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超广角眼底成像技术的发展及应用

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[摘 要] 视网膜疾病大多以周边视网膜病变为首要表现，后者的早期诊断、监测对于视网膜疾病的治疗及预防起着至关重要的作用。以往传统眼底成像技术仅能提供20°视网膜的可视范围，即便使用蒙太奇拍摄技术，也只能采集部分眼底范围。目前眼底成像技术已步入最新的超广角时代，其所提供的眼底视野至少可达200°，并且基于该技术的超广角眼底彩色照相、荧光素血管造影、光学相干断层扫描及其血管造影等已广泛应用于临床实践中，对于诊断及评估视网膜疾病发挥重要作用，如糖尿病性视网膜病变、视网膜静脉阻塞、早产儿视网膜病变、视网膜色素变性及视网膜脱离等。本文将从超广角成像技术的产生、发展及其国内外的临床应用现状作一综述，旨在为临床工作及研究提供指导意义。

[关键词] 临床应用；糖尿病性视网膜病变；视网膜静脉阻塞；早产儿视网膜病变；周边视网膜病变；视网膜色素变性

Development and application of ultra-wide-field fundus imaging

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Abstract Retinal diseases primarily feature with peripheral retinopathy, and its early diagnosis as well as the later following up both play a vital role in the treatment and prevention of retinal diseases. In the past, traditional fundus imaging technology can only provide the visual range of 20 degrees. Even if montage photography technology is used, it can only partially reveal the fundus field. At present, fundus imaging technology has entered the latest era of ultra-wide-field, which provides at least 200-degree fundus field of vision. Ultra-wide-field fundus photochromy, fluorescein angiography, optical coherence tomography and angiography based on this technology have been widely used in clinical practice, and play an important role in the diagnosis and evaluation of retinal diseases, such as diabetes

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retinopathy, retinal vein occlusion, retinopathy of prematurity, retinitis pigmentosa and retinal detachment. This article aims to review the occurrence and development of ultra-wide-field fundus imaging technology and its clinical applications up to now to provide a relative guideline for clinic and research.

Keywords clinical application; diabetic retinopathy; retinal vein occlusions; retinopathy of prematurity; peripheral retinopathy; retinitis pigmentosa

视网膜疾病是现代人群中普遍存在的严重眼病之一，可造成视力损害甚至致盲，临床上以视网膜血管性疾病、婴幼儿眼病、视网膜裂孔及脱离等疾病多见，主要表现为缺血、变性、渗出、出血及裂孔等，多累及周边，可从周边视网膜逐步影响中央视网膜导致中心视力受损[1-4]。由于这类视网膜疾病常累及周边视网膜，其早期临床表现并不明显，因此临床中常常容易漏诊。虽然以往传统眼底拍摄技术可实现视网膜可视化成像，但其眼底可视化范围十分受限，无法对周边视网膜进行有效窥视及记录[5]。即便大部分周边视网膜无法通过拍摄观察，但经验丰富的医师应用其他临床检查(如Goldmann三面镜、间接检眼镜等)也可对其进行观察及评估，可由于观察者之间的可变性及绘图差异，导致临床中对疾病的管理、监测和随访存在缺陷，尤其是在现代医疗法律及远程医疗时代，疾病的实时记录显得尤为重要。此外，眼底可视化范围是传统技术亟待解决的重要问题，虽然早期相关研究[6]尝试通过对7个标准30°视野进行图像拼接技术(即蒙太奇技术)扩大眼底可视化范围至75°，但该技术需要散瞳后患者的高度配合且耗时过长，同时对医技人员要求较高。超广角眼底成像技术(ultra-wide-field fundus imaging，UWFFI)作为近年来引进的新型技术，可以很好地解决以上问题，了解其产生、发展及目前的临床应用有助于指导临床操作及治疗，同时为临床研究提供基础指导意义。

