



Review

Developments in Non-Invasive Imaging to Guide Diagnosis and Treatment of Proliferative Diabetic Retinopathy: A Systematic Review

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Abstract: Diagnosis and management of proliferative diabetic retinopathy are reliant upon retinal imaging. A systematic literature review of non-invasive imaging to guide diagnosis and treatment of proliferative diabetic retinopathy was performed. There is a trend of moving away from invasive (e.g., fundus fluorescein angiography) to non-invasive (e.g., wide-field optical coherence tomography (OCT), OCT angiography and colour fundus photography) imaging modalities to allow for more objective assessments that can be readily repeated in a time-efficient manner without compromising patient safety. Such quantitative assessments generating large amounts of data could benefit from artificial intelligence approaches to aid clinical decision making. These non-invasive imaging modalities continue to improve both in terms of the quality of image acquisition and progress in image interpretation. It is important that newer non-invasive imaging modalities are appropriately validated in large-scale prospective observational studies or randomised clinical trials.

Keywords: proliferative diabetic retinopathy; optical coherence tomography angiography; fundus imaging; neovascularization; non-invasive imaging; artificial intelligence



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1. Introduction

Diabetic retinopathy (DR) is a leading cause of vision impairment in people aged 20–74 years [1,2]. DR is a disease of global significance affecting populations in low, middle, and high-income countries. With the projected proportion of people living with diabetes expected to rise to 700 million by 2045, the global burden of diabetic-related eye disease will increase correspondingly, placing significant demand on healthcare systems [3].

The term DR describes microvascular and neural abnormalities seen in diabetes-affected eyes which may progress to proliferative diabetic retinopathy (PDR), characterised by the presence of neovascularization on the optic disc (NVD) or elsewhere (NVE) [4–6]. The new blood vessels that develop in PDR can be described by the histopathologic definition where there is a breach of the internal limiting membrane (ILM) and growth of the new vessels into the posterior hyaloid [7]. This is distinct from one of the features of severe non-proliferative DR (NPDR), where intraretinal microvascular abnormalities (IRMA) do not extend into the vitreous [8]. Important causes of vision loss in eyes with PDR include vitreous haemorrhage and tractional retinal detachment [9,10].

The disruption of the blood–retinal barrier (BRB) in DR states leads to an accumulation of blood components in the extravascular retinal parenchyma [11]. The grading of DR severity is based on the identification of features seen in the disease state which are hypothesised to result from breakdown in the BRB and underlying capillary nonperfusion or tissue hypoxia that drives an ischemic pathologic state which affects the structure and

function of the retina [8,11,12]. Pathological features seen in DR include microaneurysms, retinal dot and blot haemorrhages, cotton wool spots, hard exudates, venous beading, IRMAs, attenuation or drop-out of retinal capillaries, and neovascularization at the vitreoretinal interface associated with tractional retinal detachment, pre-retinal haemorrhage, and vitreous haemorrhage (VH) (Table 1) [13–15].

Table 1. Summary of findings in diabetic retinopathy by non-invasive imaging.

DR Location or Feature	Imaging Findings
Retinal periphery	Capillary dropout (reduced vessel density) Dilated and tortuous capillaries
Choriocapillaris	Flow voids increase as DR level worsens Flow voids do not correlate with outer retinal changes Reduced mean subfoveal choroidal and choriocapillaris thickness on OCT
FAZ	Enlargement Loss of circularity Slower blood flow velocity in perifoveal capillaries
Capillary Integrity	Loss of vessel density in peripapillary plexuses and in parafovea Non-perfused parafoveal areas Reduced FD of vascular tree in far peripheral retina on UWF angiography Central non-perfused areas associated with macular thickening on OCT Deep capillary plexus vessel density decreases with increasing severity of PDR Vessel changes in the superficial retinal layers are present in later stages of PDR
Microaneurysms	Less easily detected on OCTA compared to FA Turnover may be used as an objective measure for therapeutic response Counts decrease following anti-VEGF treatment Usually located in the deep plexus
IRMA	Do not breach the ILM Greater calibre than adjacent capillaries Some progress to NVE
DME	Chorioscleral interface may be not clearly identified in some areas OCTA flow areas in deep plexus correspond to cystic changes OCTA demonstrates reperfusion following treatment with anti-VEGF Increased vessel density of microaneurysms in perifoveal retina
NVD	Vessels originate outside of physiologic cup Size and vascular pattern changes are visible in OCTA Arise from retinal arteries or veins, posterior ciliary arteries, or the choroid
NVE	Located adjacent to areas of non-perfusion on OCTA New classification systems based on NVE origin and branching pattern

PDR, proliferative diabetic retinopathy; OCTA, optical coherence tomography; FAZ, foveal avascular zone; IRMA, intraretinal microvascular abnormalities; DME, diabetic macular oedema; NVD, optic disc neovascularisation; NVE, neovascularisation; mERG, multifocal electroretinography; PRP, panretinal photocoagulation; FD, fractal dimension; UWF, ultrawide-field.

Classification systems have been developed which define features seen in DR to provide a standard for clinically staging the disease [13,16]. The Airlie House classification of DR stages based on colour fundus photography was published in 1968 and has since evolved into the modified Airlie House classification [13]. This system has been widely adopted into both clinical practice and are used in large multi-centre clinical research trials [15,17–20].

These earlier studies which helped to define grading systems and guide standard therapies at the time preceded modern therapeutic options available today [13,14,20,21]. Similarly, the imaging technologies at the time of the seminal studies in DR have now been proceeded by newer advancements in non-invasive imaging modalities, such as Fourier domain optical coherence tomography (FD-OCT) and ultrawide field (UWF) colour fundus imaging, each with advanced angiography capabilities. These technologies offer greater

imaging efficiencies, processing abilities, high resolution scanning, and allow for follow-up with accurate sequential image alignment.

This review will systematically present new developments in current and evolving non-invasive imaging modalities used to diagnose PDR. Advances in non-invasive imaging technologies are also described in the context of disease response to modern therapies for PDR including to anti-vascular endothelial growth factor (anti VEGF), pan-retinal photocoagulation (PRP), and pars plana vitrectomy (PPV).

