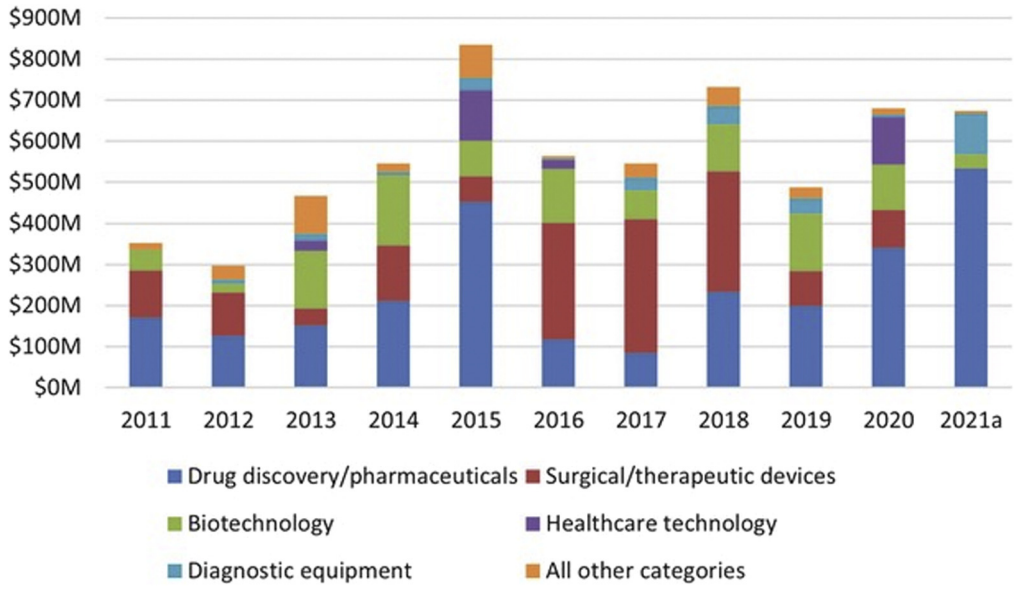

Figure 1. Total value of venture capital (VC) investments in ophthalmic companies. Source: PitchBook Data, Inc. (Disclaimer: Data were reviewed by the authors and not by PitchBook analysts.) Drug discovery/pharmaceuticals represent companies developing drugs/drug delivery technologies and manufacturing/distributing pharmaceuticals. Biotechnology refers to companies using biological systems to develop new drugs/therapies. Healthcare technology includes decision/risk analysis products, healthcare enterprise systems, medical records systems, and outcome management tools. Diagnostic equipment includes imaging and nonimaging devices used to assess and diagnose medical conditions. Surgical/therapeutic devices include devices, instruments, and equipment used in surgical procedures as well as prostheses and implants. [a]From January 1, 2021, to May 24, 2021.

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HUMAN SUBJECTS: Human subjects were not included in this study. The study was exempt from IRB review because it did not involve human subjects or patient data. The requirement for informed consent was waived because of the retrospective nature of the study. All research adhered to the tenets of the Declaration of Helsinki.

No animal subjects were used in this study.

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Data collection: Gupta, Uppal
Analysis and interpretation: Gupta, Uppal, Chang, Fetter, Hunter
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Trends in Remote Retinal Imaging Utilization and Payments in the United States

Recent increases in eye care demand and the Coronavirus Disease 2019 pandemic emphasize the need for tele-ophthalmology services such as remote eye imaging to screen for diabetic retinopathy. Only half of older Americans with diabetes undergo annual retinopathy screening as

