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Feasibility Study of a Multimodal, Cloud-Based, Diabetic Retinal Screening Program in a Workplace Environment

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Methods: A cross-sectional feasibility study was conducted at the Genentech, Inc., Campus Health Center. Eyes of participants were imaged using ultra-widefield (UWF) color fundus photography (CFP) and spectral-domain optical coherence tomography (SD-OCT). A cloud-based platform was used for the automated, seamless transfer of images to a remote reading center for evaluation for DR and other retinal pathologies. Electronic surveys collected participants'self-reported medical histories, healthcare utilization, and visual function data.

Results: Among 100 participants (mean age, 43.9 years; 44% male), 33% of them self-reported diabetes. Eye examinations within the past 12 months were reported by 71% of all participants (n = 71/100) and by 85% (n = 28/33) of those with self-reported diabetes. Among participants with complete screening images from both UWF-CFP and SD-OCT, 20% (n = 6/30) of those with self-reported diabetes and 8.5% (n = 5/59) of participants with no history of diabetes were unaware they had mild/moderate nonproliferative DR. Among all participants, 20% (20/100) had a retinal finding, on either UWF-CFP or SD-OCT, or both, which prompted a referral for further evaluation.

Conclusions: A retinal screening program deployed via a secure, scalable, and interoperable cloud-based platform was feasible and conveniently integrated into the workplace.

Translational Relevance: Cloud-based platforms could be used to promote a secure, scalable, and interoperable system for retinal screening in nontraditional environments.

Introduction

Global diabetes prevalence is growing and is projected to affect 592 million individuals by 2035.¹ Diabetic retinopathy (DR), including proliferative DR and diabetic macular edema (DME), is the leading cause of vision loss among working-aged adults in developed countries.^{2,3} Sight-threatening DR is expected to increase to more than 56 million by 2030.⁴ Despite the advent of anti-vascular endothelial growth factor treatment for DR and neovascular age-related macular degeneration (AMD), many patients with these retinal disorders remain undiagnosed and are thus deprived of early treatment and are at risk of irreversible vision loss. In the United States, only ~50% of patients diagnosed with diabetes are screened annually for DR.⁵⁻⁷ Logistical barriers preventing patient access to diabetic eye screening in the United States include lack of time or access to

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eye care providers, the need for travel (particularly in rural communities), and financial constraints.^{8,9} Such barriers reinforce the need for screening programs that are accessible, convenient, effective, and economically viable.

Integration of new screening initiatives into nontraditional environments is one approach that could be taken to improve disease detection and access to care. Indeed, teleophthalmology programs for diabetes have been shown to be effective in improving diagnosis rates for DR and other sight-threatening conditions when used in settings such as community-based clinics, mobile units, and pharmacies.^{10–12} Use of automated retinal image analysis software and other digital innovations is expanding and may help to optimize identification of patients with eye disorders, including DR.^{13,14}

Workplace screening programs have the potential to identify health risks, such as cardiovascular disease, in otherwise hard-to-reach individuals.^{15,16} There remains, however, a lack of data about whether integration of DR screening programs in nontraditional environments, such as the workplace, is feasible or beneficial from a public health perspective.

To address the need for more effective widespread screening for diabetic eye disease in nontraditional settings, we leveraged the existing internal employee health care infrastructure of a large corporation to evaluate the feasibility of workplace screening for DR in adults, regardless of known diabetes status. The objective of this study was to evaluate the feasibility of capturing and interpreting retinal images using a multimodal, cloud-based, diabetic retinal screening program combined with electronic self-reported questionnaires for collection of demographic, medical history, health care utilization, and visual function data. The study also aimed to establish the burden of DR and other retinal conditions in this setting and assess self-reported health care utilization and visual function among study participants.

Methods

Study Design and Participants

A cross-sectional feasibility study was conducted between May 2019 and June 2019. The study protocol was approved by the Western Institutional Review Board and conducted according to the tenets of the Declaration of Helsinki. Full-time Genentech, Inc., employees who were ≥ 18 years of age, who provided written informed consent, and who were able and willing to comply with the study protocol participated. Participants were recruited using convenience sampling and were seen at the Genentech, Inc., Campus Health Center (CHC) in South San Francisco, CA. Potential participants were identified by clinic staff at the CHC as having diabetes and/or having an interest in being screened for underlying DR or other retinal conditions. Individuals were excluded from the study if they were unable to comply with the study protocol, were blind, had a concurrent eye infection, had an eye patch on both eyes, or were pregnant at the time of the study. Once enrolled, participants were assigned a unique participant identification code to ensure the privacy and security of their data. All data collected were deidentified via the unique participant code.

