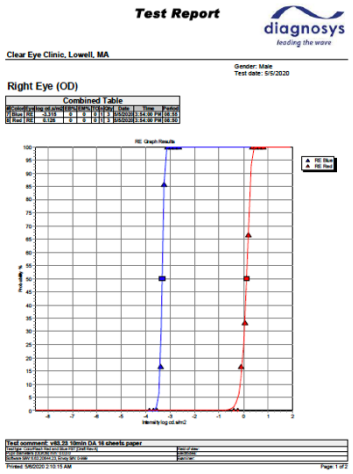
Diagnosys*FST*®
Application Note

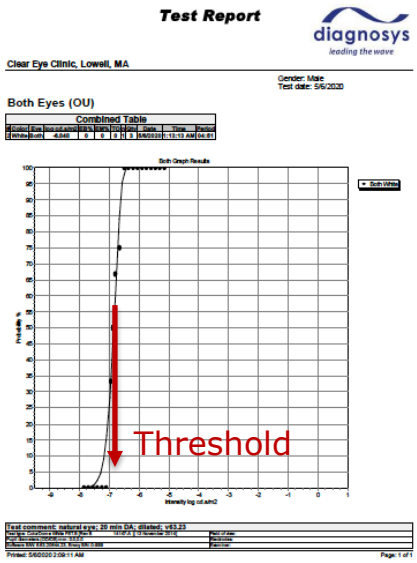
The Diagnosys*FST*®, Full-field Stimulus Threshold, module uses the ColorDome™ or ColorFlash™ stimulator. It measures the sensitivity of the visual field by testing for the lowest luminance flash which elicits a visual sensation perceived by the subject. The test is run on either dark- or light-adapted patients for one or both eyes in an automated routine to measure a reliable threshold.

Applications

- Gene therapy diagnostics
- Safety or primary endpoint in clinical trials
- Clinical low vision patient objective measure of vision
- RP, LCA, Stargardt disease, CSNB, Achromatopsia, Choroideremia, retinal prosthesis, others
- 15 years of clinical trial success



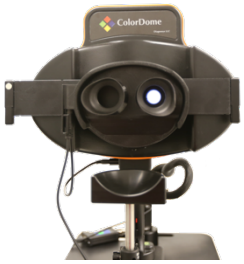
Dark adapted Red & Blue: Low vision patient



Dark adapted White: normal patient threshold

ColorDome and ColorFlash stimulator options:

ColorDome



ColorDome with iMask

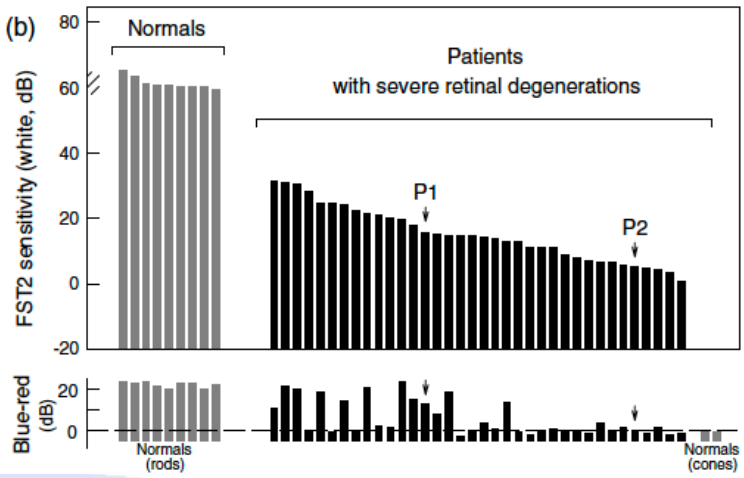
ColorFlash[1]

1. ColorFlash stimulus range is appropriate for FST tests on low vision patients only.

Why use Diagnosys*FST*®:

Roman, et al in 2007:

1. Test ultra -ow vision patients with a quantified, repeatable measure of vision
2. Up through at least 'barely light perception'
3. Patients with vision up to 60 dB (6 log units in cd·s/m^2) worse vision than Normal subjects were repeatably measured



Diagnosys*FST*® proven test-retest repeatability:

Klein and Birch in 2009:

1. 42 low vision subjects (no ERG response; unable to perform static perimetry)
2. ±2 standard deviations (95% CI) was found to be ±3 dB (±0.3 Log cd·s/m2)