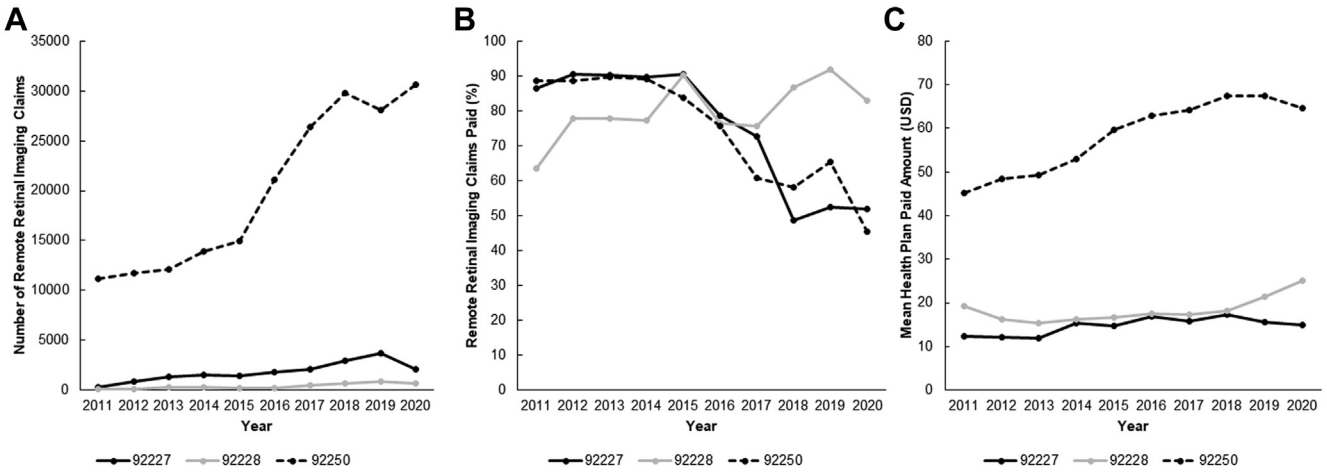

Figure 1. Utilization of remote retinal imaging services over time by diagnosis. Line graphs showing **(A)** remote retinal imaging utilization by year and Current Procedural Terminology (CPT) codes, **(B)** the proportion of approved payments by year and CPT code, and **(C)** mean insurer-paid amount in USD over time for each CPT code.

recommended by the American Academy of Ophthalmology.[1] Remote retinal imaging reduces costs, improves screening rates, and enhances care access for rural and underserved populations.[2] Before passage of the H.R. 6074 Coronavirus Preparedness and Response Supplement Appropriations Act of 2020,[3] which relaxed restrictions on telemedicine reimbursement, inconsistent insurance coverage and dwindling reimbursements were major barriers to implementing tele-retinal services.[4] In this report, we analyzed trends in remote retinal imaging utilization using a national claims database and evaluated factors associated with insurance payments.

Using the OptumLabs® Data Warehouse database of more than 160 million de-identified administrative claims for commercial and Medicare Advantage enrollees,[5] we identified claims from January 1, 2011, to December 31, 2020, with Current Procedural Terminology (CPT) codes for remote eye imaging (92227 and 92228) by any provider and fundus photography (92250) by non−eye care providers. Visit diagnoses were categorized using International Classification of Disease 9th and 10th Revision codes (Table S1, available at www.aaojournal.org). Provider specialty, practice settings, insurance types, patient demographic, and socioeconomic status variables including Rural Urban Commuting Area codes were collected (Table S1, available at www.aaojournal.org). Claim incidences were standardized to total claims in 2020. Insurance payment coverage (paid vs. denied) and insurer-paid amounts (United States dollars [USD]; inflation adjusted to 2020 using the Consumer Price Index) were reported by year and stratified by CPT, visit diagnosis, insurance type, demographic, and socioeconomic factors. For each CPT code, a multiple logistic regression model was fit with the binomial outcome insurance payment and year as a continuous, main independent variable. Common mediators that affect likelihood of claim payment—visit diagnosis, provider specialty, provider setting, and insurance—were chosen a priori and were also adjusted for in the models. General estimating equations were used to adjust for patients with multiple visits. Analyses were conducted in SAS (v9.4; SAS Institute Inc). Using the Department of Health and Human Services regulations, the IRB determined that this research project does not constitute human subject research and does not require IRB oversight. All research adhered to the tenets of the Declaration of Helsinki. The requirement for informed consent was waived because of the retrospective nature of the study.

Remote retinal imaging use increased from 11 603 claims in 2011 to 33 392 in 2020 (Fig 1A). Most claims used CPT 92250 (90.0%) rather than more specific remote imaging codes 92227 (8.2%) or 92228 (1.8%). The proportion of claims paid to physicians decreased from 88% in 2011 to 47% in 2020, with claims for 92227 and 92250 showing the greatest decline in coverage in recent years (Fig 1B). For claims that were paid, the mean [standard deviation] inflation-adjusted, insurer-paid amounts (USD) for codes 92227 and 92228 remained mostly unchanged from 2011 to 2020 from $12.38 [$14.54] to $14.85 [$7.15] for 92227 and from $19.31 [$9.04] to $25.10 [$10.74] for 92228. By contrast, payments for 92250 were higher and increased from $45.15 [$36.17] in 2011 to $64.70 [$37.38] in 2020 (Fig 1C).