2. Methods: Systematic Literature Search

2.1. Selection of Studies

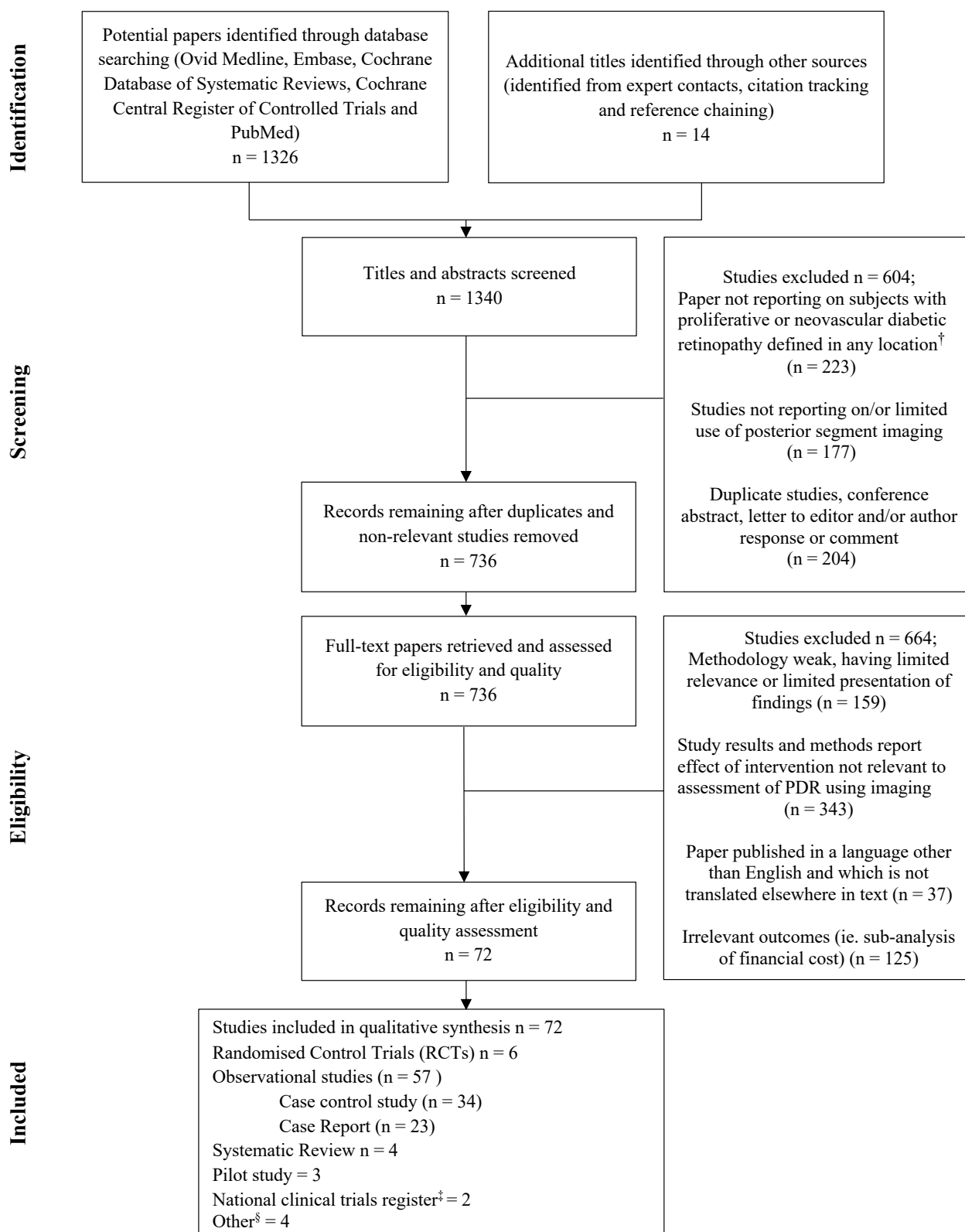
A systematic literature search was conducted on 1 June 2021 using Ovid Medline, Embase, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials and PubMed databases to identify potentially eligible studies. The literature search included papers published between 1947–1 June 2021. Further references were identified by manually searching included articles by citation tracking and consulting experts in the field. The following multipurpose search terms were used which looked in the Title, Original Title, Abstract, Subject Heading, Floating Sub-heading, Keywords, Name of Substance, Supplementary Concept Words, Synonyms and Unique Identifier fields: ‘proliferative diabetic retinopathy’ OR ‘new vessels elsewhere’ OR ‘new vessels at the disc’ OR ‘PDR’ OR ‘NVE’ OR ‘NVD’; AND ‘diagnosis’ OR ‘management’ OR ‘therapies’ OR ‘therapy’ OR ‘treatment*’; AND ‘color fundus imaging’ OR ‘colour fundus imaging’ OR ‘optical coherence tomography’ OR ‘OCT’ OR ‘optical coherence tomography angiography’ OR ‘OCTA’.

The preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines were followed in reporting. The modified PRISMA flow chart of the literature search and selection of studies for systematic review is reported in Figure 1.

2.2. Eligibility Criteria and Study Content

Duplicated or non-relevant studies were excluded. No date or language restrictions were applied. One thousand three hundred and forty titles and abstracts were retrieved and assessed against pre-determined inclusion and exclusion criteria. Paper abstracts were reviewed by a single reviewer for exclusion criteria. Full publications were retrieved for all citations accepted at the initial screening. Full publications were then re-screened and reviewed using pre-piloted eligibility and exclusion criteria (Figure 1). Differences were discussed and agreed with the input of an adjudicator where necessary.

Pilot studies, national clinical trials methods (where full-text publications of results were not yet available) were eligible for selection. Conference abstracts without full publication of results were excluded. Studies were excluded if they did not report on subjects with proliferative or neovascular diabetic retinopathy defined in any location, or if the study did not report on posterior segment imaging tools or intervention relevant to the assessment of PDR. Anterior segment complications, such as iris rubeosis, were not included, and only posterior segment imaging modalities were included in this review.



[†] Study reports on patients with alternative diagnosis including non-PDR, retinal vein or artery occlusion/s, pathological myopia, epiretinal membrane, vitreomacular traction, macular degeneration, punctate inner choroidopathy, macular telangiectasia. [‡] recent or currently conducted clinical trials with results not yet published in scientific journal. [§]epidemiological study.

Figure 1. Modified PRISMA flow diagram of systematic literature search.

3. Invasive Fundus Imaging Modalities to Guide Diagnosis of PDR

3.1. Fundus Fluorescein Angiography (FFA)

FFA is an invasive procedure whereby fluorescein dye is injected in a vein such as the antecubital fossa and then retinal perfusion and leakage associated with disease states affecting the microvasculature can be assessed with a series of fundus photographs [22]. FFA is the gold standard imaging technique for the assessment of PDR, characterised by fluorescein leakage from neovascular tissue, increasing in intensity and area over time. FFA can also identify areas of peripheral retinal and macular non-perfusion (Figure 2).

