veins and their successive divisions run in the superficial nerve fiber layer until the immediate precapillaries, which divide into two basic groups

- Superficial capillary plexus
- Deep capillary plexus

Retinal Vascular Density Measurements

- Looks at tissue perfusion, which is more tightly linked to tissue metabolism and physiologic function
- Quantification software generates OCTA parameters that quantify the density of blood perfusion in different slabs of the retina



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SUPERFICIAL RETINAL VASCULAR DENSITIES

(AGE- AND GENDER-ADJUSTED MIXED MODELING)

Anatomic Region	Vascular Complex Density Percentage
Superior hemi-macula	49.7 – 56.3
Inferior hemi-macula	48.3 – 55.7
Temporal parafovea macula	51.4 – 60.2
Nasal parafovea macula	54.4 – 59.0
Superior parafovea macula	52.8 – 60.4
Inferior parafovea macula	49.7 – 59.3

Fard MA, Ghahvechian H, Sahraian A, Subramanian PS. Early Macular Vessel Density Loss in Acute Ischemic Optic Neuropathy Compared to Papilledema: Implications for Pathogenesis. *Translational Vision Science & Technology*. 2018 Sep; 7(5): 10. doi: 10.1167/tvst.7.5.10

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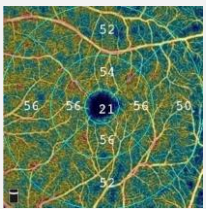
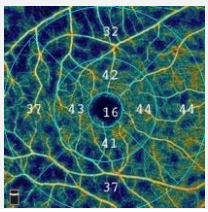
SUPERFICIAL RETINAL VASCULAR DENSITIES

OCTA RETINAL IMAGING
NORMAL PERFUSION



OCTA RETINAL IMAGING
ABNORMAL PERFUSION



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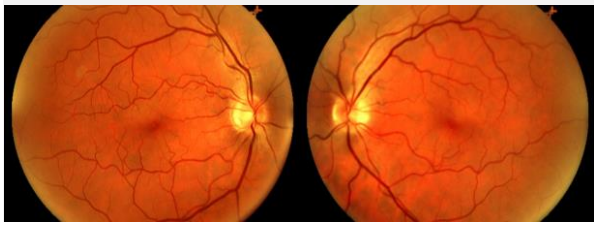
SUBCLINICAL DIABETIC RETINOPATHY

- 54-year-old white man with a 20-year history of diabetes
- Treatment is oral meds – poor compliance on diet/exercise
- 20/20 best corrected visual acuity in each eye
- No complaints of decreased vision
- No apparent diabetic retinopathy



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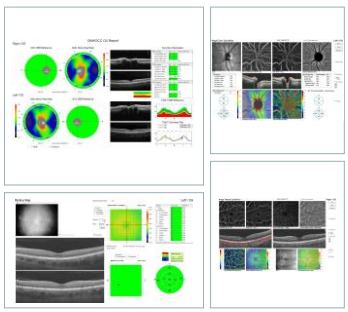

STRUCTURAL ASSESSMENT

The advent of optical coherence tomography angiography (OCTA) has demonstrated the presence of vascular abnormalities in patients with diabetes that are not visible with an ophthalmoscopic exam

This form of the disease is called subclinical diabetic retinopathy and retinal imaging studies have shown that it is characterized by the following clinical features

- Alterations in capillary density
- Increased foveal avascular zone
- Remodeling of the perifoveal capillaries
- Alterations in vessel density and tortuosity
- Abnormal branching angles
- Abnormal ratio of vessel length to diameter

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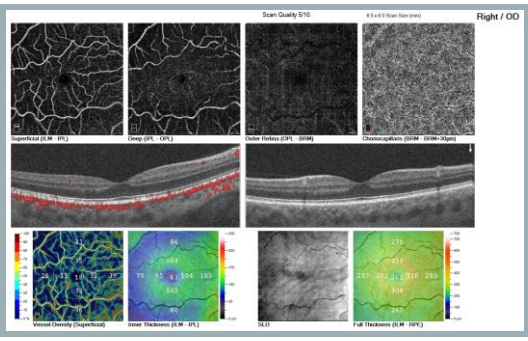

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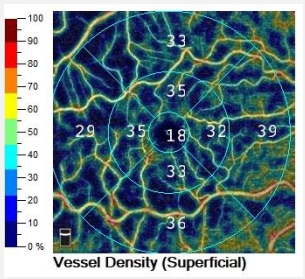

Botto de Barros Garcia JM, Lima TT, Louzada RN, Rassi AT, Isaac DL, Avila M. Diabetic Macular Ischemia Diagnosis: Comparison between Optical Coherence Tomography Angiography and Fluorescein Angiography. *Journal of Ophthalmology*. 2016;2016:3989310. Published 2016 Nov 7. doi:10.1155/2016/3989310