While use of remote imaging for diabetic and nondiabetic eye conditions remained unchanged, screening for diabetes without eye disease increased, especially over the latter half of the decade, and constituted the majority of claims by 2019 (Fig S1A−C, available at www.aaojournal.org). Current Procedural Terminology 92227 was inappropriately utilized for nondiabetic eye diseases after the code's inception in 2011, but its use declined after 2015. Insurance payments for 92227 and 92250 decreased the most for diabetic patients without eye disease (Fig S1D and F, available at www.aaojournal.org), whereas coverage for 92228 varied between years, likely due to the overall lower utilization, and did not impact the overall trend of declining insurance coverage (Fig S1E, available at www.aaojournal.org). The adjusted odds ratio (95% confidence interval) for claims payment per year was 0.90 (0.88−0.93) for 92227 and 0.84 (0.88−0.93) for 92250, and increased for 92228 (odds ratio, 1.16 [1.11−1.21]) (Table S1, available at www.aaojournal.org).

Payments for remote imaging across all demographic and socioeconomic factors decreased over time (Fig S2A−G, available at www.aaojournal.org). The decline in insurance coverage was greatest for older patients, more in women than men, and among Black patients compared with other racial groups. Coverage for lower-income enrollees was also lower and exhibited greater decline, but did not

differ between education levels or population densities. Reimbursement rates were lower for Medicare Advantage than commercial insurance enrollees and decreased with time.

Our study showed a major decline in proportion of claims paid for remote retinal imaging over the decade, especially for CPT 92227, which decreased from 86.5% in 2011 to 51.9% in 2020, similar to findings from our tele-retinal screening program in California that used the same billing code.[6] Yet, this decline is occurring at a time of rapid expansion in using remote imaging to screen diabetic patients without eye diseases. In fact, claims for these patients were more often denied compared with those with eye diseases, even for 92227, which is designated for screening patients without retinopathy. This inconsistency in insurance coverage illustrates the confusing reimbursement landscape for tele-ophthalmology services.

Mean payment amounts were higher for 92250 than 92227 or 92228, consistent with their total relative value units in 2020 of 1.27, 0.38, and 0.96, respectively. However, while inflation-adjusted payments for remote imaging codes 92227 and 92228 remained stagnant over 10 years, payment amounts for the less-specific fundus photography code 92250 steadily increased. These differences may incentivize providers to utilize billing codes with higher reimbursements rather than the appropriate indications. Also jarring is the striking difference in coverage between Medicare Advantage and commercial insurance enrollees, which likely explains the disproportionate decrease in coverage of older individuals, a group most likely to benefit from remote eye care. We additionally found payment frequencies lower among women, Blacks, and lower-income households, further emphasizing the differential impact of declining payments.

This study may have limited generalizability because OptumLabs Data Warehouse only includes commercially insured and Medicare Advantage enrollees. Furthermore, while CPT 92227 and 92228 are used for asynchronous or "store-and-forward" remote retinal imaging, tele-ophthalmology using synchronous or live interfaces may not be captured.[7] Because we included 92250 billed by non−eye care providers only, ophthalmologists billing 92250 for remote services were excluded.

Although remote retinal imaging can reduce screening costs and detect vision-threatening disease earlier, declining and inconsistent insurance coverage pose substantial barriers against widespread adoption. Stakeholders and payers should be encouraged to expand coverage for remote imaging to improve eye care access and reduce vision loss.

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No animal subjects were used in this study.

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Efficacy and Safety of Adalimumab and Infliximab for Noninfectious Uveitis

Noninfectious uveitis (NIU) is an immune-mediated response commonly associated with systemic diseases (e.g., Behçet's disease) and nonsystemic inflammatory conditions (e.g., birdshot choroidopathy), or it may be idiopathic. Although corticosteroids are a mainstay of NIU treatment, steroid-sparing therapies such as anti−tumor necrosis factor α biologics and systemic immunomodulators allow for steroid tapering and mitigation of long-term side effects.

Adalimumab is the first and only anti−tumor necrosis factor α with United States Food and Drug Administration and Health Canada approval for NIU, and infliximab also has been explored as an off-label treatment for NIU.[1,2] The comparative evidence for these 2 agents has yet to be summarized. The objective of this systematic review and meta-analysis was to compare the efficacy and safety of adalimumab and infliximab in the treatment of NIU in adults to guide clinical decision making and to inform future studies.

A search of MEDLINE, EMBASE, SCOPUS, clinicaltrials.gov, clinicaltrialsregistry.eu, CENTRAL, and WHO ICTRP from inception through August 19, 2021, was conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines.[3] Efficacy outcomes included best-corrected visual acuity (BCVA; in logarithm of the minimum angle of resolution [logMAR] units), corticosteroid-sparing effects, relapse rate, remission proportion, and central macular thickness (CMT). Safety outcomes included discontinuation proportion resulting from adverse events (AEs) and frequency of various types of AEs.