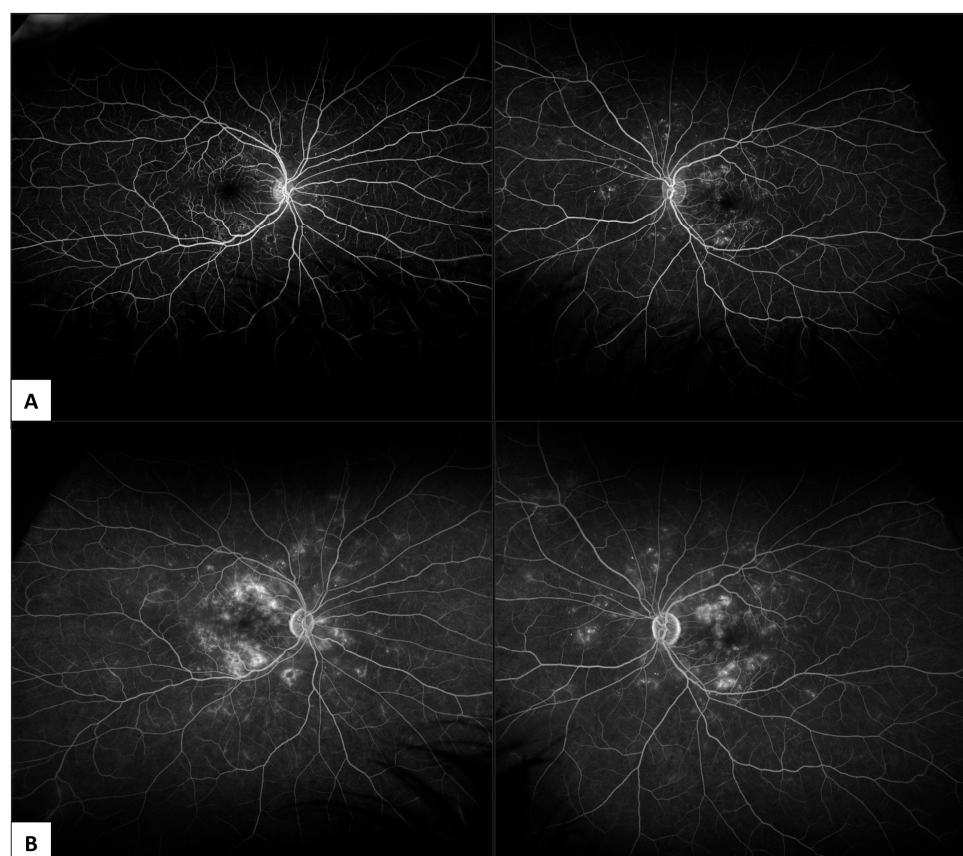


Figure 2. Ultrawide field (UWF) fluorescein fundus angiography (FFA) in non-proliferative diabetic retinopathy (NPDR) captured on 200° Optos (Optos California, Optos PLC, Dunfermline, UK): (A) showing early phase leakage at 1-minute following fluorescein dye injection; (B) showing late phase leakage at 6 minutes following fluorescein dye injection.

Limitations of FFA imaging are that patients require intravenous injection of an exogenous dye. This may be contraindicated in some diseases with end-stage microvascular disease including diabetic nephropathy. Some patients may develop life threatening severe allergy. The FFA procedure takes longer to perform and may be less well-tolerated by patients when compared to other non-invasive imaging procedures, limiting the number of times the test can be repeated.

Furthermore, FFA has a relatively low spatial resolution compared with newer OCT-A machines [23]. Importantly, FFA is unable to separately distinguish superficial from deep capillary networks due to its limits of two-dimensions, and retinal details become progressively obscured over the time-course of FFA imaging due to extravasation of the dye [24]. Whilst FFA may better identify microaneurysms, some of which may be missed by OCT-A in some studies, it is unable to identify the histological layer of positive findings, nor reliably follow-up identified areas of retina in serially aligned scans [23].

3.2. Indocyanine Green Angiography (ICG-A)

ICG-A is an invasive test similar to FFA with a different dye. Indocyanine green (ICG) dye has been histologically localised to both the choroidal intravascular space as well as extravasating into the choroidal stroma and accumulating within the RPE [25]. ICG therefore passes through local blood and pigmentary obscurations, adding to its utility in imaging the deep retinal and choroidal layers.

ICG-A can identify hypo-fluorescence in zones which represent a filling delay or defect at the level of the choriocapillaris which have been observed in DR [26]. Retinal avascular zones are more likely to be identified by FFA compared to ICG-A. Studies in DR have shown no leakage of ICG on angiographic studies in eyes with known diffuse diabetic macular oedema [27].

Limitations of ICG-A are similar to FFA; the principal of these being that repeated imaging is limited by the potential morbidity from an invasive dye test. Additionally, images are only able to be captured in two-dimensions. ICG-A is not routinely recommended for the diagnosis or management of PDR.

3.3. Ophthalmic B-Scan Ultrasonography

Ophthalmic B-scan ultrasonography has a role in imaging in the context of DR where VH obscures the direct view of the retina [28]. B-scan ultrasound can demonstrate whether a tractional retinal detachment accompanies other retinal pathology such as VH, a thickened posterior hyaloid, posterior vitreous detachment, or sub-retinal haemorrhage. Although examination with a B-scan may be considered less invasive by comparison to FFA and ICG angiography, it does require contact and manipulation of the ultrasound probe position with the patients closed eye making it more invasive than other non-touch, non-invasive imaging modalities.

4. Non-Invasive Fundus Imaging Modalities to Guide Diagnosis and Treatment of PDR

4.1. Colour Fundus Imaging

Seminal studies from the 1980s that established a gold-standard evidence base to inform management of DR include the Diabetic Retinopathy Study (DRS) [20], the Diabetic Retinopathy Vitrectomy Study (DRVS) [14,29], and the Early Treatment Diabetic Retinopathy Study (ETDRS) [21]. These early studies used 30-degree fundus cameras to image the posterior pole of the retina. The ETDRS defined seven-standard, central 30-degree photographic fields for viewing which was used for grading the severity of DR.

Pathologic features of DR which are captured by colour fundus imaging include haemorrhages, microaneurysms, IRMA, venous beading, cotton wool spots, hard exudates, drusen, retinal thickening, papillary swelling, new vessels on the disc (Figure 3) and NVE, pre-retinal and subretinal haemorrhage, vitreous haemorrhage, and tractional retinal detachment (Table 1). The extended modified Airlie House DR classification grading scale characterises the location and extent of these specific retinal lesions, which have been shown to be highly predictive of disease severity and the risk of DR progression over time. It is the accepted gold standard for grading which is used widely in research settings including large multi-centre clinical trials. Aspects of the classification system also form a basis for estimated risk of progression of DR to guide follow-up and treatment decisions in clinical practice.

The modified Airlie House classification uses non-simultaneous stereoscopic pairs of seven-standard photographic fields plus additional photographs to better define the grading scale for hard exudates, soft exudates, arteriovenous nicking, retinal elevation, and vitreous haemorrhage. The modified Airlie House classification also separates arterial abnormalities previously pooled as venous characteristics. The seven-standard ETDRS photographic fields are; field one centred on the optic disc, field two centred on the macula, field three temporal to the macula, fields four to seven are tangential to horizontal lines passing through the upper and lower poles of the disc and to a vertical line passing through the disc centre. Besides the seven-standard fields, an optional eighth field was added

in the ETDRS for follow-up to document new vessels, fibrous proliferations, pre-retinal haemorrhage, or vitreous haemorrhage outside of the standard defined seven fields [13].



Figure 3. Non-invasive Optos (Optos California, Optos PLC, Dunfermline, United Kingdom) colour fundus photograph of proliferative diabetic retinopathy. Sheathed retinal arteriole inferior to macula (arrow). Neovascularisation of the disc (*). Scattered intraretinal haemorrhages. Previous grid retinal laser nasal to disc (right eye).