Capture, Transfer, and Evaluation of Retinal Images

Samples for Science program technicians at the Genentech, Inc., CHC who had no prior experience in ophthalmic image acquisition or transfer provided clinical support. They were first trained by Carl Zeiss Meditech, Inc. (Dublin, CA) and Heidelberg Engineering, Inc. (Franklin, MA) personnel and certified by the Fundus Photograph Reading Center (FPRC) at the University of Wisconsin to utilize retinal ultrawidefield color fundus photography (UWF-CFP) with a single-shot Zeiss Clarus fundus imaging system to capture 200° images of the retina and Heidelberg Spectralis spectral-domain optical coherence tomography (SD-OCT; 20° × 20°, 97 B-scans, 9-14 automatic real-time modes).⁷ These processes were then integrated into the technician's workflow. Retinal images from both eyes were captured using these methods without pharmacological pupillary dilation. The initial part of pilot study was conducted with SD-OCTs from only 10 participants, and UWF-CFPs were added thereafter.

Captured images were automatically uploaded to the Roche Apollo Global Imaging Platform, which was created and deployed at the CHC (Fig. 1; Supplementary Fig. S1). The platform was built on the Amazon Web Services cloud on the Roche Science Infrastructure Roche Science Cloud owned by F. Hoffmann La-Roche (Basel, Switzerland). Access to the platform and data was restricted and based on roles. The data pipeline and other platform components were monitored by a dedicated security team. The platform utilized a number of Amazon Web Services to establish security controls and data safeguards, which were mapped to National Institute of Standards and Technology (NIST) Cybersecurity Framework domains. Each service



Figure 1. Study process and cloud-based platform overview.

provided various security capabilities to identify, protect, detect, respond, and recover, as described in the NIST Cybersecurity Framework.

Data were reviewed prior to access to identify and address any legal, regulatory, or other risks. All data on the Roche Apollo Global Imaging Platform were encrypted at rest and in transit and followed a semi-automated onboarding process, which moved through segregated zones to scan the data for malware; identified any personally identifiable information or protected health information and removed, anonymized, or tokenized those data; verified the data values and formats; and readied the data for analysis. This DICOM standard platform facilitated a seamless process for de-identifying and transferring images directly from the imaging devices to the FPRC at the University of Wisconsin for assessment, using the Ophthalmic Photography 8 Bit Image IOD for UWF-CFPs and Ophthalmic Tomography Image Storage for the SD-OCT images.

All images were evaluated in their respective proprietary software. The FPRC graders assessed the UWF-CFPs for image quality and retinal pathologies. A seven-field masked grid was overlaid on the UWF-CFP images to evaluate the Early Treatment Diabetic Retinopathy Study DR severity score for each eye.¹⁷ This was re-categorized into the International Clinical Diabetic Retinopathy Severity Scale as no apparent retinopathy; mild, moderate, or severe nonproliferative DR (NPDR); or proliferative DR (PDR).¹⁸ FPRC analyzed the SD-OCTs for the presence of subretinal fluid (SRF) or intraretinal fluid (IRF) and

vitreoretinal interface abnormalities. Macular edema was defined as the presence of SRF or IRF on SD-OCT. FPRC also noted any incidental findings from the UWF-CFPs and SD-OCTs. Results were then fed back to the CHC from the FPRC via the same secure cloud-based platform. If a patient had a significant retinal finding per National Health and Examination Survey referral¹⁹ or FPRC guidelines, the health care staff from the CHC contacted the participant and helped connect them with a local eye care specialist. In particular, individuals were referred if they had severe NPDR, PDR, macular edema, suspicious cup-to-disc ratio, epiretinal membranes with macular traction, choroidal neovascularization, macular holes, or any other retinal signs that the reading center noted as important for further evaluation. Additionally, individuals with no history of diabetes who showed evidence of any retinopathy were contacted by the CHC staff and referred to a local eye care specialist for further evaluation.