SUBCLINICAL DIABETIC RETINOPATHY

Diabetic retinopathy has always been defined as a complication of diabetes that starts with damage to the retinal blood microcirculation

The diabetes-induced vasculopathy is characterized by the following

- Constriction and occlusion of the vascular lumen
- Fallout of the capillary network
- Increased vascular permeability
- Retinal perfusion alterations

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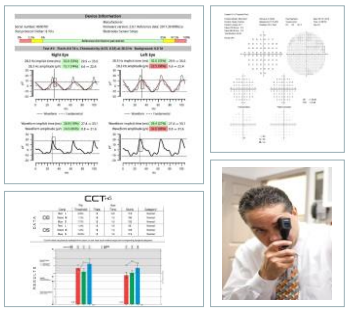

FUNCTIONAL VISION ASSESSMENT

Subclinical diabetic retinopathy is also a neurogenerative disorder of the retina that is characterized by a loss/derangement of the following neural elements

- Ganglion cell bodies
- Retinal nerve fiber layer
- Photoreceptors

This neuropathic form of subclinical diabetic retinopathy is known as retinal diabetic neuropathy (RDN) and can be quantified either structurally or functionally

Jackson GR, Scott IU, Guillen DA, Walter LE, Gardner TW. Inner retinal dysfunction is a sensitive marker of non-proliferative diabetic retinopathy. *British Journal of Ophthalmology*. 2012;96:699-703.

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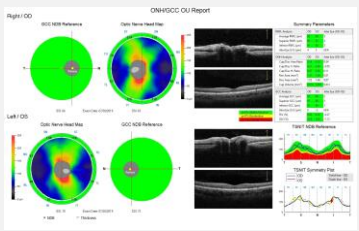
GANGLION CELL COMPLEX ANALYSIS



Hegazy AI, Zedan RH, Macky TA, Esmat SM. Retinal ganglion cell complex using spectral domain coherence tomography in diabetic patients without retinopathy. *Int J Ophthalmol* 2017;10(3):427-433.doi:10.18240/ijo.2017.03.16

- Diabetes-induced retinal neurodegeneration occurs in people with diabetes regardless of clinical markers of diabetic metabolic control
- Clinically significant ganglion cell complex Focal Loss Volume predates ophthalmoscopy-based detection of diabetic retinopathy in 22% of patients with diabetes
- In some patients, this generalized neural-glial dysfunction can produce sensory abnormalities and a loss of visual function
- Psychophysical measures of visual function such as contrast sensitivity, color vision, retinal sensitivity and electroretinography can all be abnormal in patients with retinal diabetic neuropathy

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DIABETIC RETINOPATHY ASSESSMENT

Thomas Classification System

A proposed new classification system for diabetic retinopathy

- The goal of including subclinical diabetic retinopathy is to represent all stages and manifestations of diabetic retinopathy
- The Diabetic Macular Edema Scale is replaced with a Diabetic Maculopathy subdivision to more accurately reflect what OCT retinal imaging is showing us about the pathophysiology of diabetes-induced macular disease
- Remember, clinically significant macular edema can be present at any stage of diabetic retinopathy

(1) No apparent diabetic retinopathy
(2) No apparent diabetic macular edema
(3) Subclinical Diabetic Retinopathy
  - Vascular abnormalities
  - Retinal diabetic neuropathy
    - Loss/derangement of neural elements
    - Sensory abnormalities and loss of visual function
(4) Clinical Diabetic Retinopathy
  - Mild
  - Moderate
  - Severe
  - Proliferative
(5) Diabetic Maculopathy
  - Focal edema
  - Diffuse edema
  - Ischemic
  - Mixed

Sayin N, Kara N, Pekel G. Ocular complications of diabetes mellitus. *World Journal of Diabetes*. 2015 Feb 15;6(1):92-108. doi:10.4239/wjd.v6.i1.92

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MEDICAL DECISION-MAKING

The clinical diagnosis of "no apparent diabetic retinopathy" is changed to a physical diagnosis of subclinical diabetic retinopathy

Prescribe a treatment program that is designed to delay the development of clinical diabetic retinopathy with tighter metabolic control

- Diet
- Exercise
- Medicine
- Nutritional supplementation
- Patient education

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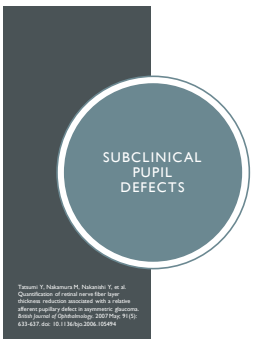

