Frequently Asked Questions

1) Is RETeval-DR the same as a fundus camera, or is there a difference?

a) A fundus camera typically takes a 45-degree digital image of the retina of the eye. This image is then examined for various types of damage caused by advancing diabetic retinopathy (DR) or other disease. A fundus image can reveal **STRUCTURAL** damage that is visible in the digital photograph. The fundus image is typically sent digitally to a reading center for evaluation. The reading center then assesses the image, assigns a level of disease (no DR, Mild, moderate, or severe non-proliferative diabetic retinopathy, or proliferative DR).

b) The RETeval-DR is not a fundus camera; it does not image the retina. RETeval-DR performs a **FUNCTIONAL** test of the retina to assess the level of ischemia present. Over time the retina of a diabetic patient becomes deprived of oxygen (ischemic)[1]. The level of ischemia gets progressively worse and this is the underlying condition that leads to the damage that is visible in a fundus photo. Just like an EKG can perform a functional assessment of the condition of the heart without physically seeing the heart, RETeval-DR performs an electroretinogram (ERG) to assess the function and condition of the retina without actually seeing the retina[2].

c) One way to think about the difference between fundus imaging and the RETeval-DR is as follows:

i) **The Dashboard only your Physician can Interpret**
Using fundus imaging for DR is like having a car dashboard that only highly-trained physicians or medical technicians can interpret. Using a car dashboard, you can look at the fuel gauge, for example, and determine the fuel tank is very full, moderately full, or dangerously low. You might be able to identify other issues as well, such as the oil pressure is low. Similarly, eye specialists can look at the fundus and determine if DR is present, and classify it as mild, moderate, or severe retinopathy. In addition to identifying, classifying and documenting all levels of diabetic retinopathy from very mild to vision threatening, it is also possible for the physician to diagnose an assortment of important systemic diseases based on a fundus image—including papilledema, hypertension, macular degeneration (AMD), cancer and stroke.

ii) **The Warning Light Anyone Can Interpret**
Continuing with the same dashboard analogy, RETeval-DR is like the WARNING LIGHT that glows when there is a dangerous issue in the car that needs immediate attention (e.g., Check Engine!). Unlike structural tests such as fundus imaging, objective tests like RETeval-DR can be interpreted by anybody and does not require a physician or highly trained medical technician to interpret the "WARNING LIGHT". The RETeval-DR retinal assessment is a binary test (i.e., pass/fail; warning light is ON or OFF). RETeval-DR will identify with 99.2% accuracy the patients with diabetes that do not have vision threatening DR, enabling the remaining patients to obtain a complete retinal examination (i.e., take the car to the shop), typically by visiting an eye specialist, but potentially by remote fundus imaging if access to eye specialists is limited.

2) Is Welch Allyn RETeval-DR available in the USA?

a) RETeval-DR is currently intended for export, and is not sold or offered for sale in the U.S.A.

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3) How, exactly, does RETeval-DR work?

a) Just like an EKG is using electrophysiology to capture a waveform of the function of the heart, RETeval-DR captures a waveform of the function of the retina. RETeval-DR uses a specifically designed skin electrode that comfortably adheres to the skin under the eye and attaches to the RETeval-DR device via a cable with a simple clip connector.

b) The RETeval-DR is completely, non- invasive. Nothing touches the eye itself. When the operator presses the button to begin the test the device flashes white light 30 times per second at three different flash intensities. The brightest intensity is approximately the same intensity as the ambient light in a typical office. The operator can watch the test using the image on the screen from the infra-red camera in the device. The camera also monitors pupil size on a real-time basis and adjusts the flash intensity to the pupil size so that a constant level of light reaches the retina regardless of pupil size. This patented capability eliminates the need for pupil dilation.

c) The device ends the test automatically and tells the operator immediately if there was a problem. It also displays a "score" on the device screen. The score was developed via a 468 person multi-center clinical trial and it uses three parameters to generate the score. This study compared the RETeval-DR results to the universally accepted gold standard of dilated 7-field color stereo photography, double read and adjudicated[3-5].