1 广角与超广角定义

早期，随着蔡司公司的商用眼底照相设备产生，临床中出现了眼底照相设备视野范围的概念，此前临床认为30°为眼底照相设备的正常视野(即标准视野；图1)，超过该视野范围的视野角度则默认为广角。然而，随着UWFFI的产生，眼底视野范围的广角与超广角定义未能得到明确区分，因此在以往许多文献中两者的概念可以相互转换使用。就两者区别而言，糖尿病视网膜病变临床研究网络(Diabetic Retinopathy Clinical Research Network)曾提出超广角应至少具有100°眼底视野范围[7]。但在2019年，众多专家[8]认为可以通过漩涡静脉壶腹部对两者进行明确定义，即广角为采集后可在所有4个象限中显示后极部以外、漩涡静脉壶腹部以内视网膜特征的图像范围，而超广角则仅限于在一次正位采集中便可显示所有4个象限中漩涡静脉壶腹部前方视网膜特征的图像范围。目前，将UWFFI与蒙太奇技术相结合可生成全视网膜图像，即360°完整展示整个视网膜特征的图像[9]，可单靠一次采集获取全视网膜图像的设备仍有待进一步探究。

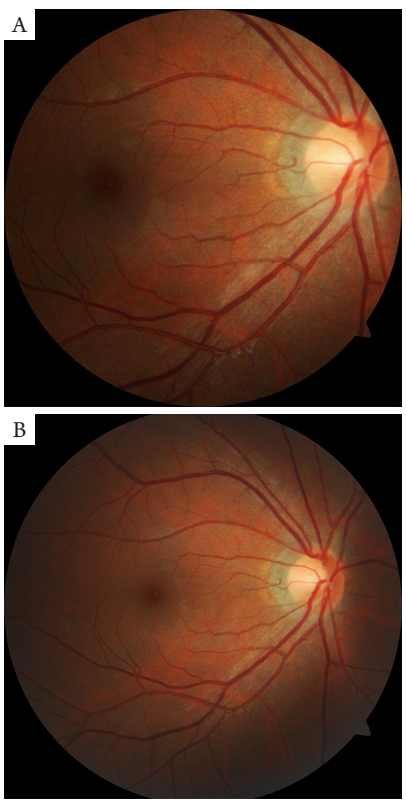

图1 正常成年人右眼眼底彩色图像

Figure 1 Fundus color images of the right eye of a normal adult

(A)右眼30°眼底图像；(B)右眼45°眼底图像。

(A) 30° fundus color image of the right eye; (B) 45° fundus color image of the right eye.

2 眼底成像技术的发展

1926年，蔡司公司生产了一台可提供20°眼底可视范围的眼底照相设备[5]，由此，眼底成像技术正式登上历史舞台，并在接下来的几十年里逐步发展。早期传统眼底照相设备由相机及光学系统组成，后者包括非球面物镜及与之齐平的35 mm单面反射透镜，在患者充分散瞳并配合操作情况下记录所有反射光线所形成的图像[10]，将所得图像利用蒙太奇技术观察眼底情况。在此基础上，Lotmar[11]配备固定灯及可旋转镜器材将眼底可视范围扩展至96°。但即便如此，早期传统眼底照相需散瞳、患者条件要求高、成像范围小、图像分辨率欠佳等局限性仍然未得到解决，因此逐渐被淘汰。

直到1971年，Pomerantzeff等[12]提出广角检眼镜的设计理论，利用与角膜接触镜相连的光纤照明及巩膜透照原理增加眼底可视范围，眼底成像技术开始步入广角眼底成像技术(wide-field fundus imaging，WFFI)时代，并且由其设计的148°广角检眼镜也于4年后首次报道[13]，该装置成像范围大幅度增加，应用不同波长的单色激光配合干扰滤波器的作用，在87%的临床试验对象中获得良好的眼底图像，但由于光源的限制，所得图像的分辨率在一定程度上呈现欠佳[14]。而为了增加图像对比度及分辨率，Pomerantzeff[15]利用消除角膜和透镜表面的光反射原理提出90°非接触式广角相机和高分辨率黄斑盘式相机，但眼底可视化范围则受到较大限制。此外，另一接触式成像系统——RetCam同样带有光纤电缆光源的角膜接触镜，利用Pomerantzeff等[12]的相似原理对周边视网膜成像，不同的是该系统的光缆电源直接连接到电子计算机，同时配备便携式成像系统，以数字化形式呈现眼底图像，其最大眼底成像范围为130°(图2)，在婴幼儿眼病诊断及筛查中具有重要作用[16-17]。然而该系统高度依赖患者正常的屈光介质，即使屈光介质存在微小混浊也将严重影响其图像质量，因此RetCam很难应用于成年人群的眼病诊断及筛查。2003年，Shields等[18]结合Pomerantzeff此前的设计理念，设计了一种可在小瞳下成像的100°非角膜接触式眼底成像设备，提供了非接触式小瞳成像的新思路，由此针对改良WFFI局限性的研究[19-21]也相继被报道。