Since the advent of commercially available UWF fundus imaging systems, numerous studies have compared images captured from UWF to the stereoscopic seven-standard ETDRS fields. The level of agreeability between the imaging fields for grading DR severity has been demonstrated to be high, but UWF images have also been demonstrated to provide additional prognostic value with regard to the risks of DR onset, progression and outcomes compared to areas only visualised by seven-standard field ETDRS photography.

Newer imaging modalities, such as models of the Optos fundus camera (Optos plc, Dunfermline, Scotland, UK), enable mydriatic non-simultaneous stereoscopic 200-degree UWF images of the retina [22]. High-resolution UWF scanning laser ophthalmoscopes enable approximately 80–85% of the retinal surface to be captured in a single image. The benefits of this newer technology pertain to added efficiencies with reducing total imaging time, the number of images required, greater ease of image evaluation, reduced rates of poor-resolution images and a reduction in the areas of retina missed by imaging as result of operator error. Such benefits and commercial availability of these UWF imaging systems have meant that they are now widespread in clinical practice (Figure 4) and are used by newer clinical trials.

Limitations of technology at the time when the original ETDRS criteria was developed meant that the far retinal periphery was not able to be systematically captured by imaging systems. Over the past thirty years since the ETDRS, numerous retinal imaging studies and clinical observations have demonstrated the significance of PPL as pathologic features of DR which are not evaluated by seven-standard field ETDRS photography. A lesion is considered to be predominantly peripheral if more than half of the area of the lesion being graded is in the peripheral retinal field compared to the modified seven-standard ETDRS photographic fields. A 4-year follow-up study by Silva et al. [22] found that eyes which had no PDR at baseline but did have PPLs on UWF imaging had a 3.2 increased risk of DR progression compared to eyes without PPLs ($p = 0.005$). Additionally, eyes with PPL were found to have a 4.7-fold increased risk for progression to PDR over 4 years even after correcting for diabetes duration and HbA1c levels [22]. This finding is supported by other studies similarly using UWF imaging [7,15,30].



Figure 4. Case series of patient showing progression of proliferative diabetic retinopathy. Diagnosis (A) to 5 years follow-up patient re-presents with vitreous haemorrhage (B). (C) 1-month post vitrectomy and pan-retinal endolaser photocoagulation for management of VH due to PDR. (D) right eye showing grid laser 360 PRP and left eye showing PRP delivered with endolaser during vitrectomy.

Intraoperative visualization of areas of traction and source of PDR can assist vitreo-retinal surgery (Figures 5 and 6).

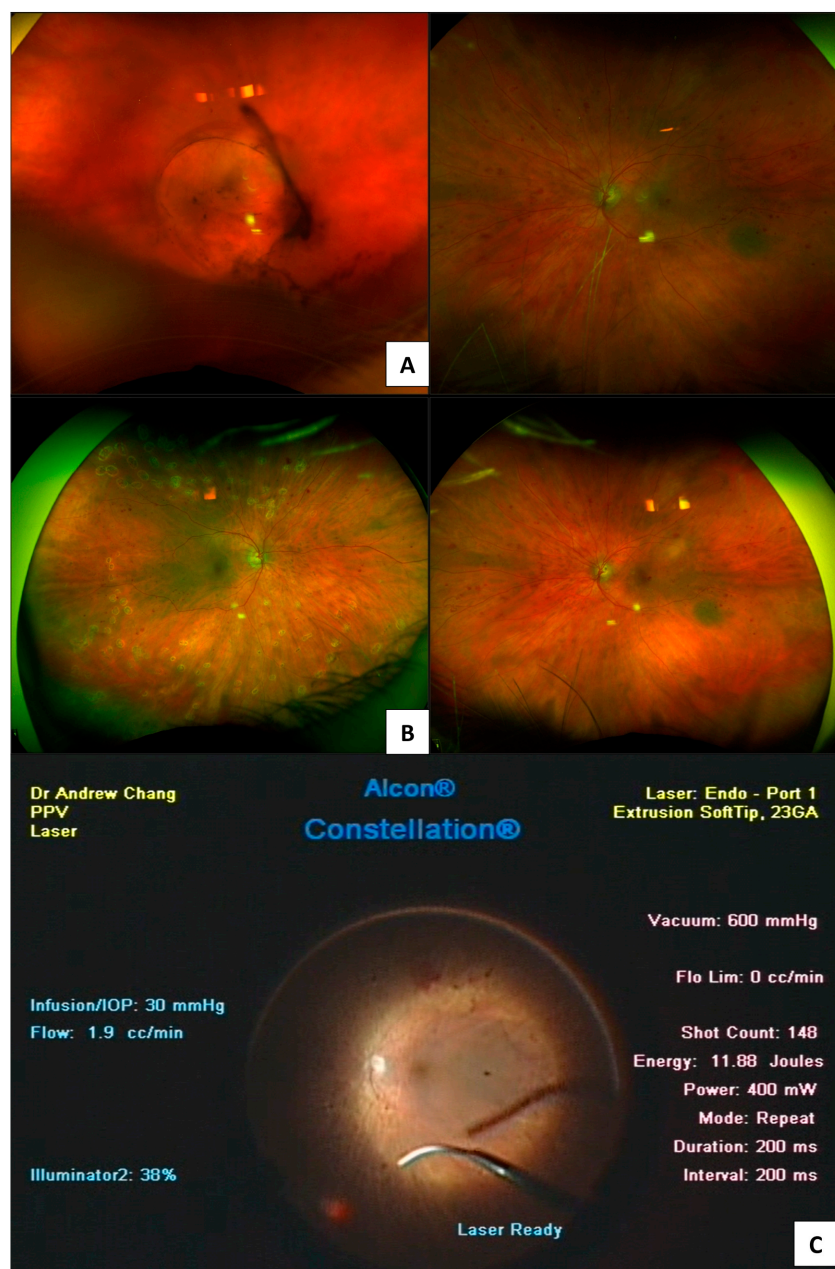


Figure 5. Proliferative diabetic retinopathy presents in (A) with vitreous haemorrhage in the right eye. Post vitrectomy Optos (Optos California, Optos PLC, Dunfermline, UK) colour fundus photograph 200° (B) showing targeted endolaser to areas of neovascularisation during vitrectomy (C).