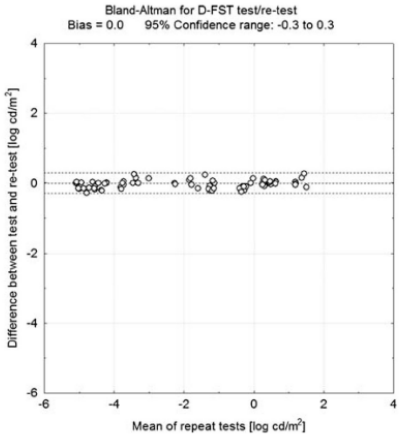
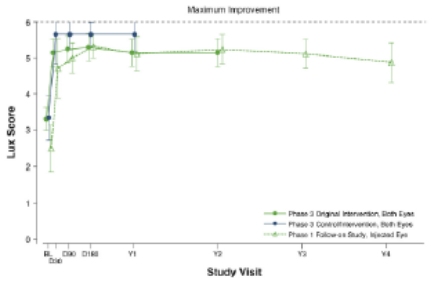


Fig. 4.
Bland–Altman analysis for the test/retest variability of the D-FST. The difference in threshold between test and retest within a session (*y*-axis) is plotted against the mean threshold for all sessions (*x*-axis). The 95% confidence range (*dashed lines*) is ±0.3 log cd/m^2

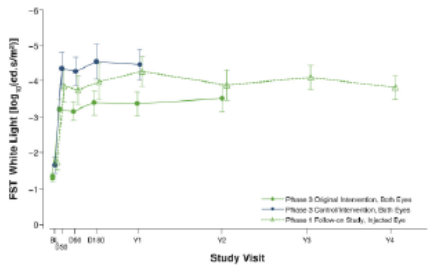
Relied on for over a decade of Gene Therapy clinical trials:

Albert M. Maguire, et al; 'Efficacy, Safety, and Durability of Voretigene Neparvovec-rzyl in RPE65 Mutation - Associated Inherited Retinal Dystrophy'; 2019

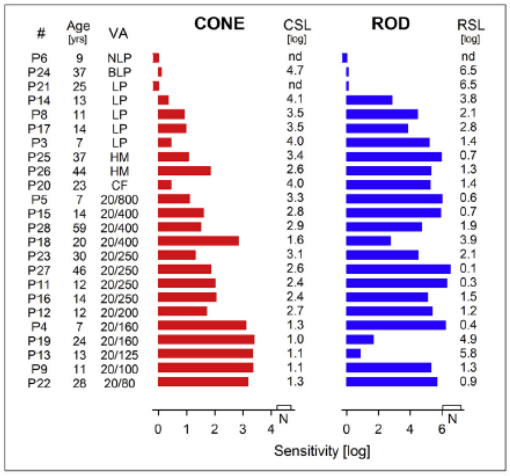
Mean **Multi-Luminance Mobility Test (MLMT)** lux scores from administration baseline in evaluable phase 1 follow-on subjects (n = 8) and phase 3 subjects.



Mean **full-field light sensitivity threshold (FST),** white light, averaged over both eyes, from administration baseline in evaluable phase 1 follow-on subjects (n = 8) and phase 3 subjects.



Samuel G. Jacobson et al; 'Defining Outcomes for Clinical Trials of Leber Congenital Amaurosis Caused by GUCY2D Mutations'; 2017



Benchmarked against all other diagnostic tests

Multi-Luminance Mobility Test (MLMT), other courses	Maguire 2019; Jacobson 2017; Russell 2017; Bennett 2016; Jacobson 2012
Visual fields, perimetry	Stingl 2019; Aleman 2018; Utz 2018; Stunkel 2018; Dimopoulos 2017; Ghazi 2016; Bennett 2016; Collison 2014; Bittner 2014; Messias 2013; Jacobson 2012; Lorenz 2012; Jacobson 2011; Cideciyan 2011
OCT	Aleman 2018; Utz 2018; Stunkel 2018; Jacobson 2017; Ghazi 2016; Collison 2014; Ahuja 2013; Jacobson 2012; Jacobson 2009; Hauswirth 2008
ERG	Stingl 2019; Utz 2018; Stunkel 2018; Collison 2014; Messias 2013; Cideciyan 2011; Klein 2009; Jacobson 2009
Pupillometry	Stingl 2019; Jacobson 2017; Collison 2015; Collison 2014; Jacobson 2012; Lorenz 2012; Jacobson 2011; Maguire 2009
Fundus photography, autofluorescence	Dimopoulos 2017; Jacobson 2017; Ahuja 2013
Contrast sensitivity	Bittner 2014