1. First, RETeval-DR uses the implicit time. Every time a flash of light hits the retina the cells in the retina respond by generating a small electrical response. The device accurately times how long it takes the retina to respond to each of the flashes (flickering 30 times per second) by knowing when it does each flash and when it captures the electrical response of the retina using the skin electrode placed below the eye. As the eye becomes more ischemic, this implicit time increases—peer reviewed literature[6-11] and our study results indicate that this correlates well to the level of ischemia and level of DR present.
2. Second, RETeval-DR looks at the amplitude of the electrical response of the retina. This is an indication of the strength of the response of the retina to a flash of light. The amplitude of the signal will get smaller as disease progresses[7,11-13].
3. Third, it looks at the change in pupil size between the dimmest flash used and the brightest flash used. As disease progresses the pupil will change less in response to different intensities of light[14-18].

d) The three parameters above are then combined using a proprietary patent-pending algorithm to determine the score on the device.

4) Is there a body of peer reviewed literature that supports use of electroretinographs in assessing patients with diabetes for sight threatening diabetic retinopathy?

a) Yes. There have been about a dozen peer reviewed publications from the United States, Japan, and Korea that documented the correlation of ERG results, ischemic level, and their correlation to the level of DR present[6-13]. Some of these publications date back to the 1980's. This correlation has long been known. Additionally, a peer reviewed article specific to the RETeval device was published in *Journal of Diabetes and Its Complications*, December 2015, "A novel device for accurate and efficient testing for vision-threatening diabetic retinopathy"[23].

b) Similarly, there are peer reviewed publications that documented the correlation between pupil size change and DR[14-18].

5) What does the RETeval-DR score mean?

a) The device will generate a single numerical score. This score was statistically generated from study results. Patients with a score of 20 or above would be referred to an eye specialist for further evaluation as they are more likely to have vision threatening diabetic retinopathy (VTDR)—defined as severe non-proliferative diabetic retinopathy (NPDR), any level of proliferative diabetic retinopathy (PDR), or clinically significant macular edema (CSME) regardless of underlying DR level.

b) Anyone with a score of 19.9 or less has a 99% chance of not having VTDR, and therefore does not be referred for further follow-up.

6) What about "borderline" RETeval-DR scores that are near the cutoff of 20? Should they be referred out of an abundance of caution?

a) No. This is a binary test. If you change the cutoff to a lower value, sensitivity will increase but specificity will decrease (you'll refer more people) as shown in the table below.

RETeval cutoff value	Sensitivity	Specificity	Predictive Power of test		Percent of Tested Sample			
					Positive Test		Negative Test	
			Positive	Negative	True	False	True	False
17.6	93%	52%	8%	99.5%	4.1%	46%	50%	0.2%
18.1	90%	57%	9%	99.2%	3.8%	41%	55%	0.5%
19.1	88%	67%	11%	99.1%	3.8%	31%	64%	0.5%
20.0	83%	78%	15%	99%	3.6%	21%	75%	0.7%
21.2	73%	84%	17%	99%	3.1%	15%	80%	1.2%

7) How sure can you be that a diabetic patient with a normal test result does not have sight threatening DR?

a) The RETeval-DR device has a 99.2% negative predictive value to Severe NPDR or PDR. This means that you are 99.2% certain that those that you say are healthy actually do not have sight threatening DR. If CSME is also included, you still have 99% certainty that those that you say are healthy actually do not have severe NPDR, PDR or CSME.