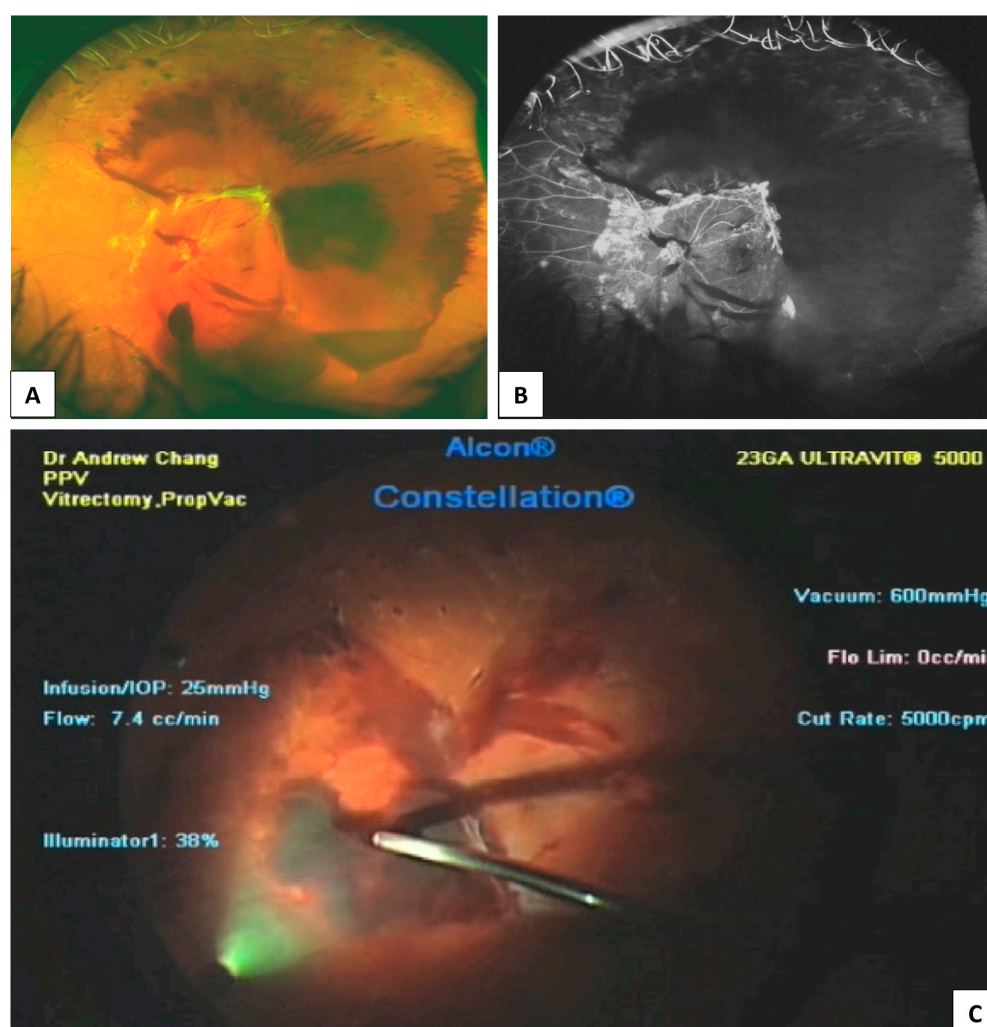


Figure 6. Traction retinal detachment and vitreous haemorrhage in proliferative diabetic retinopathy. Colour fundus photograph (A); Fluorescein angiography (B); Intraoperative video stills from recording during vitrectomy surgery showing pre-retinal, posterior hyaloid haemorrhage (C).

4.2. Optical Coherence Tomography (OCT)

OCT is a non-invasive imaging technique with three-dimensional volume information which provides micron level high-resolution cross-sectional retinal images. Segmentation of OCT allows for clearer differentiation of retinal layers, however earlier OCT used a shorter wavelength of 800 nm, which had limited penetration beyond the RPE to the choriocapillaris. Newer models have longer wavelength capabilities to 1050 nm which allow better visualization of the choroidal structures [3]. OCT is now the current clinical standard for observing the structural changes seen in diabetic macular oedema (DMO) [3,31].

Commercially available spectral-domain (SD-OCT) machines; Heidelberg Spectralis (Heidelberg Engineering, Heidelberg, Germany), Zeiss Cirrus (Carl Zeiss Meditec, Dublin, CA, USA), swept-source OCT (SS-OCT, Topcon, Tokyo, Japan), and Optovue RTVue (Optovue Inc., Fremont, CA, USA) machines, and one time-domain OCT Zeiss Stratus (Carl Zeiss Meditec) are used by clinical studies described in the body of this review [32].

With OCT technology it is possible to non-invasively evaluate cross-sectional images of the posterior vitreous and retinal layers to assess the ILM and posterior hyaloid for breaches in keeping with diagnostic criterion for NVE in the PDR stage of disease [24]. A summary of non-invasive imaging features to help diagnose PDR is included in Table 2. Assessment of the vitreoretinal interface plays an important role in management decisions for DR, both for prognostication and timeliness for interventional therapies. In assessment of eyes

with contraction of fibrovascular tissue and tractional retinal detachment for consideration of vitrectomy, imaging of the extent of the traction in particular macular involvement is essential [33]. Macular threatening traction or direct involvement is an indication for vitrectomy and membrane segmentation and delamination to relieve the traction to restore the macular anatomy [34]. Inner retinal traction and disruption of neural layers is well imaged with OCT [35,36].

Techniques used for imaging an extended field with earlier OCT technology have been described by Mishra et al. [37] in 2017, where the authors used a wide-field 12 mm × 12 mm radial swept source OCT together with a convex +90 diopter double aspheric noncontact slit-lamp lens placed between the eye and the OCT machine to theoretically expand the imaging field by increasing the imaging light incidence angle. This technique however has been shown to have a higher incidence of rim artefacts and reflection on OCT images, and, as each pixel is magnified without the enhanced hardware capabilities of the OCT system, there is some loss of retinal architectural detail and resolution [37]. Whilst this technique provides a panoramic OCT view of a large segment of fundus to define the vitreoretinal relationship at one time, there are compromises in resolution and image quality which may be further degraded by poor media or lens clarity, poor patient fixation and smaller pupil size. OCT and OCTA technologies have been further enhanced since the years of recruitment in these studies (2016–2017) [8,37] with faster scan rates, wider fields of view, denser scan volumes, pseudocolour imaging acquisition modules and enhanced depth range of OCT imaging now available. Summaries of published non-invasive imaging changes after panretinal laser photocoagulation (Table 3) and anti-VEGF therapy (Table 4) are included.

Table 2. Studies reporting diagnostic features of proliferative diabetic retinopathy by non-invasive imaging modalities, published within the past 5 years (2016–1 June 2021).

Study (Year, Author)	Non-Invasive Imaging Modality	Main Findings
2020, Um et al. [38]	OCTA 3 mm × 3 mm field AngioVue OCT-A system using an Avanti SD-OCT device (Optovue, Inc., Fremont, CA, USA)	The FAZ area in both the superior and deep capillary plexus increased with DR progression, whereas VD progressively decreased. Changes in the FAZ area and VD were greater in the deep capillary plexus compared to the superficial capillary plexus in PDR.
2020, Vaz-Pereira et al. [39]	SD-OCT (Spectralis, Heidelberg Engineering, Heidelberg, Germany)	Near-infrared reflectance imaging with OCT was used to qualitatively grade both NVE and NVD neovascular complexes and IRMA growing into NVE over a mean follow-up 3.2 ± 1.7 years of DR progression in 20 eyes. Neovascular complexes were observed for progression or regression by the identification of hyporeflective vascular fronds.
2020, Tan et al. [12]	Wide-field OCTA 12 mm × 12 mm field SS-OCT system (PlexElite 9000; Zeiss Meditec)	Wide-field (12 mm × 12 mm) fovea-centred OCTA examined retinal perfusion density, capillary perfusion density, large vessel density and capillary dropout density in 76 diabetic eyes. Microvascular perfusion may be useful for detecting predominant peripheral capillary dropout in eyes with DR.
2020, Schwartz et al. [40]	OCT 12 mm × 9 mm field & OCTA 6 mm × 6 mm field Topcon OCT (DRI OCT-1, Triton, Topcon, 151 Tokyo, Japan)	Structural OCT had a higher detection of new-onset NVD and NVE compared to B-scan OCTA, en face OCTA and colour photography. Change in NVD or NVE (either regression or progression) was best detected by B-scan OCTA.