The effectiveness of the image transfer was evaluated by the percentage of gradable images with linked data out of the total number of images successfully collected. The efficiency of the cloud-based infrastructure was evaluated by the time when the retinal image was taken and sent to the FPRC.

Evaluation of Visual Function

Self-reported functional difficulties secondary to vision problems were assessed over multiple categories as an additional assessment of feasibility, including

reading; doing close-up work; finding objects on a crowded shelf; walking down steps, stairs, or curbs; noticing objects to the side during ambulation; and driving. For each category, participants described difficulty on a Likert scale: (1) no difficulty, (2) little difficulty, (3) moderate difficulty, (4) extreme difficulty, or (5) unable to do because of eyesight. Participants were categorized as having difficulty with a specific task if they reported moderate or extreme difficulty or being unable to do the activity because of their vision.

Evaluation of Self-Reported Eye Condition and Health Care Utilization

Participants completed electronic surveys to collect demographic, medical history, health care utilization, and visual function data. Individuals were categorized as having underlying diabetes if they responded "yes" when asked if they had been diagnosed with diabetes or who had "borderline or pre-diabetes." Selfreported eye conditions and utilization of ophthalmic care were assessed with methodologies included in the Centers for Disease Control and Prevention Vision and Eye Health Surveillance System-National Health Interview Survey and the National Health and Examination Survey Diabetes Questionnaire.^{20,21} In particular, participants were asked whether they had undergone an eye examination with dilation within the past year, the examination date, and whether they had seen a diabetic specialist within the past year.

Study Outcomes

The primary outcome of this study was the feasibility of capturing and interpreting retinal images using a multimodal, cloud-based, diabetic retinal screening program combined with electronic self-reported questionnaires for collection of demographic, medical history, health care utilization, and visual function data in a workplace environment. The secondary outcome was a description of the burden of DR and other retinal conditions in this setting, and the tertiary outcome was an assessment of self-reported health care utilization and self-reported visual function among the study participants. Each outcome was then linked to the others in the cloud-based platform. Together, the outcomes aimed to provide holistic insight into the burden of DR and other retinal conditions in the workplace environment.

Sample Size and Statistical Analysis

The aim was to recruit a sample of 100 participants. This convenience sample size was chosen because it was considered to be sufficient to achieve the primary outcome of system feasibility testing and provide an initial perspective on the burden of retinal conditions at Genentech, Inc. Descriptive analyses were carried out to describe the prevalence of retinal pathology, visual function burden, and health care utilization patterns among the study population.

Results

Participant Demographics and Image Quality

One hundred employees participated in the study (Fig. 2). Participants had a mean age of 43.9 years; 44% (n = 44/100) were males, and 42% (n = 42/100) were of white ethnicity (Table 1). At study enrollment, one-third (33%; n = 33/100) of participants self-reported having diabetes. The quality of the captured images showed that 100% of SD-OCTs (n = 198/198) and 100% of UWF-CFPs (n = 178/178) were gradable for image interpretation (Fig. 2). A total of 89 participants completed screening images from both UWF-CFP and SD-OCT.

Experience With the Cloud-Based Transfer System

The software application that connected the CHC onsite devices to the cloud storage used point-topoint connections to securely transfer scanned images outputted from DICOMs to the cloud using powering workflows. The FPRC's proprietary software was also connected with another onsite software application in the reading center premises. This application delivered the scans from the cloud to FPRC using the same pointto-point connection technology. From an efficiency perspective, the cloud transfer system ensured secure, efficient, and real-time transfer of images to the reading center as soon as the scan was produced in the CHC devices.

Burden of Diabetic Eye Disease

The majority of participants (71%; n = 71/100) reported that they had undergone an eye examination within 12 months before the study. At study start, only 2% (n = 2/100) of participants self-reported as having diabetic eye disease, and none reported macular



Figure 2. Participant disposition and data availability. ^aOne participant was excluded from the analysis due to missing patient-reported outcome data. ^bImages were evaluated for diabetic retinopathy and other retinal pathologies by the Fundus Photograph Reading Center. All employees were given a copy of their ocular images and received a notification of their results after the images were graded. ^cThe initial part of pilot study was only conducted with SD-OCTs from 10 participants, and UWF-CFPs were added thereafter. PRO, patient-reported outcome.