8) What is the sensitivity and specificity of RETeval-DR?

a) Sensitivity = 87%, Specificity = 78% to sight threatening DR (not considering CSME)

b) Sensitivity = 83%, Specificity = 78% to sight threating DR and/or CSME

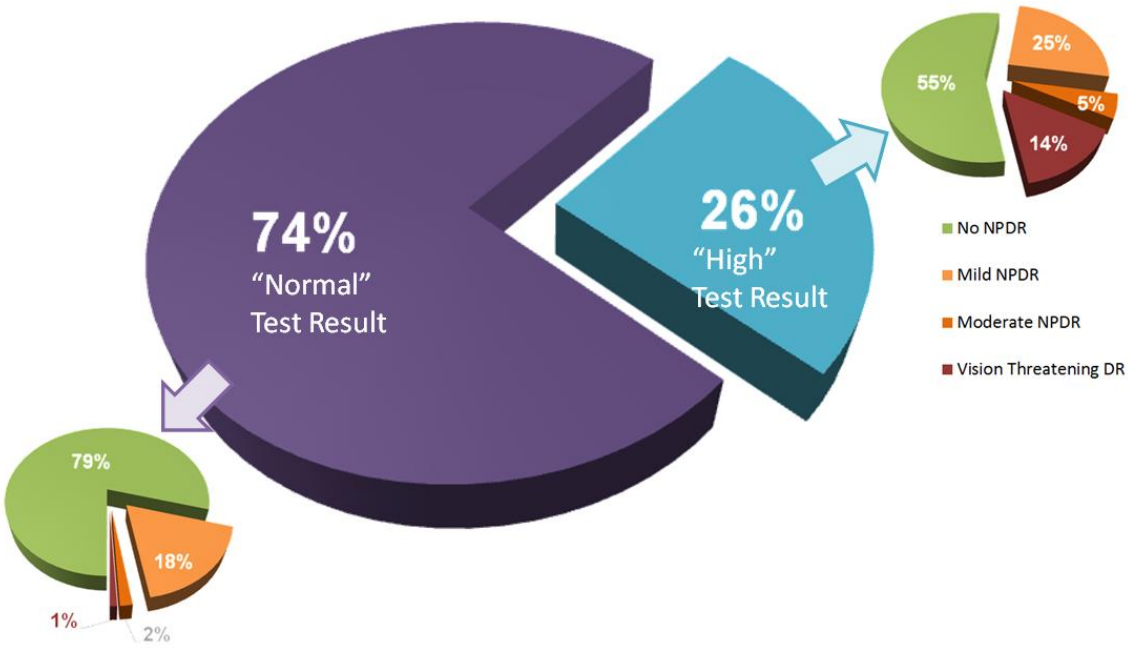
9) How many patients typically receive "high" test results?

a) The expected distribution of disease among patients who are screened with RETeval-DR is that 74% will receive "normal" test results and 26% will receive "high" test results (based on the United States VTDR prevalence of 4.4%). For example, if the test result is normal, there is a 99% chance the patient does not have VTDR and a 97% chance the patient does not have VTDR or even Moderate DR.

Patients with diabetes who might not have regular access eye specialists can now be screened in convenient, lower-cost primary care settings where RETeval-DR will safely identify the 74% of the diabetic population that does not require treatment, enabling eye-specialist resources to be more efficiently focused on the 26% of this population—many of whom require immediate treatment to preserve their vision or closer monitoring.

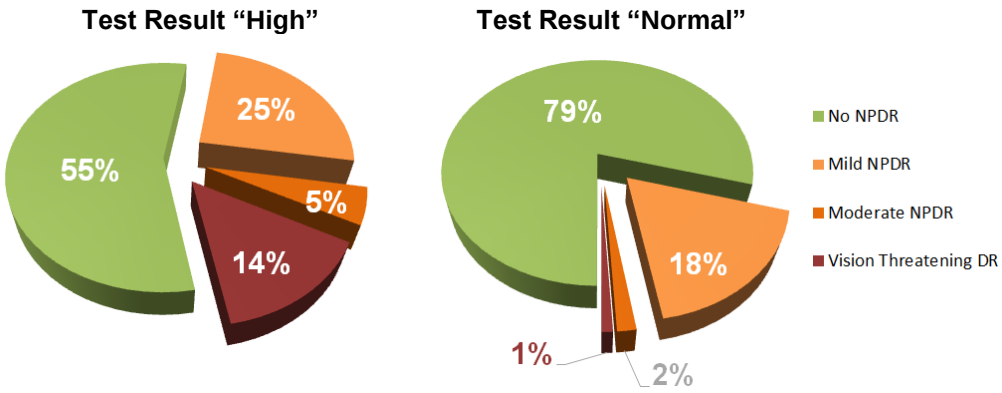
If the RETeval-DR test result is high, there is a 45% chance that some level of retinopathy is present, and a 14% chance the patient has VTDR that could require immediate treatment to preserve vision.