A random-effects model or fixed-effects model (for analyses with ≤5 studies) was used to estimate Mantel-Haenszel risk ratios, mean difference (MD), or incidence rate ratio and their corresponding 95% confidence intervals (CIs) for dichotomous outcomes, continuous outcomes, or relapse rate per 100 patient-years, respectively. The Fisher exact test was used to compare proportions of AEs between groups. Detailed statistical methods are available in Supplemental Material 1 (available at www.aaojournal.org).

Of 5836 studies screened, 23 articles met the inclusion criteria, and 12 were included in the meta-analysis (Fig S1A, available at www.aaojournal.org). Study characteristics (Table S1A, available at www.aaojournal.org) and risk of bias (Fig S1B, C) were recorded. Meta-analysis showed that the reported final logMAR BCVA in studies was significantly better for adalimumab compared with infliximab (MD, 0.09; 95% CI, 0.04−0.15; I^2 = 84%; P = 0.001; Fig 2A). No significant differences between treatment with adalimumab or infliximab were found for corticosteroid-sparing effect (MD, −0.84; 95% CI, −2.70 to 1.02; I^2 = 0%; P = 0.38; Fig 2B). Evidence suggested that adalimumab may result in better CMT when compared with infliximab at last follow-up (MD, 13.46; 95% CI, 2.97−23.94; I^2 = 0%; P = 0.01; Fig 2C). The average CMT was 252.6 ± 37.1 μm and 259.0 ± 20.1 μm for infliximab and adalimumab, respectively. Pooled analysis demonstrated no significant difference in the remission proportion between adalimumab and infliximab (risk ratio, 0.98; 95% CI, 0.86−1.12; I^2 = 35%; P = 0.76; Fig 2D). Relapse rates aggregated from 11 studies showed no significant difference between treatment with infliximab or adalimumab (incidence rate ratio, 0.161; 95% CI, −0.45 to 0.19; I^2 = 33%; P = 0.42; Fig 2E). The comparative mean relapse rates were 0.071 and 0.104 events per 100 patient-years for adalimumab and infliximab, respectively. Risk of bias assessment with GRADE showed that all outcomes were of low quality because of the presence of confounding bias in observational studies, except for final logMAR BCVA, which was very low quality because of the heterogeneity in outcome measures.

Regarding safety outcomes, pooled analysis showed lower rates of discontinuation proportion resulting from AEs for adalimumab compared with infliximab (risk ratio, 1.66; 95% CI, 1.13−2.44; I^2 = 0%; P = 0.01; Fig 2F). Patients receiving infliximab experienced significantly more AEs compared with those who received adalimumab (20.9% infliximab vs. 13.7% adalimumab; P = 0.001). Patients receiving adalimumab showed significantly lower rates of acute reactions (e.g., injection site reaction, allergic reaction, skin rash) and nonspecific reactions (e.g., headache, myalgia, arthralgia, fatigue, etc.) compared with infliximab (P < 0.01 and P = 0.03, respectively; Table S1B).

In summary, our findings suggest a comparable efficacy between adalimumab and infliximab treatment for NIU, where corticosteroid-sparing effect, remission proportion, and relapse rate were not statistically significantly different. We also showed improved CMT, one of the main determinants of visual outcome in NIU, in eyes of patients receiving adalimumab treatment compared with infliximab. We also found that adalimumab treatment improved BCVA more than infliximab at last follow-up. A mean difference in visual acuity of 0.09 logMAR (Snellen equivalent, 20/25 or 1 line) between treatment with adalimumab compared with treatment with infliximab is a clinically significant improvement.[4] Of note, BCVA was difficult to compare because of heterogeneity between studies, nonstandardized measures of visual acuity, lack of reported baseline BCVA, and other ocular complications that may interfere with vision outcomes, such as cataract and cystoid macular edema. Interestingly, a recent meta-analysis by Maccora et al[5] found adalimumab to be more efficacious in reducing intraocular inflammation than infliximab in treatment of chronic NIU in children.

Our meta-analysis also demonstrated that adalimumab resulted in lower discontinuation proportion resulting from AE and less AEs overall compared with infliximab. This finding is consistent with head-to-head comparison studies in Crohn's disease, which have demonstrated higher overall rates of AE in infliximab compared with adalimumab.[6] Most infliximab-related AEs were nonspecific symptoms and acute reactions, both of which impact medication compliance and patient quality of life. Similar rates of infection-related AEs were found between infliximab and adalimumab, which is in keeping with the literature.[7]

We would like to point out the heterogeneity of nonrandomized observational studies, which may create a risk of bias and may affect generalizability of findings because of an inability to control for confounding variables. Also, inconsistencies exist in reporting