Table 1. Participant Baseline Characteristics

Characteristic	Study Participants ($N = 100$)
Age (y), mean (\pm SD)	43.9 (9.61)
Sex, % male (n)	44 (44)
Race, % white (n)	42 (42)
Self-reported diabetes, a % (n)	33 (33)
Self-reported diabetic eye disease, % (n)	2 (2)
Self-reported macular degeneration, $\%$ (<i>n</i>)	0 (0)
Self-reported eye exam within past 12 mo, $\%$ (<i>n</i>)	71 (71)
Completion of UWF-CFPs, % (n)	89 (89)
Completion of SD-OCTs, % $(n)^{b}$	100 (100)
Completion of UWF-CFPs and SD-OCTs, % (n)	89 (89)
Patient-reported outcome survey, % (n)	99 (99)
Complete UWF-CFP, SD-OCT, and patient-reported outcome survey data, % (n)	89 (89)

^aSelf-reported diabetes included participants who responded "yes" when asked if they had been diagnosed with diabetes or who had "borderline or pre-diabetes."

^bThe initial part of the pilot study was only conducted with SD-OCTs from 10 participants, and UWF-CFPs were added thereafter.

degeneration (Table 1). The prevalence of NPDR was 20% among evaluable participants with self-reported diabetes (n = 6/30), compared with 8.5% (5/59) of those who did not self-report diabetes. No participants had severe NPDR or PDR (Table 2). Macular edema (defined as the presence of SRF or IRF) was identified in 3.4% of patients with complete images (n = 3/89).

Incidental Ocular Findings and Referrals for Further Care

Dry AMD, defined by the presence of drusen with or without associated pigment changes or geographic atrophy, was identified in 4.5% (n = 4/89) of participants with complete images but in considerably more participants with self-reported diabetes (Table 2).

Table 2.	Prevalence of Diabetic Retinopathy an	d Othei	r Incidental	Retinal	Abnormalities	Identified	From	Retinal
Imaging i	n Participants With UWF-CFP and SD-O	CT Data						

Retinal Abnormalities	Self-Reported Diabetes ($n = 30$)	No Self-Reported Diabetes ($n = 59$)	Total ($n = 89^a$)
Mild/moderate NPDR	20 (6)	8.5 (5)	12.4 (11)
Severe NPDR or PDR	0 (0)	0 (0)	0 (0)
Macular edema (presence of SRF or IRF)	10 (3)	0 (0)	3.4 (3)
Dry AMD	10 (3)	1.7 (1)	4.5 (4)
Enlarged cup-to-disc ratio (>0.7)	3.3 (1)	0 (0)	1.1 (1)
Epiretinal membrane	16.7 (5)	3.4 (2)	7.9 (7)
Other ^b	6.7 (2)	20.3 (12)	15.7 (14)

^aOne participant was excluded from the analysis due to missing data. Ten participants had SD-OCT data only, and none of these individuals had pathologies based on SD-OCT findings.

^bIncludes chorioretinal scars (n = 5), asteroid hyalosis (n = 1), photoreceptor disruption (n = 2), circular area of retina disturbance next to macular (n = 1), pigmentary abnormality (n = 1), and nevus (n = 1) and peripapillary atrophy (n = 3).

 Table 3.
 Participants' Self-Reported Visual Function Questionnaire Results

	% (n)				
Any Difficulty With	Self-Reported Diabetes ($n = 33$)	No Self-Reported Diabetes ($n = 66$)	Total ($n = 99^{a}$)		
Reading	33.3 (11)	25.8 (17)	28 (28)		
Close-up work	33.3 (11)	27.3 (18)	29 (29)		
Steps, stairs, or curbs ^b	18.2 (6)	6.1 (4)	10 (10)		
Peripheral vision	9.1 (3)	0 (0)	3 (3)		
Finding objects on shelf	12.1 (4)	16.7 (11)	15 (15)		
Driving	0 (0)	3 (2)	2 (2)		

^aOne participant was excluded from the analysis due to missing data.

^bIn dim light or at night.