Table 2. Cont.

Study (Year, Author)	Non-Invasive Imaging Modality	Main Findings
2020, Levine et al. [41]	OCTA 3 mm × 3 mm field SD-RTVue XR Avanti with AngioVue (Optovue, Inc., Fremont, CA, USA), the SD- Cirrus HD-OCT 5000 (Carl Zeiss Meditec, Dublin, CA, USA), and the swept-source PLEX Elite 9000 (Carl Zeiss Meditec, Dublin, CA, USA)	Full retinal layer vessel density is more precise for follow-up than OCTA images of the superficial or deep capillary plexus alone when comparing progression of PDR in the same and among different OCTA devices.
2020, Kase et al. [42]	OCT 9 mm × 9 mm field (Cirrus HD OCT; Carl Zeiss Meditec, Dublin, CA, USA)	Choroidal morphology analysis in treatment-naïve eye with DR showed significantly lower ratio of luminal area to total choroidal area in diabetic eyes compared to normal eyes. No change in central choroidal thickness was noted between eyes with and without DR.
2020, Hirano et al. [43]	OCTA 12 mm × 12 mm field PLEX Elite 9000 (Carl Zeiss Meditec, Dublin, CA, USA)	The efficacy of OCTA for detecting NVD and NVE in PDR was comparable to the sensitivity of that detected by FA. Additionally, OCTA may be better than FA for detecting IRMA.
2020, Ashraf et al. [44]	OCTA 3 mm × 3 mm field RTVue XR Avanti SD- OCT device with AngioVue software (Optovue, Fremont, CA, USA)	OCTA metrics showed reducing vessel density in the superficial, intermediate and deep layers of the capillary plexus with increasing severity of DR. In eyes with advanced DR vascular changes were present primarily in the superficial capillary plexus.
2019, Wang & Tao [45]	OCTA (Spectralis, Heidelberg Engineering, Heidelberg, Germany)	The ratio of the luminal to choroidal area was decreased in eyes with DR compared to normal controls. The choroidal vascularity index decreased with increasing severity of DR. Changes in the luminal area to choroidal area ratio may predict DR development before other clinical signs are evident.
2019, Motulsky et al., [46]	Wide-field OCTA 12 mm × 12 mm field PLEX Elite 9000 (Carl Zeiss Meditec, Dublin, CA, USA)	Decreased retinal perfusion, increased retinal thickness and neovascularization can be identified from 12 mm × 12 mm OCTA imaging in PDR.
2019, La Mantia et al. [47]	OCTA 4.5 mm × 4.5 mm & 3 mm × 3 mm field Topcon DRI OCT Triton device (Topcon Corporation, Tokyo, Japan)	There is good agreement between FFA and 4.5 mm × 4.5 mm and 3 mm × 3 mm OCTA FAZ area measurements in grading diabetic macular ischaemia in patients with DR.
2019, Hsiao et al. [48]	OCTA 3 mm × 3 mm field (AngioVue; Optovue Inc., Fremont, CA, USA)	Nineteen eyes with PDR showed reductions in vascular density with increasing progression of DR. Decreased deep retinal vascular density were proportional to severity of DR.
2019, Hirano et al. [49]	OCTA 3 mm × 3 mm, 6 mm × 6 mm & 12 mm × 12 mm field (PLEX Elite 9000; Carl Zeiss Meditec, Dublin, CA, USA)	Twenty-three eyes with PDR showed worse perfusion density, vessel length density and fractal dimension with worsening DR in all scan sizes compared to normal eyes. Of all OCTA parameters, perfusion density, vessel length density, and fractal dimension best predict DR.
2019, Cui et al. [50]	Wide-field OCTA 15 mm × 9 mm field PLEX Elite 9000 (Carl Zeiss Meditec, Dublin, CA, USA)	Motion artifacts and segmentation errors in montage images may affect reliability of results in widefield OCTA analysis. Higher levels of motion artefact limit the ability to visualise fine capillary vessels and DR features.

Table 2. Cont.

Study (Year, Author)	Non-Invasive Imaging Modality	Main Findings
2019, Alonso-Plasencia et al. [51]	OCTA 4.5 mm × 4.5 mm field Nidek RS-3000 Advance 2 AngioScan (Nidek, Japan) Microperimetry MP-3 (Nidek, Gamagori, Japan)	OCTA: Reduced vessel density in DR patients compared to normal controls. Microperimetry: Reduced mean retinal sensitivity in DR (27.68 ± 2.71 dB) compared to normal controls (31.68 ± 1.46) ($p < 0.05$). Correlation ($r = 0.501$, $p = 0.01$) between microperimetry and OCTA in the area temporal to the fovea was found in patients with DR.
2018, Savastano et al. [52]	OCTA 3 mm × 3 mm & 6 mm × 6 mm fields (AngioVue; Optovue Inc., Fremont, CA, USA)	OCTA shows blood flow in neovascularisations without artefacts due to dye leakage in PDR. Direct morphological signs of pathologic microvessels were able to be visualised to diagnose NVD in PDR.
2018, Pan et al. [8]	OCTA 3 mm × 3 mm & 4.5 mm × 4.5 mm fields RTVue XR Avanti (RT-VUE XR, Optivue, Fremont, CA, USA)	OCTA was able to detect microstructure of new vessels to identify their origins and locations and to distinguish preretinal new vessels from IRMAs. Thirty-five eyes with PDR showed three distinct origins of NVE and NVDs; originating from the venous side, originating from capillary networks, or originating from IRMAs.

OCTA, optical coherence tomography; DR, diabetic retinopathy; CFT, central foveal thickness; FAZ, foveal avascular zone; VD, vascular density; NVD, neovascularization of the disc; NVE, neovascularization elsewhere; FFA, fluorescein angiography.

Table 3. Studies reporting response to pan-retinal photocoagulation treatment in proliferative diabetic retinopathy by non-invasive imaging modalities, published within the past 5 years (2016–1 June 2021).