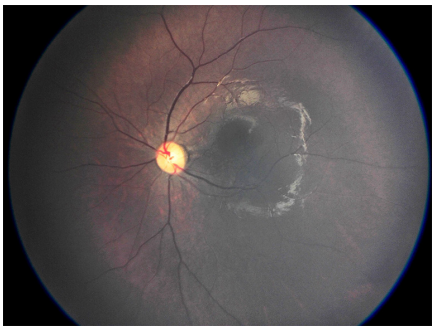

图2 正常儿童左眼RetCam眼底图像

Figure 2 Fundus image of the left eye of a normal child using RetCam

随着该项技术的不断改良，Friberg等[19]在此前报道的扫描激光检眼镜[22]基础上设计了一种通过大型椭圆镜增加眼底成像范围至200°的免散瞳非接触式扫描激光检眼镜(ultra-wide-field scanning laser ophthalmoscopy，UWF SLO)，标志着WFFI发展至UWFFI，其中以UWF SLO与超广角眼底荧光素血管造影(ultra-wide-field fundus fluorescein angiography，UWFFA)为主要代表，目前前者应用更为广泛，其配备有双焦点凹面椭圆镜与共焦扫描激光检眼镜，利用椭圆镜点对点反射激光原理并通过眼内中心视角测量方式实现小瞳下采集水平200°、垂直170°的超大眼底视野范围[10,23]，采集单张正位(后极部)眼底图像即可清晰成像至锯齿缘(图3A)，配合其鼻颞侧眼位引导甚至可以达到水平220°~240°的眼底范围[24]。此外，UWF SLO利用红绿双色激光成像原理实现视网膜的彩色图像，克服以往采集图像颜色单一的不足，而不同颜色的激光波长不同，其所观察到眼底结构也各有差异，绿色激光(532 nm)图像主要显示前视网膜结构及其血管，而红色激光(633 nm)图像则突出显示脉络膜结构及其血管(图3B，3C)；同时，该设备还配备有蓝色激光(488 nm)，可用于UWFFA[10]。即便如此，早期UWF SLO图像周边存在显著的非线性扭曲，这与三维球立体面转换为二维平面图像的数字化投影无法得到完全精准实现密切相关[25]。由于椭球镜非对称光学特性[23]与眼睑、睫毛伪影[26]等因素影响，导致上、下方成像及对比度更为受限；并且其严重的红绿伪色仍是该设备目前有待解决的主要问题之一[27-28]。而作为另一主流UWFFI的UWFFA在成像方面则优

于UWF SLO，虽然其采集视网膜范围仅有102°(图4)，但它可提供更好的上、下方视网膜可视区、更少的眼睑睫毛伪影和更均匀的对比度[29-30]，因为目前UWFFA就上述问题配备了相应程序，可使图像失真被自动校正并增强上、下方可视化对比度，同时利用其相关程序将平面图像转换成立体投影图像，以此测量更为精确的眼底长度及面积[9,31]。

针对这一新型技术在临床应用中的规范性，国内就其特性制定了详细的操作指南[32]，但对于目前每日门诊病患数量庞大的国内医疗机构而言，完整进行指南中五方位图像的采集要求或许具有一定的难度，因为能否采集到可用于临床诊疗的清晰图像取决于患者的配合程度，然而在实际临床中大部分眼科患者由于其病情严重并不能配合操作，导致大幅度增加了临床中的时间及医疗成本，这并不符合我国的医疗现状，并且有悖于该技术高效、快速筛查病变的设计理念。因此近期有关研究[33-34]显示：散瞳后配合眼位引导采集后极部及上、下方图像即可完成患者的眼底初筛，在很大程度降低了诊疗过程中的成本消耗，同时并不影响后续需要散瞳后完善的检查，虽然这与UWF SLO免散瞳这一优势不相符，但目前对眼底筛查的临床标准仍是散瞳后的Goldmann三面镜与间接眼底镜检查，UWF SLO仅作为后者的辅助检查，因此这些研究对于制定符合我国医疗现状的UWF SLO操作规范具有一定的参考及指导意义。