Other retinal abnormalities, including chorioretinal scars, non-central epiretinal membrane, and peripapillary atrophy, were identified in 15.7% (n = 14/89) of participants. One participant with self-reported diabetes had an enlarged cup-to-disc ratio of >0.7 (indicative of glaucoma), requiring urgent referral to an ophthalmologist (Table 2).

Twenty percent (n = 20/100) of participants had an ocular finding that met criteria for further ocular evaluation. Specifically, three patients with macular edema showed evidence of retinal fluid, four patients had high-risk drusen, one patient had a cup-to-disc ratio of >0.7, one patient had epiretinal membranes with macular traction, one patient had a chorioretinal scar, and one patient had anomalous OCT findings possibly related to AMD changes. Additionally, nine patients with no prior history of diabetes or hypertension had signs of early or moderate NPDR and were prompted to obtain further medical evaluation.

Visual Function Outcomes

Overall, the proportion of participants reporting some deficit in visual function was similar between participants with or without self-reported diabetes; however, higher percentages of those with diabetes reported difficulties with peripheral vision (9.1% [n = 3/33] vs. 0% [n = 0/66], respectively), and with going down steps, stairs, or curbs in dim light or at night (18.2% [n = 6/33] vs. 6.1% [n = 4/66], respectively) (Table 3).

Health Care Utilization Outcomes

Among all study participants, 37% (n = 37/100), 71% (n = 71/100), and 49% (n = 49/100) reported that within the past year they had seen a diabetic specialist, had an eye examination, or had their pupils dilated for examination, respectively. In those participants with self-reported diabetes, 85% (n = 28/33) had

undergone an eye examination during the past year. Among individuals with mild or moderate NPDR, 54.5% (n = 6/11), 81.8% (n = 9/11), and 63.6% (n = 7/11) reported that within the past year they had seen a diabetic specialist, had an eye examination, or had their pupils dilated for examination, respectively. Among participants who did not have any retinopathy diagnosed by imaging, 34.8% (n = 31/89), 70.8% (n = 63/89), and 66.3% (n = 59/89) reported that within the past year they had seen a diabetic specialist, had an eye examination, or had their pupils dilated for examination, for had their pupils dilated for examination, for had their pupils dilated for examination, had an eye examination, or had their pupils dilated for examination, respectively.

Discussion

To assess the feasibility of deployment in a nontraditional setting and understand the burden of undiagnosed DR in a workplace environment, we introduced a retinal screening program at the CHC where images were captured and interpreted utilizing a professional ophthalmic reading center (FPRC). We showed that a cloud-based diabetic retinal screening program is feasible and that all aspects of the program, from installation of imaging equipment to training of non-specialist health care personnel, seamless image transfer, and specialist referrals, can be conveniently integrated into a workplace environment. Twenty percent of participants had a retinal finding from UWF-CFP and/or SD-OCT that prompted a referral for further evaluation; this underlies the potential public health benefit of a retinal screening program in a large workplace environment.

Ample evidence supports the effectiveness of teleophthalmology based on high-quality imaging for diabetic eye disease detection.^{22–25} Use of teleophthalmology enables screening for retinal eve disease to be conducted in nontraditional settings; however, electronic transfer of images to a reading center means that evaluation is still undertaken by clinicians with specialist expertise. In addition, UWF-CFP and SD-OCT imaging combined with reading center evaluation can reduce costs and enhance efficiency by enabling ophthalmologists to focus on more complex examinations and treatment.³ Over time, additional automation and application of artificial intelligence (AI)-based tools and algorithms may enable instantaneous onsite detection of referable disease and immediate automated specialist referral for monitoring and/or treatment. 5,26,27 AI therefore has the potential to enhance the clinical effectiveness and efficiency of and capacity for DR screening,^{27,28} as shown by its successful implementation within ophthalmology

programs in the United Kingdom.^{28,29} Autonomous deep learning diagnostic systems for DR screening are currently in development and, to date, two have performed acceptably in comparison with expert readers and have been authorized by the US Food and Drug Administration.^{30–32}

Employees were invited to participate in this teleophthalmology-based DR screening program regardless of a diabetes diagnosis. Typically, however, DR screening is only recommended for patients already diagnosed with diabetes,³ although screening of the general population has been shown to be effective for identifying asymptomatic retinal abnormabilites.³³ In our study, only 2% of all participants self-reported having diabetic eve disease and none self-reported having AMD. However, NPDR was subsequently identified in 12.4% of all study participants with complete images (20% of participants with selfreported diabetes and 8.5% of those with no history of diabetes). Additionally, 3.4% and 4.5% of participants were identified as having macular edema and dry AMD, respectively, highlighting the potential benefit of including patients without a diabetes diagnosis in screening programs.