Thoroughly studied in peer-reviewed papers (select list):

1. Alejandro J Roman, et al; 'Full-field stimulus testing (FST) to quantify visual perception in severely blind candidates for treatment trials'; Physiol. Meas. 28 (2007) N51–N56. doi:10.1088/0967-3334/28/8/N02
2. William W. Hauswirth, et al; 'Treatment of Leber Congenital Amaurosis Due to RPE65 Mutations by Ocular Subretinal Injection of Adeno-Associated Virus Gene Vector: Short-Term Results of a Phase I Trial'; HUMAN GENE THERAPY 19:979–990 (October 2008). doi: 10.1089/hum.2008.107
3. Albert M Maguire, et al; 'Age-dependent effects of RPE65 gene therapy for Leber's congenital amaurosis: a phase 1 dose-escalation trial'; Lancet. 2009 November 7; 374(9701): 1597–1605. doi:10.1016/S0140-6736(09)61836-5.
4. Samuel G. Jacobson, et al; 'Defining the Residual Vision in Leber Congenital Amaurosis Caused by RPE65 Mutations'; Invest Ophthalmol Vis Sci. 2009 May; 50(5): 2368–2375. doi:10.1167/iovs.08-2696
5. M Klein and DG Birch; 'Psychophysical assessment of low visual function in patients with retinal degenerative diseases (RDDs) with the Diagnosys full-field stimulus threshold (D-FST)'; Doc Ophthalmol. 2009 December ; 119(3): 217–224. doi:10.1007/s10633-009-9204-7
6. Artur V. Cideciyan, et al; 'Cone photoreceptors are the main targets for gene therapy of NPHP5 (IQCB1) or NPHP6 (CEP290) blindness: generation of an all-cone Nphp6 hypomorph mouse that mimics the human retinal ciliopathy'; Human Molecular Genetics, 2011, Vol. 20, No. 7. doi:10.1093/hmg/ddr022
7. Samuel G. Jacobson et al; 'Human Retinal Disease from AIPL1 Gene Mutations: Foveal Cone Loss with Minimal Macular Photoreceptors and Rod Function Remaining'; Investigative Ophthalmology & Visual Science, January 2011, Vol. 52, No. 1. doi:10.1167/iovs.10-6127
8. Samuel G. Jacobson et al; 'Gene Therapy for Leber Congenital Amaurosis caused by RPE65 mutations: Safety and Efficacy in Fifteen Children and Adults Followed up to Three Years'; Arch Ophthalmol. 2012 January ; 130(1): 9–24. doi:10.1001/archophthalmol.2011.298
9. Birgit Lorenz, et al; 'Chromatic Pupillometry Dissects Function of the Three Different Light-Sensitive Retinal Cell Populations in RPE65 Deficiency'; Invest Ophthalmol Vis Sci. 2012;53:5641–5652) DOI:10.1167/ iovs.12-9974
10. AK Ahuja, et al; 'Factors Affecting Perceptual Threshold in Argus II Retinal Prosthesis Subjects'; Trans Vis Sci Tech. 2013;2(4):1. doi/full/10.1167/tvst.2.4.1
11. Katharina Messias, et al; 'Psychophysically determined full-field stimulus thresholds (FST) in retinitis pigmentosa: relationships with electroretinography and visual field outcomes; Doc Ophthalmol (2013) 127:123–129. doi:10.1007/s10633-013-9393-y
12. Ava K Bittner, et al; 'A pilot study of an acupuncture protocol to improve visual function in retinitis pigmentosa patients'; Clin Exp Optom. 2014 May; 97(3): 240–247. doi:10.1111/cxo.12117
13. Frederick T. Collison, et al; 'Psychophysical Measurement of Rod and Cone Thresholds in Stargardt Disease with Full-Field Stimuli'; Retina. 2014 September ; 34(9): 1888–1895. doi:10.1097/IAE.0000000000000144