3 UWFFI的国内外应用研究

目前，各种UWFFI更多的应用于绝大部分眼后段疾病的诊断及治疗中，其临床作用与潜在的临床价值得到国内外研究人员和临床工作者的广泛认可。

其中，UWF SLO检测视网膜病变的良好特异性及敏感性早已得到证实[35-36]，尤其对眼底赤道后部具有高度特异性及中度敏感性[36-37]，可在人类免疫缺陷病毒(human immunodeficiency virus，HIV)感染者或获得性免疫缺陷综合征(acquired immune deficiency syndrome，AIDS)患者中筛查巨细胞病毒性视网膜炎或其他后极部病变与前置镜检查保持较好的一致性[38]。同时，与Goldmann三面镜保持高度一致性[39-40]，对于不同近视度数的视网膜病变和不同类型视网膜病变的检出率也几乎完全一致[41]。

3.1 血管性疾病

糖尿病性视网膜病变(diabetic retinopathy，DR)与视网膜静脉阻塞(retinal vein occlusions，RVO)是两大最为常见的视网膜血管疾病，可引起周边视网膜缺血形成大小不一的毛细血管无灌注区(capillary nonperfusion，CNP)[42]，可促进黄斑水肿及新生血管的形成，对患者视觉功能造成严重影响[43-44]。因此，对于评估DR及RVO患者病情进展及临床治疗效果而言，测量周边视网膜CNP显得尤为重要。

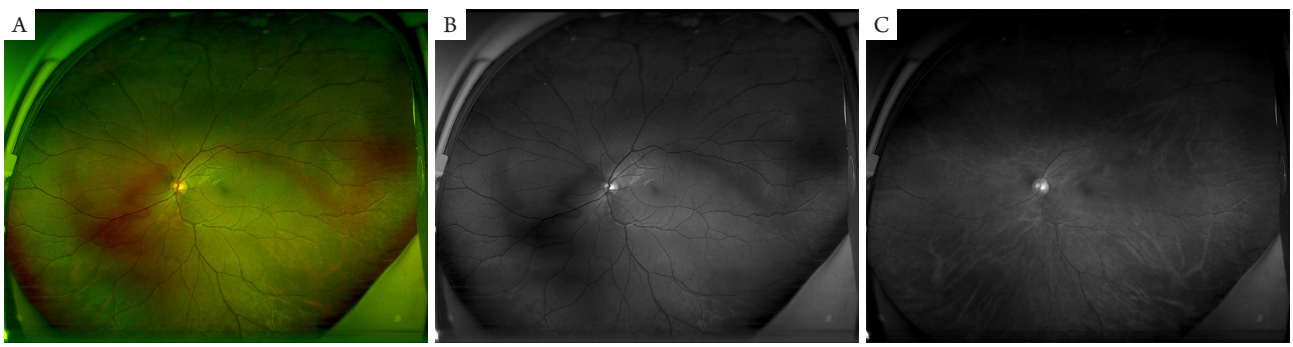

图3 正常成年人左眼UWF SLO

Figure 3 Fundus color images of the left eye of a normal adult using UWF SLO

(A)200°超广角彩色眼底图像；(B)绿色激光超广角图像；(C)红色激光超广角眼底图像。

(A) 200° UWF SLO fundus color image; (B) UWF SLO fundus image using the green laser; (C) UWF SLO fundus image using the red laser.