Distribution of disease among patients screened with RETeval-DR



10) Will some diabetic patients who receive a high test result <u>not have any</u> diabetic retinopathy?

a) Yes. By definition, a test specificity of 78% suggests some patients will receive a high test result but will not have any diabetic retinopathy, or will have mild-to-moderate retinopathy that is not immediately vision threatening. The graphs below illustrate the average expected distribution of disease among patients who test "high" and test "normal" (based on the United States VTDR prevalence of 4.4%). For example, if the test result is normal, there is a 99% chance the patient does not have VTDR. If the test result is high, there is a 14% chance the patient has VTDR that could require immediate treatment to preserve vision, and a 45% chance that some level of retinopathy is present, and may qualify for more frequent monitoring.



11) Why not adjust RETeval-DR to detect mild or moderate NPDR?

a) Mild and moderate NPDR are not treatable conditions. That being said, on average, 30% of patients with high test results will be classified with mild or moderate NPDR upon evaluation and diagnosis by an ophthalmologist.

12) Can RETeval-DR distinguish among various types of CSME?

a) No. RETeval-DR is not diagnostic; it is pass/fail screening test. After referral, the patient needs to be evaluated by an ophthalmologist to determine exactly what is wrong (if anything) and determine a management and/or treatment plan.

13) Can people who do not have diabetes have a "high" test result?

a) Some people who do not have diabetes may receive a "high" result if they take the test. This does not suggest that disease is present or follow-up is warranted. Keep in mind that RETeval-DR is measuring the response of the retina and pupil to a light stimulus. There is a normal distribution of how quickly people's eyes will respond – some respond faster and stronger than others. It is possible for a person who does not have diabetes to have naturally slow and/or weak response times that trigger a "high" test result. RETeval-DR is designed, and validated, to identity VTDR based upon the physical response characteristics of patients with diabetes, and results are not applicable to a non-diabetic patient.

b) **Is it possible that a non-diabetic patient with a high test result has some eye disease?** Although not likely, it is possible, particularly with other ischemic diseases such as central retinal vein occlusion (CRVO).

14) Does RETeval-DR require the eyes to be dilated?

a) No. RETeval-DR is effective from a pupil size of 1.3 mm to 9.0 mm without dilation. This is effectively the entire pupil size range in a given population.

15) Is there any interpretation required to evaluate the results from RETeval-DR?

a) No, the results are immediate and they are automatically generated by the device.

b) No waveform interpretation is necessary by the physician or electrophysiologist.

16) Is there a report generated by RETeval-DR?

a) Yes, the device automatically generates a PDF report that can be printed, uploaded into a patient record and/or shared with the patient or eye care specialist.

b) This report includes all of the patient information, the score, and all of the individual waveforms, amplitudes, and implicit times should they be required by the retinal specialist.

17) Does RETeval-DR connect to a PC?

a) Yes, the device easily plugs into a docking station that recharges RETeval-DR's lithium ion battery and provides a USB connection to any PC.

18) How do you know that the result provided by RETeval-DR is valid?

a) The device does extensive self-checking and confidence interval testing. If RETeval-DR does not obtain a valid result the device will notify the operator and will not generate a score.

b) If the device generates a result, then it is valid.

