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Letter to the Editor

Functional screening devices for diabetic retinopathy

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Diabetic retinopathy (DR) is a leading cause of blindness in Australia. Visual outcomes for patients with DR improve with early detection and treatment, thus screening programs are essential. Automated identification of DR based on retinal imaging is progressing. Functional screening detects retinal neuropathy prior to vascular changes, hence adjunctive functional testing has potential to further improve identification of patients at highest risk of blinding DR.

Early studies using electroretinography (ERG) show retinal response to white light flickering at 30 Hz, particularly response latency, can be used as a biomarker for diabetic retinal ischaemia with response abnormalities highly correlated with retinopathy severity.[1,2] An ideal functional screening test will have a strong scientific basis, be optimized for detection of vision-threatening DR (VTDR) rather than any DR, be non-invasive, non-mydriatic, have negligible test complications, brief test time, inexpensive (capital outlay, consumables, staff costs), and have high intra-test and inter-test reproducibility. National Health and Medical Research Council (NHMRC) minimum recommendations for DR screening tests are: sensitivity at least 60%, specificity 90-95%, acceptable technical failure rate 5-10%. UK National Institute for Clinical Excellence (NICE) guidelines are more rigorous, stipulating minimum sensitivity 80%, specificity 95% and technical failure <5%.

RETeval-DR™ is a recently released handheld flicker ERG device recommended as a screening tool for VTDR.[3, 4] RETeval-DR™ is a lightweight dome approximately 10 cm diameter which emits a white light flash (luminance between 0.002 and 30 Candela-s/m^2, 28.3 Hz), with no background illumination. Active, reference and ground electrodes are contained in a single patch applied to lower lid skin. Non-mydriatic testing is performed uniocularly, without light adaptation. Research equipment can have luminance adjusted and raw data extracted. Responses in commercially available units are reported as a single number which incorporates ERG data, as well as pupillometry

where luminance is adjusted according to pupil area. A reference interval is provided, and patients with VTDR are stated to return retinopathy scores greater than 20. Features of RETeval-DR™ suitable for screening include portability, low cost, non-mydriatic and non-invasive testing, test time less than 5 minutes/eye and low technical failure rate. However, at present a number of issues preclude use of RETeval-DR™ in community-based screening. Correlation between International Society for Clinical Electrophysiology of Vision (ISCEV) ERG and RETeval-DR™ responses has not been established. Two small studies directly compared 30 Hz flicker responses recorded with RETeval-DR™ and conventional ISCEV ERG. Results for amplitude appear comparable, but correlation between implicit time measured with RETeval-DR™ and conventional ERG is variable, and further studies are needed. (Accordingly, RETeval-DR™ does not fulfil criteria for Medical Benefit Schedule subsidy in Australia). Studies using RETeval-DR™ show responses are affected by pupil size and cataract, with delayed latency responses with larger pupil size and cataract, and in different clinical settings. The significance of incorporated pupillometry is yet to be clarified, as is the calculated retinopathy score. Reproducibility of responses is not yet demonstrated, particularly amplitude responses. Optimized settings for detection of VTDR are not yet established; published studies use differing stimulus intensity and latency cut-off points. Studies in populations enriched with diabetics detecting VTDR show sensitivity 83-85% and specificity 78-85%.[3, 4] Litvin *et al* in a real-world setting found sensitivity at best 92%, with specificity 53%.[5] RETeval-DR™ does not yet pass NHMRC or NICE requirements for use in screening. Maa *et al*[3] elaborate that in a population of 1000 diabetic patients, 4.4% (44 patients) would be expected to have VTDR. The RETeval-DR™ if used as the sole means of detection of VTDR would generate 247 referrals to ophthalmology care for VTDR, of whom only 37 would have VTDR (210 false positive results); 6 patients with VTDR would be missed (false negatives). Unfettered false positive results would

overwhelm the Australian public healthcare system that already has capacity issues. Finally, these studies do not confirm that detected ERG abnormalities are associated with progression to proliferative DR and significant vision loss, in contrast to clinical examination and retinal photography.

Additional research-based electrophysiology tests showing promise in assessing diabetic retinopathy include multifocal ERG (mfERG), multifocal visual evoked potential (mfVEP) and multifocal pupillography (mfPOP). mfERG implicit time used in quantitative models with other risk factors predicts DR and DME in patients with no clinical retinopathy with high accuracy.[6] mfVEP responses are similar but less marked,[7] and correlate with mfPOP responses.[8]

Screening for VTDR using handheld flicker ERG devices may be a useful adjunct to future automated identification systems for DR. However, the high false positive rate and lack of long term clinical correlation precludes it from use as the sole screening modality. At present, we recommend this test may be used by qualified practitioners as an adjunctive test and support the continued implementation of current collaborative care models based on clinical examination and/or retinal photography. Further studies are needed to better understand the role of functional devices in detecting and monitoring DR.

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