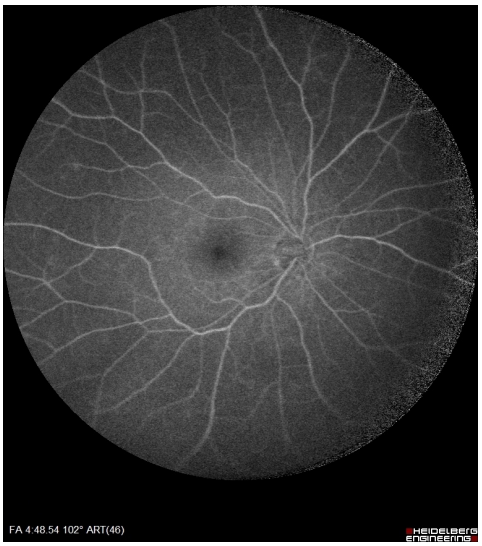

图4 正常成年人右眼UWFFA

Figure 4 Fundus image of the right eye of a normal adult using UWFFA

早期，对于DR评估、分类的公认标准是早期DR研究所采用的7个标准30°视野眼底立体图像[6]，但其仅覆盖全视网膜的30%左右[45-46]，而单张小瞳下的UWF SLO图像便能呈现约80%视网膜范围[47]，整体可视范围提高了近3倍，甚至UWFFA所能呈现的眼底范围是其3.2倍，所观察到的非灌注区、新生血管形成以及全视网膜光凝术范围可分别增加3.9倍、1.9倍及3.8倍[48]，对DR及视网膜周围病变的评估有很大帮助，有助于明确DR的分期，指导激光治疗。同时随着眼底可视范围的增加，即便是在正常人群中也可观察到其外周部血管不同的异常荧光表现[49]，尤其是65岁以上的老年群体，其视网膜血管总面积及血管密度均明显减小[50]。因此，超广角眼底血管成像技术成为当前主流，为DR的诊疗及评估陆续提供新思路，如虹膜血管造影联合UWFFA方案[51]、超广角扫描源光学相干断层扫描血管造影成像方法[52]等。同时，Fan等[53]认为采用UWFFA量化的视网膜血管床面积是评估DR严重程度的重要指标。

近年来，基于UWFFA的发展应用，临床中对于RVO的评估也更为便捷，因为相对于蒙太奇眼底荧光素血管造影而言，UWFFA单张图像的可视范围便足以评估周边视网膜CNP[43]，实现将以往抽象的CNP运用客观的物理单位(即mm^2)进行计算及表示[42-43]，可有效显示RVO患者或继发于RVO的难治性黄斑水肿患者手术前、后周边视网膜CNP的范围及变化[54-55]，便于评估治疗期间眼内药物变化及疗效。不仅如此，超广角光学相干断层扫描血管造影所显示的视网膜分支静脉阻塞患者周边视网膜血管无灌注状态与UWFFA结果无明显差异[56]，有助于对RVO患者的病情进行动态观察。

3.2 婴幼儿眼病

以早产儿视网膜病变(retinopathy of prematurity，ROP)为主的婴幼儿眼病可破坏婴幼儿未成熟的视网膜血管生长，以周边血管为主，导致患儿早期视力障碍或失明，因此对婴幼儿进行视网膜病变筛查是必不可少的。临床中，ROP筛查所采取的方式(如RetCam、间接检眼镜检查)均需进行散瞳及角膜压迫，甚至有时会进行麻醉以确保检查顺利完成，这些操作往往可能导致受检婴幼儿血氧饱和度下降，严重时可引起呼吸窘迫和心率异常[57]。而WFFI则无需考虑以上情况，甚至可以在操作时监测婴幼儿的视网膜血氧饱和度[58]，对于识别需要治疗的ROP具有100%的敏感性和97.9%的特异性，其中敏感性随其病变严重程度逐渐提高[59]。

近年来，ROP的相关研究逐渐向周边视网膜可视化范围更广的UWFFI发展，甚至倾向于便携式发展。2014年，Fung等[60]首次报道UWFFA应用于ROP，后续相关研究[61-62]验证后认为其对ROP的筛查、诊断及随访具有重要意义，可显示不同分期的ROP及其血管异常表现。随后，一种手持便携式的超广角光学相干断层扫描及光学相干断层扫描血管造影设备[63]也相继被报道，在临床筛查中具有良好的临床前景，若其临床应用价值得到进一步证实，将大幅度改善临床诊疗流程及效果，尤其是对于配合程度低的婴幼儿早期ROP筛查，单次图像采集获得高分辨率全景视网膜视图显得尤为重要。

此外，UWFFA对于评估影响周边视网膜的其他婴幼儿眼病也具有一定的临床意义，如家族性渗出性玻璃体视网膜病变(familial exudative vitreoretinopathy，FEVR)、Coats病以及色素失调综合征[64-67]。与标准眼底荧光素血管造影相比，UWFFA不仅在FEVR患者的无症状家庭成员中诊断FEVR非常有效，敏感性和特异性分别可达93.0%和97.5%[65]，同时也可检测Coats病患者对侧无症状眼