Tatsumi Y, Nakamura M, Nakanishi Y, et al. Quantification of retinal nerve fiber layer thickness reduction associated with a relative afferent pupillary defect in asymmetric glaucoma. *British Journal of Ophthalmology*. 2007 May; 91 (5): 633-637. doi: 10.1136/bjo.2006.105494

- The relative afferent pupillary defect (RAPD) is an important clinical sign of asymmetric retinal ganglion cell and axonal damage
- In patients with glaucoma, an asymmetry of 27% or more in retinal nerve fiber layer thickness will likely produce a RAPD
- During a clinical examination, the detection of a RAPD is human observation-based assessment
- If detected, a RAPD is quantified by performing the swing flashlight test and equalizing the pupil response with 0.3-log unit neutral density filters

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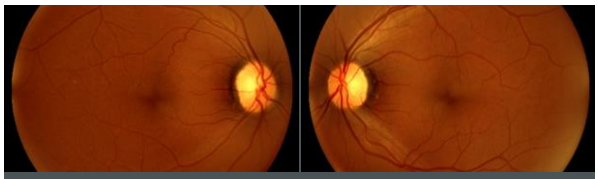

SUBCLINICAL PUPIL DEFECTS

- 62-year-old black man presents for a routine eye exam
- Good health – physically fit – no medications
- 20/20 uncorrected visual acuity in each eye
- Intraocular pressures are 11 mm Hg in each eye

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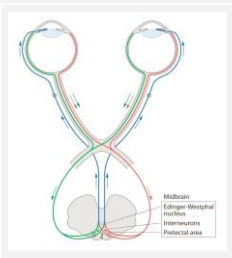
PUPILLARY LIGHT REFLEX

Afferent Neural Pathway

Ganglion cells connect to the pretectal nucleus of the upper midbrain, bypassing the lateral geniculate nucleus

Efferent Neural Pathway

Axons from the Edinger-Westphal nucleus run to both the right and left oculomotor nerves to innervate the constrictor muscle of the iris



Structures involves in the transmission of sensory information along the neural pathways

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TESTING PUPILLARY REACTIVITY

Normal pupils have equal response to light stimulus

Testing pupillary reactivity involves comparing the velocity and amplitude of the pupillary responses

During a clinical examination, the procedure is usually accomplished by performing the "swinging flashlight test" on the patient with a penlight or transilluminator

Abnormal findings include an asymmetry in the pupillary light reflex, a condition known as relative afferent pupillary defect (RAPD)

Neutral density filters in 0.3 logarithmic unit steps aid in the detection and quantification of RAPD

Goal of pupil light reflex testing is to determine if there is a defect in either neural light reflex pathway

Functional Vision Assessment

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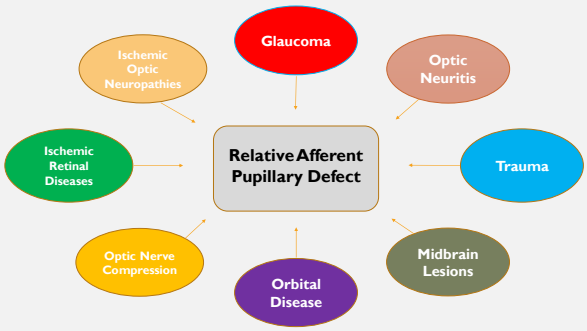

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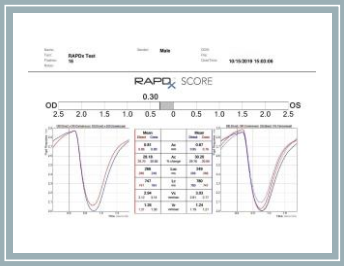
COMPUTER-ASSISTED PUPIL TESTING

Non-invasive, non-contact automated pupillometry enhances the ability to detect a RAPD

RAPDx Scores > 0.30 may be abnormal

The RAPDx Score has been shown to have a strong correlation with the difference in mean deviation between each eyes of patients with glaucoma



Functional Vision Assessment

Sarasky D, Krupin T, Cohen A, Stewart CW, Volpe NJ, Tanna AP. Correlation between intereye difference in visual field mean deviation values and relative afferent pupillary response as measured by an automated pupillometer in subjects with glaucoma. *Journal of Glaucoma*. 2014;23:419–423.