Study	Non-Invasive Imaging Modality	Main Findings
2021, Kim et al. [53]	SD-OCT 12 mm × 12 mm field Cirrus HD-OCT (Carl Zeiss Meditec, Inc., Dublin, CA, USA) OCTA 3 mm × 3 mm & 12 mm × 12 mm fields (PLEX Elite 9000, Carl Zeiss Meditec, Dublin, CA, USA)	Retinal microvascular changes in 27 treatment-naïve eyes with PDR subjected to argon laser PRP; SD-OCT: Mean sub-foveal choroidal thickness progressively decreased at 1, 3, 6, and 12 months following PRP, although the change was not statistically significant ($p = 0.108$). Mean CFT progressively increased over 12 months following PRP ($p = 0.103$). Mean macular ganglion cell inner plexiform layer thickness progressively decreased over 12 months following PRP ($p = 0.351$). OCTA: FAZ area in the superficial capillary plexus and deep capillary plexus decreased after 12 months from PRP treatment. Perfusion density and vessel length density of the superficial capillary plexus increased from 3 months after PRP treatment. The total non-perfusion area progressively decreased over 12 months ($p = 0.082$).
2020, Vergmann et al. [54]	OCTA 4.5 mm × 4.5 mm field DRI OCT Triton, swept source OCT, (Topcon Corporation, Tokyo, Japan)	Retinal microvascular changes in 21 treatment-naïve eyes with PDR subjected to PRP; the area of NVE measured by OCTA was able to distinguish between progression and non-progression of PDR from 6 months after PRP treatment.
2020, Russell et al. [55]	Wide-field OCTA 12 mm × 12 mm field WF SS-OCTA (PLEX Elite 9000, Carl Zeiss Meditec, Inc., Dublin, CA, USA)	Areas of retinal non-perfusion identified on wide-field OCTA co-localised with areas identified by invasive UWF FA. No significant changes in retinal non-perfusion areas were seen on OCTA 3 months following PRP in patients with PDR.

Table 3. Cont.

Study	Non-Invasive Imaging Modality	Main Findings
2020, Lupidi et al. [56]	OCTA 3 mm × 3 mm field (Spectralis HRA OCT, Heidelberg Engineering, Heidelberg, Germany)	Retinal neovascular area, vascular perfusion density, and fractal dimension were assessed by OCTA pre- and post-PRP in 15 eyes with PDR. A reduction in the retinal neovascular area detected by non-invasive imaging is predictive of PRP treatment efficacy and may reveal those eyes that may not require additional treatment.
2020, Zacharias et al. [57]	OCT SD-OCT (Heidelberg Engineering, Heidelberg, Germany)	PRP was not found to cause significant changes in peripapillary RNFL thickness in diabetic PDR patients 12 months following treatment.
2019, Mirshahi et al. [58]	OCTA 12 mm × 12 mm field DRI OCT swept source Triton Plus, (Topcon Corporation, Tokyo, Japan)	The FAZ area was unchanged, whilst foveal vascular density and retinal thickness increased in 11 eyes with PDR following PRP.
2019, Lorusso et al. [59]	OCTA (AngioVue XR Avanti; Optovue, Fremont, CA, USA)	Vessel density in the superficial and deep capillary plexus and the size of the foveal avascular zone was unchanged 6 months after PRP treatment for PDR.

PDR, proliferative diabetic retinopathy; OCTA, optical coherence tomography; CFT, central foveal thickness; FAZ, foveal avascular zone; IRMA, intraretinal microvascular abnormalities; DME, diabetic macular oedema; NVD, optic disc neovascularisation; NVE, neovascularisation; mERG, multifocal electroretinography; PRP, panretinal photocoagulation; FD, fractal dimension; UWF, ultrawide-field; RNFL, retinal nerve fibre layer.

Table 4. Studies reporting response to intravitreal anti-VEGF therapy in proliferative diabetic retinopathy by non-invasive imaging modalities, published within the past 5 years (2016–1 June 2021).

Study	Non-Invasive Imaging Modality	Main Findings
2020, Choi et al. [60]	SD-OCT SD-OCT device (Spectralis OCT, Heidelberg Engineering, Franklin, MA, USA)	Intravitreal bevacizumab injection before PRP leads to decreased CMT in patients diagnosed with PDR ($p = 0.002$).
2020, Chatziralli et al. [61]	OCT Spectralis HRA + OCT, Heidelberg Engineering, Germany	Twenty-four patients with PDR treated with concurrent PRP plus at least three intravitreal injections of ranibizumab showed greater regression of neovascularization with a smaller number of injections over twenty-four months compared to twenty-three patients receiving anti-VEGF injections alone.
2020, Bressler et al. [62]	OCT (multi-centre RCTs)	Anti-VEGF therapy to manage DMO or PDR was not found to increase the risk of TRD. In eyes with PDR without macula-threatening TRD, anti-VEGF therapy did not increase the risk of developing TRD in a pooled analysis from the five DRCR Retina Network RCTs.
2019, Arevalo et al. [63]	OCT (multi-centre RCT)	Preoperative intravitreal bevacizumab reduced the risk of intraoperative bleeding and improved surgical field visualization in 102 eyes with TRD secondary to PDR undergoing PPV compared to PPV alone.

VEGF, Vascular endothelial growth factor; CMT, central macula thickness; PDR, proliferative diabetic retinopathy; OCTA, optical coherence tomography; PRP, panretinal photocoagulation; DMO, diabetic macular oedema; PDR, proliferative diabetic retinopathy; TRD, tractional retinal detachment; PPV, pars plana vitrectomy.

4.3. OCTA

The OCT-A uses multiple, sequential OCT B-scans in cross-section to produce reconstructed images of the network of blood vessels enabling three different vascular layers to be visualised: the superficial capillary plexus, the deep capillary plexus, and the choriocapillaris. OCT-A allows quantitative, serial assessments of areas of capillary non-perfusion, including high-resolution images which are aligned to allow ease of monitoring disease progression at specific identified retinal areas. This feature makes OCT-A better suited

to follow-up for DR with less risk to the patient when compared to invasive imaging modalities [23]. There is currently a lack of clinical studies which examine the role of OCT-A in DR peripheral lesions. Most recent (2020) studies in PDR patients using OCT-A principally examine the posterior pole [12,38].

A classification system distinguishing NVE by topographic distribution, origin, and morphologic features has been described by Pan et al. [8,64]. This system relies on a combination of FA and OCTA to describe NVE as either originating from the venous side (Type 1) with tethering to the posterior hyaloid surface, from capillary networks (Type 2), or from intraretinal microvascular abnormalities (type 3) where the posterior hyaloid was still attached to the retina, as opposed to vitreoschisis or partial PVD in Type 1 NVE. The clinical implications of this classification system are that the three types of NVE may have varying topographical distribution features, and the authors have described distinguishable risk for complications including vitreous haemorrhage and traction retinal detachment, and differing responsiveness to treatment observed in a recently published study [64]. Limitations of the study [8] describing this classification of NVE according to OCTA features include the cross-sectional study design with a small cohort (35 eyes), and the reliance on only a small field of OCTA view (6 mm × 6 mm); therefore, NVE in the periphery were not included.

Recently, OCT-A has been suggested to more accurately measure areas of capillary dropout across the total, superficial, and deep capillary plexus in regions of ischaemia compared to images obtained by FFA [24].