In a pooled analysis of studies from around the world, Yau et al.² reported a prevalence rate of 35% for any DR and 7% for DME in patients with diabetes. In patients with self-reported diabetes in our study, the prevalence of DR was lower at 20%, but DME was almost twofold greater at 13%; the latter is likely a result of inclusion of SD-OCT and UWF-CFP in our study, whereas Yau et al.² analyzed studies where CFP, not SD-OCT, was used. The pivotal trial of IDx autonomous AI-based care, which utilized a gold-standard comparator of a CFP system for detection of DR in primary and OCT images, identified DR in 24% of patients with diabetes, a similar proportion to our study, but identified DME in only 5% of patients.³¹

We have not conducted a cost-benefit evaluation of the program in our study. From a health economic viewpoint, expansion of DR screening programs may lead to increased referrals and resource use, especially in the short term. During the first 5 years of the Scottish National Diabetic Retinopathy Screening Programme, more than 180,000 individuals underwent at least one successful retinal screening, and, although rates of referable eye disease were as high as 7% in the first 2 years, they subsequently stabilized at approximately 4%, with suspected DME being the most frequent reason for referral.³⁴ A separate retrospective analysis of teleophthalmology screening of patients with diabetes in a community-based Veterans Affairs medical center evaluated resource use in patients who were referred following DR

screening. The mean cost incurred per patient over a 2-year period (2008–2009) was \$1000. The authors commented that community ophthalmologists should prepare for an increased workload following implementation; however, they noted reductions in vision loss and substantial long-term cost savings.¹⁰ A UK study found that incorporating a cloud-based referral system with both face-to-face and virtual clinics reduced the need for hospital eye specialist referrals by more than half and facilitated rapid access to care. This approach may therefore alleviate the impact of large-scale screening programs on available health care resources.²⁹

Previously, factors such as computing and telecommunications costs have been barriers to the implementation of teleophthalmology programs; however, they no longer present such a substantial challenge to clinicians.⁶ Screening costs may also be reduced in the future with cloud-based image transfer systems like the one described in our study, as well as the increased deployment of AI-based image analysis and diagnostics.

This study had limitations that could affect study interpretation and generalizability. First, conducting the study among employees at a single site, a pharmaceutical corporation in the United States, may restrict the applicability of findings to other settings. This was a feasibility study and was therefore restricted to a sample of 100 employees. Furthermore, participants were not randomly selected to undergo screening, and willingness to participate could have been a source of sample bias. Additionally, the data on the participants' current ocular health history and diabetes status depended on the accuracy of participant-reported information rather than being derived from clinical examinations and/or medical records. Finally, this was not a typical screening population, as many participants were under the care of a diabetologist and had undergone prior ocular examinations, yet we still detected disease in people not known to have diabetes. In real-world studies in diabetic populations, the rate of ungradable images is up to 43.4% using non-mydriatic imaging.³⁵ Use of AI- and cloud-based systems could potentially help detect ungradable images automatically so images can be retaken immediately, if needed.

In summary, we designed a secure, interoperable, cloud-based platform that enabled seamless flow of imaging data between an employee health care center and a remote ophthalmic reading center. We demonstrated that a retinal screening program utilizing UWF-CFP and SD-OCT imaging is feasible and can be conveniently integrated into a workplace environment. This screening protocol enabled diagnosis of previously undetected retinal diseases such as AMD, DR, and DME in patients with and without a prior diabetes diagnosis. Early retinal disease diagnosis enables early treatment, avoiding the risk of undetected damage causing irreversible vision loss. Screening can also help identify individuals at risk from other undiagnosed underlying disorders, such as diabetes. Although in this case screening was carried out in a specific workplace setting, key aspects of this program could be transferred to other community-based settings and used to screen other populations. Future studies will evaluate the scalability of this system in the workplace and explore its wider applicability.

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