14. Frederick T. Collison, et al; 'Full-Field Pupillary Light Responses, Luminance Thresholds, and Light Discomfort Thresholds in CEP290 Leber Congenital Amaurosis Patients'; Invest Ophthalmol Vis Sci. 2015;56:7130–7136. doi:10.1167/iovs.15-17467
15. Nicola G. Ghazi, et al; 'Treatment of retinitis pigmentosa due to MERTK mutations by ocular subretinal injection of adeno-associated virus gene vector: results of a phase I trial'; Hum Genet, doi:10.1007/s00439-016-1637-y
16. Jean Bennet, et al; 'Safety and durability of effect of contralateral-eye administration of AAV2 gene therapy in patients with childhood-onset blindness caused by RPE65 mutatons: a follow-on phase 1 trial'; Lancet. 2016 August 13; 388(10045): 661–672. doi:10.1016/S0140-6736(16)30371-3
17. Samuel G. Jacobson et al; 'Defining Outcomes for Clinical Trials of Leber Congenital Amaurosis Caused by GUCY2D Mutations'; AmJOphthalmol 2017;177:44–57. http://dx.doi.org/10.1016/j.ajo.2017.02.003
18. Stephen Russell, et al; 'Efficacy and safety of voretigene neparvovec (AAV2-hRPE65v2) in patients with RPE65-mediated inherited retinal dystrophy: a randomised, controlled, open-label, phase 3 trial'; Lancet 2017; 390: 849–60. doi: http://dx.doi.org/10.1016/S0140-6736(17)31868-8
19. Samuel G. Jacobson, et al; 'Outcome Measures for Clinical Trials of Leber Congenital Amaurosis Caused by the Intronic Mutation in the CEP290 Gene'; Invest Ophthalmol Vis Sci. 2017;58:2609–2622. DOI:10.1167/iovs.17-21560
20. Ioannis S Dimopoulos, et al; 'The Natural History of Full-Field Stimulus Threshold Decline in Choroideremia'; RETINA 0:1–12, 2017.
21. Maria L. Stunkel, et al; 'Expanded retinal disease spectrum associated with autosomal recessive mutations in GUCY2D'; AJOPHT 10455. doi:10.1016/j.ajo.2018.03.021
22. Virginia Miraldi Utz, et al; 'Presentation of TRPM1-Associated Congenital Stationary Night Blindness in Children'; JAMA Ophthalmol. doi:10.1001/jamaophthalmol.2018.0185
23. Tomas S Aleman, et al; 'RDH12 Mutations Cause a Severe Retinal Degeneration With Relatively Spared Rod Function'; Invest Ophthalmol Vis Sci. 2018;59:5225–5236. https://doi.org/10.1167/iovs.18-24708
24. Krunoslav T. Stingl, et al; 'Chromatic Full-Field Stimulus Threshold and Pupillography as Functional Markers for Late-Stage, Early-Onset Retinitis Pigmentosa Caused by CRB1 Mutations'; Trans Vis Sci Tech. 2019;8(6):45, https://doi.org/10.1167/tvst.8.6.45
25. Artur V. Cideciyan, et al; 'Effect of an intravitreal antisense oligonucleotide on vision in Leber congenital amaurosis due to a photoreceptor cilium defect'; Nature Medicine, VOL 25, FEBRUARY 2019, 225–228. doi:10.1038/s41591-018-0295-0
26. Albert M. Maguire, et al; 'Efficacy, Safety, and Durability of Voretigene Neparvovec-rzyl in RPE65 Mutation - Associated Inherited Retinal Dystrophy'; Ophthalmology 2019;126:1273-1285. doi:10.1016/j.ophtha.2019.06.017

www.diagnosysllc.com

US: Diagnosys LLC; 55 Technology Drive, Suite 100, Lowell, MA 01851; 978-458-1600; sales@diagnosysllc.com
EU: Diagnosys Vision Ltd; Office 117, DOC Building, Balheary Road, Swords, Dublin, K67 E5A0, Ireland; +44 (0) 1223 520699; mail@diagnosysvision.com
UK: Diagnosys UK Ltd; 5 Trust Court, Chivers Way, Vision Park Histon, Cambridge, CB24 9PW, UK; +44 (0) 1223 520699; mail@diagnosysuk.co.uk

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