Wide-field swept-source OCT-A has been used to provide information on microvascular perfusion in DR and may have a role in detecting peripheral capillary dropout, however it is not selective to excluding larger vessels so may not distinguish between different stages of DR progression [12].

OCT-A may have a role in better understanding the integrity of microvascular perfusion and how this relates to the maintenance of oxygen delivery to the retina, which has not yet been adequately explored in patients with PDR. Vitrectomy has been shown to improve rates of hypoxia and reduce VEGF production from ischaemic areas of retina [65]. Reduced VEGF levels reduces the stimulus for neovascularization processes as in diabetic neovascularization. Vitrectomy results in changes in oxygen flux across the retina and removes VEGF away from the retina at a faster rate than eyes without vitrectomy [65,66]. Therefore, vitrectomy could have additional benefits in diabetic eyes with retinal ischaemia [67]. There is presently a lack of OCT-A evidence in PDR patients post-vitrectomy (Table 5).

Table 5. Studies reporting response to pars plana vitrectomy surgery in proliferative diabetic retinopathy by non-invasive imaging modalities, published within the past 5 years (2016–1 June 2021).

Study	Non-Invasive Imaging Modality	Main Findings
2020, Rush et al. [9]	OCT (Zeiss Cirrus HD-OCT; Carl Zeiss Meditec, Inc., Dublin, CA, USA)	Improved vision, fewer postoperative diabetic macular oedema treatments and lower incidence of epiretinal membrane when ILM peeling was performed in patients ($n = 207$) with PDR undergoing PPV for VH. CMT tended to be lower in patients who had ILM peeled compared to those who did not.
2020, Abd Elhamid et al. [68]	Fundus examination with indirect ophthalmoscopy	Early vitrectomy for diabetic VH leads to faster gains in visual acuity with less incidence of recurrent VH compared to intravitreal anti-VEGF alone.

PDR, proliferative diabetic retinopathy; OCTA, optical coherence tomography; CMT, central macular thickness; ILM, internal limiting membrane; VH, vitreous haemorrhage.

5. Future Directions

5.1. AI Approaches

Screening for DR is currently based on human grading, which is labour intensive. Extrapolating the current UK annual DR screening protocol globally would require 2.2 billion retinal images to be graded in 2030 [69]. Emerging automated retinal image analysis systems are artificial intelligence machine learning algorithms that may provide a cost-effective alternative to human grading for sight-threatening complications of DR, such as PDR.

The use of computerised, automated platforms to detect clinically relevant biomarkers such as pan-retinal microaneurysm count in PDR have been proposed to enable assessment of disease response to therapy and for grading of different stages of disease progression [30]. Further angiographic metrics which may be analysed include retinal non-perfusion areas and retinal leakage [70].

Abdelsalam, 2020 [71] described AI methods which can accurately classify fundus OCTA in diabetic patients to distinguish DR with or without NPDR with a sensitivity and specificity of >96% in a small sample. The methodology uses an artificial neural network (ANN) as an automatic classifier to distinguish between normal subjects without diabetes ($n = 40$), diabetics without DR ($n = 30$), and mild to moderate NPDR subjects ($n = 30$) [71]. The ANN are a set of algorithms modelled closely to the human brain which are designed to perform non-linear statistical modelling using a biologically inspired paradigm where a computer learns from observational data feeds. OCTA images of the mean of the intercapillary areas as are shown to the ANN which develops predictive models from dichotomous outcomes. This methodology relies on features of the FAZ based on the previously established generalisation that DR patients have an enlarged FAZ region, reduced vascular density and circularity index [71,72].

With the increase in the number of acquired OCT scans and the technical complexity associated with analysis of layer segmentation in DR, new automated techniques for detection of local tissue alterations are becoming more relevant.

AI algorithms which integrate both imaging and clinical parameters for decision support may have an advantage over imaging algorithms alone. This would require collecting a structured minimum dataset of patient-centred outcomes in electronic medical records. Additionally, this would require exchange of data across different imaging and electronic medical record platforms that may be facilitated by initiatives such as FHIR (Fast Healthcare Interoperability Resources).

5.2. Development of Other Non-Invasive Imaging Modalities

As well as wide-field OCT, OCTA and colour fundus photography other non-invasive imaging modalities have been suggested for the diagnosis and monitoring of PDR. For example, there has been interest in hyperspectral imaging, which is similar to conventional retinal photography, but instead of using a single white light flash, a series of images is captured using different wavelengths of light in a fraction of a second. These images are then stacked to yield an image cube with spectral (wavelength) and spatial dimensions that can be interrogated to identify features that are not discernible with conventional retinal photography. Exploratory parameters include retinal non-perfusion and retinal nerve fibre layer thinning [73]. In 2020, Vaz-Pereira et al. [39] reported high-contrast near infrared reflectance imaging with a field of view of 30° was able to observe changes in the neovascular complexes at the disc and elsewhere in 20 eyes with PDR.

5.3. Training, Education, and Equipment Maintenance

The transition from invasive to non-invasive imaging modalities to guide diagnosis and treatment of proliferative diabetic retinopathy requires both the image acquisition and image interpretation skills of healthcare professionals to be updated. This can be facilitated by updates in training curricula for both doctors and allied healthcare professionals. With modern web-based education tools, there is the opportunity for this teaching to be delivered remotely and for high-income countries to develop partnerships with low-middle income

countries. There are also opportunities to share expertise with clinicians and patients who are located remotely via telemedicine approaches.

It is also important to consider the high costs of acquiring and maintaining new imaging devices as well as networking them. This might limit the uptake of such devices particularly in low-middle income countries.

5.4. Validation in Prospective Observational Studies and Randomised Clinical Trials

The non-invasive imaging modalities are at different stages of clinical validation. It is important that they have been proven to be effective in large-scale prospective observational studies or randomised clinical trials. Large-scale observational studies offer the opportunity to explore the utility of novel non-invasive imaging modalities. A number of currently running clinical trials have included exploratory analyses with wide-field OCT, OCTA and colour fundus photography and we await the results with interest [74–76]. In a recent multi-centre, head-to-head, real-world validation study of seven automated AI DR screening systems, the algorithms showed significant performance differences; for example, one system missed 25% of cases of PDR. These results argue for rigorous testing of all such algorithms on local real-world data before clinical implementation [77].

6. Conclusions

Diagnosis and management of proliferative diabetic retinopathy are reliant upon retinal imaging. There is a trend of moving away from invasive (e.g., FFA) to non-invasive (e.g., wide-field OCT, OCTA, and colour fundus photography) imaging modalities to allow for more objective assessments that can be readily repeated in a time-efficient manner without compromising patient safety. Such quantitative assessments generating large amounts of data could benefit from AI approaches to aid clinical decision making. These non-invasive imaging modalities continue to improve both in terms of the quality of image acquisition and progress in image interpretation. It is important that newer, non-invasive imaging modalities are appropriately validated in large-scale prospective observational studies or randomised clinical trials.

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