19) How do you know that RETeval-DR is within calibration and does not need to be cleaned?

a) The RETeval-DR device has a built-in photodiode and does a self-calibration before each patient test. The device will also alert the operator when it is necessary to clean the inside of the integrating sphere with compressed air to blow out any dust.

20) Is RETeval-DR affected by the presence of a cataract or a small pupil size?

a) No. Light can pass through cataracts so the presence of a cataract will not affect test results[19]. During the clinical trial, RETeval-DR was successful in generating a result on 99.2% of the patients tested.

21) What is the average per patient test time for RETeval-DR?

a) The average test time in the 468 person multi-center clinical trial was 2.3 minutes from start to finish.

22) How does RETeval-DR compare/contrast with fundus photography?

a) RETeval-DR is a mass illumination test giving an assessment of the entire retina, including the periphery.

i) Fundus photographs provide a field of view, typically 37 degrees for smaller pupils (> 3.5 mm) and 45 degrees for larger pupils (> 4 mm). A one-image fundus photograph at best gives an indication of disease within its 45 degree view of the retina. This image is blind to damage in the remaining 75% of the retina.

b) RETeval-DR is unaffected by pupil size or the presence of a cataract[19] (unless it is occluding all light and the patient is blind).

   i) Fundus cameras fail to capture a gradable image about 35% of the time[20]. This is due to small pupil size, the presence of a cataract, or shadows produced by the flash on the retina.

c) RETeval-DR results are immediate.

   i) Fundus photographs must be graded, typically offline with results coming later.

d) RETeval-DR is easy to learn and intuitive to operate.

   i) It can be difficult and tedious to get an acceptable image using a hand-held fundus camera. Table mounted versions are not very portable, are more costly, but make image capture easier.

e) RETeval-DR does not impact practice patient flow and productivity. It can easily be done by any member of the staff and takes less than three minutes per patient with immediate results.

   i) Some skill and training is required for fundus photography to determine whether an image is likely to be gradable or not. Welch Allyn's RetinaVue solution overcomes this issue with an automatic image quality algorithm.

   ii) Test time is variable and can take up to 7-15 minutes per patient if the pupil is small and they have to sit in a darkened room before photography and have recovery time between photographs and eyes.

f) Using artificial dilation drops can reduce the ungradable rate with fundus photography, but has several drawbacks.

   i) It takes 20-30 minutes to dilate, so the total testing time for photography can be up to ten times longer than testing with the RETeval-DR device.

   ii) In eye-care settings, typically a physician is required to administer the eye drops in order to watch for angle closure glaucoma – a risk factor caused by the drugs in the drops.

   iii) In primary care settings, mild pupil dilation with 0.5% tropicamide is safe and effective method to obtain high quality digital retinal images. No demonstrated risk factors exist for angle closure glaucoma using this dilation method.

   iv) The patient takes several hours to recover their vision after artificial dilation.

   v) The eye drops sting when administered, making the test more unpleasant.

23) LKC Technologies, Inc. manufactures RETeval-DR for Welch Allyn. Who is LKC Technologies?

a) LKC is a pioneer in visual electrophysiology introducing the world's first commercial ERG system to the market in 1976.

b) LKC manufactures and sells the LKC UTAS visual electrophysiology system which runs the entire spectrum of testing prescribed by the International Society of the Clinical Electrophysiology of Vision (ISCEV). These systems typically sell for $50,000 USD to $100,000 USD depending upon configuration. Aravind Eye Hospital is a user of this system in India.

c) LKC also sells a RETeval model called "RETeval Complete" to eye care specialists around the

world. Where the Welch Allyn RETeval-DR is designed and priced for primary care markets with just one diabetic retinopathy protocol, RETeval-Complete has a total of 30 possible protocols. The RETeval Complete is priced about three times more than RETeval-DR. LKC brand sensor strips will not work with Welch Allyn RETeval-DR devices and vice versa.