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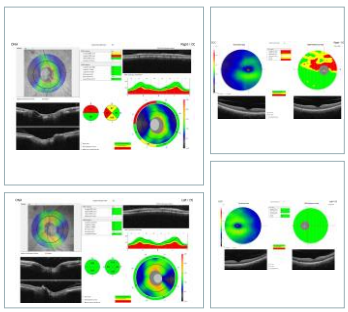

STRUCTURAL ASSESSMENT

- Glaucomatous optic atrophy on OCT retinal imaging is characterized by a thinning of the retinal nerve fiber layer and the ganglion cell complex
- Macular ganglion cell complex parameters include Focal Loss Volume (FLV), global loss volume (GLV), mean, superior and inferior thickness
- Highest diagnostic accuracy for early glaucomatous optic atrophy is GLV parameter

Kim N, Lee, Seong G, et al. Structure-Function Relationships and Diagnostic Value of Macular Ganglion Cell Complex Measurement Using Fourier-Domain OCT in Glaucoma. *Investigative Ophthalmology Visual Science*. 2010; Vol.51:4646-4651. doi:10.1167/iovs.09-5053

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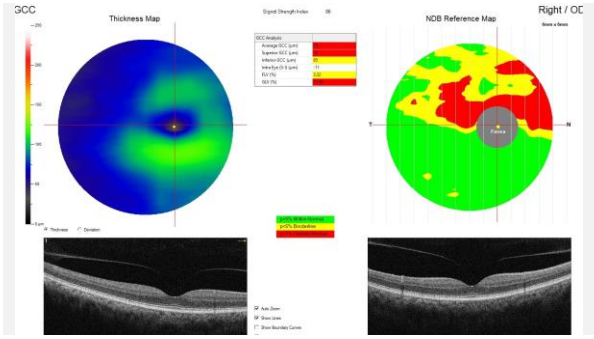

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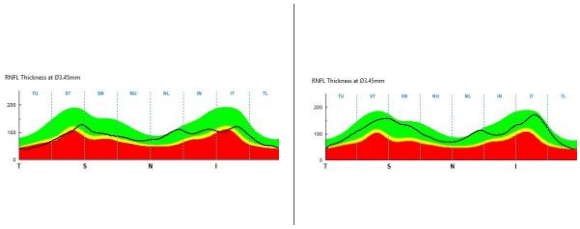
TSNIT CURVE PROFILE



Because glaucomatous damage to the retinal nerve fiber layer has a predilection for the inferotemporal and superotemporal regions of the optic disc, focal defects in these areas are strongly suggestive of glaucoma

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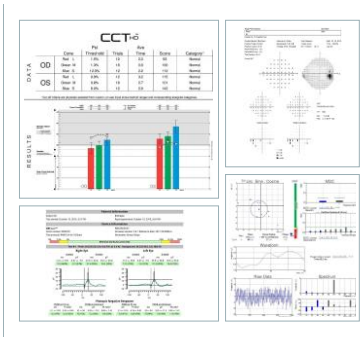

FUNCTIONAL VISION ASSESSMENT

- Color contrast thresholds are depressed in some patients with glaucoma
- Electroretinography measure the photopic negative response (PhNR) to evaluate the function the innermost retinal layers and the ganglion cells and abnormal test results can be a diagnostic marker for glaucoma
- Visual evoked potential testing evaluates the integrity of the afferent visual sensory system

Niwa Y, Muraki S, Naito F, Minamikawa T. Evaluation of acquired color vision deficiency in glaucoma using the Rabin Cone Contrast Test. Invest Ophthalmol Vis Sci. 2014 Oct;55:6686-90.

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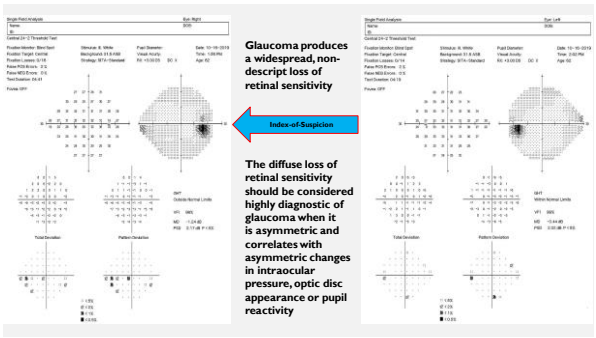

Glaucoma produces a widespread, non-descript loss of retinal sensitivity

Index-of-Suspicion

The diffuse loss of retinal sensitivity should be considered highly diagnostic of glaucoma when it is asymmetric and correlates with asymmetric changes in intraocular pressure, optic disc appearance or pupil reactivity

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MEDICAL DECISION-MAKING

The clinical diagnosis of relative afferent pupillary defect is changed to a physical diagnosis of partial optic nerve atrophy

Prescribe a treatment program that is designed to monitor the patient for optic neuropathy disease progression

- More intense eye exam surveillance schedule
- More intense OCT and OCTA structural assessments
- More intense functional vision assessments

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CONCLUSION

- The measurement of subclinical disease provides an approach for identifying individuals who may be candidates for more active intervention to delay or prevent the development of clinical disease
- For patients with established risk factors for clinical disease, manage this increased risk by increasing your index-of-suspicion for subclinical disease and deploying advanced diagnostic technologies to assist in early detection

"Risk Management Through Early Detection"

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