细微的血管变化[66]，证实Coats病是一种双侧非对称性疾病，甚至在疑难性儿童遗传性视网膜疾病的诊断中也具有高达94.9%的敏感性[68]。

3.3 视网膜变性、视网膜裂孔及视网膜脱离

临床中，以格子样变性为主的视网膜变性是视网膜裂孔及孔源性视网膜脱离(retinal detachment，RD)的高危因素[69]，与眼的近视度数[70]及眼轴长度[71]相关，多位于外周视网膜，既往常规检查多容易漏诊。对此，UWFFI的使用可以有效减少漏诊率，尤其是UWF SLO有助于这类视网膜疾病患者的临床管理及记录保存。但即便如此，Mackenzie等[37]仍认为UWF SLO对于视网膜病变的敏感性偏低，尤其是赤道前部病变，容易遗漏上、下方的裂孔或RD[72]。这与汤云霞等[41]的研究结果完全相反，后者认为UWF SLO几乎可以筛查出Goldmann三面镜所能观察到的视网膜裂孔及RD，同时有研究[33-34]发现仅需散瞳后使用UWF SLO配合眼位引导采集后极部与上下方图像即可筛查绝大部分视网膜变性区域。类似研究产生以上两种不同结果或许与RD后视网膜的隆起程度有关。临床中，RD后的视网膜将受液化玻璃体影响呈现不同程度的隆起，如果视网膜隆起较高、范围较大，同时若伴随视网膜褶皱，掩盖本该存在的视网膜裂孔，那么这将对眼底窥视检查产生遮挡，从而无法对眼底进行诊断，导致敏感性降低；相反，如果视网膜仅发生轻微隆起或者未发生隆起，那么眼底窥视检查将不受影响，即UWF SLO几乎可以筛查出所有临床可见的视网膜裂孔或轻、中度的RD。另外，医技人员的培养同样不可忽视，经验丰富的医技人员仅通过散瞳后采集的后极部与上下方图像便可进行全视网膜变性的初步筛查[33-34]；相反，经验不足的医技人员将只会增加医疗成本，无法为疾病治疗提供有效的临床证据。

视网膜色素变性(retinitis pigmentosa，RP)是一种遗传性视网膜退行性疾病，可由夜盲发展至失明状态，眼底主要呈现不同程度的视乳头异常、视网膜血管狭窄和骨细胞样色素沉着，各阶段患者的UWFFA表现不同，但最常见的表现为点状或网状自发荧光减弱[73]，并存在一定的固定模式，即黄斑处呈均匀弥漫的旁中心凹环状高荧光，并伴有黄斑回避现象，表现为牛眼样黄斑病变[74]，Chen等[74]认为这可能是视网膜营养不良和RP基因型相关联的成像生物标志。而对于其他RP相关性疾病或视网膜营养不良的诊断及评价，UWFFI也是一个不容或缺的重要工具，如色素性静脉旁视网膜脉络膜萎缩[75]、Cockayne综合症[76]等。

3.4 其他

UWFFI不仅可以更为高效地记录各种葡萄膜炎的反应、进展以及病变的严重程度[77]，如结节病性葡萄膜炎[78]、伏格特-小柳-原田综合征[79]等，同时在发现及诊断其他全身性或免疫性疾病引起的眼部改变中也起着重要作用，如镰状细胞性视网膜病变[80]、Berger's IgA肾病[81]、大动脉炎相关性视网膜病变[82]、Susac综合征[83]及Birdshot视网膜脉络膜炎[84]等。Fujimoto等[85]认为异常的UWFFA改变是Stickler综合征眼部病变的特征性表现。另外，近期研究[86]发现使用UWFFA测量视锥-视感细胞营养不良患者的自发荧光可反映其视野的退化程度，有助于评估其病情进展变化。

4 结语

在目前的临床和研究中，UWFFI的临床价值及潜在优势得到广泛认可，并应用于当前各类临床科室的管理工作及研究中，尤其是在眼底病科及屈光科。近年来，随着现代自动化水平发展，疾病的自动化检测、分级及管理未来将逐步得以实现，同时这项技术的临床应用已朝着便携式医疗服务发展，尤其是当前新冠肺炎流行期间，常规远程医疗服务已基本实现并处于初级阶段，未来很大可能步入将现代医疗体系与人工智能完美结合的医疗诊治时代。此外，UWFFI在确定与预后相关的特异性方面具有一定帮助，在全视网膜激光、预测视网膜激光需求等临床治疗策略中也有一定的应用前景。然而，该技术并不能代替Goldmann三面镜或间接检眼镜成为眼科医疗中的临床标准，其在眼科中的地位需进一步研究确定，或许在特定条件下，该技术将有可能替代成为某种疾病的主要诊疗标准。目前，更快采集更广的高清眼底视野图像仍是理想首选，但由此所带来的高昂成本及维护可能阻碍该技术的广泛应用。

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开放获取声明

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