The LKC Complete version contains five ISCEV[a] defined standard flash ERG protocols including; Maximal response in dark adapted eye, Rod response in dark adapted eye, Oscillatory potential, Cone response, Response to flicker. RETeval Complete also includes an optional bright flash protocol, Photopic Negative protocol, S-Cone protocol, an on/off protocol, and the RETeval DR protocol. These are offered in both Troland second for use without dilation or candela's for dilated testing. Flash VEP protocols are also provided.

d) LKC invented the RETeval-DR and patented its unique capabilities. We have partnered with Welch Allyn to manufacture the RETeval-DR device for Welch Allyn for sale everywhere outside of the United States.

24) Is RETeval-DR FDA approved?

a) Yes, 510(k) number is K142567, RETeval™ Visual Electrodiagnostic Device

i) RETeval is indicated for use in the measurement of visual electrophysiological potentials, including electroretinogram (ERG) and visual evoked potential (VEP). RETeval is also indicated for use in the measurement of pupil diameter.

ii) RETeval is intended as an aid in diagnosis and disease management in visual pathway dysfunctions or ophthalmic disorders (e.g., diabetic retinopathy, glaucoma).

25) What is the resolution of RETeval-DR?

a) Resolution is a metric for fundus camera, not an ERG device such as RETeval.

26) What can go wrong when using RETeval-DR?

a) Sensor strip placement incorrect

b) Putting dilation or other drops in the eye before the RETeval test.

c) Doing fundus photography before the RETeval test.

d) Not pressing the device against the eye orbit (trying to hover it near the eye instead).

e) The contralateral eye not being covered.

27) Are there any contraindications for screening with RETeval-DR?

a) Photosensitive epilepsy.

b) No adverse events have been reported to date.

28) Where is RETeval-DR approved and licensed for clinical sale and use?

a) RETeval-DR is currently intended for export, and is not sold or offered for sale in the U.S.A.

b) RETeval-DR is approved for sale and clinical use in Japan, Australia, Canada, Israel, and Saudi Arabia and is CE marked and approved for sale in the E.U. and wherever CE mark is accepted.

[a] International Society for Clinical Electrophysiology of Vision (www.iscev.org).

29) How does RETeval-DR compare with fundus photography and/or a dilated eye examination by an ophthalmologist when compared to the same gold standard?

a) The following table was generated from peer reviewed publications comparing fundus photography and dilated eye examinations to the same gold standard.

	RETeval-DR	3 stereoscopic nonmydriatic photography[20,21]	Ophthalmologists[22]
Study sample size (n)	468	54	352
Sensitivity	87%	85%	33%
Specificity	78%	66%	99%
PPV	15%	10%	60%
NPV	99.2%	99.0%	97.0%
Number of false positives per 1000 tested	210	325	10
Number of false negatives per 1000 tested	6	7	29
Number of disease negative identified as negative per 1000 tested (true negatives)	746	631	946
Number of disease positives identified as positive per 1000 tested (true positives)	38	37	15

30) Is there an age limit for the RETeval-DR device?

a) There is not an age limit on the RETeval-DR device, but diabetic retinopathy typically does not manifest in young children due to the slow progressive nature of the disease. For example, the recommendation from the American Diabetes Association indicates screening is generally not necessary below 10 years of age[24], see below.

> *Patients ≥10 years of age with type-1 diabetes should have an initial dilated and comprehensive eye examination by an ophthalmologist or optometrist within 3–5 years after the onset of diabetes. In general, screening for diabetic eye disease is not necessary before 10 years of age. However, some evidence suggests that the prepubertal duration of diabetes may be important in the development of microvascular complications; therefore, clinical judgment should be used when applying these recommendations to individual patients. Patients with type-2 diabetes should have an initial dilated and comprehensive eye examination by an ophthalmologist or optometrist shortly after the diagnosis of diabetes is made*[24].

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